The Surgeon General's Report on NUTRITION AND HEALTH

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DEPARTMENT OF HEALTH & HUMAN SERVICES

The Surgeon General of the
Public Health Service
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MESSAGE FROM THE SURGEON GENERAL

I am pleased to transmit to the Secretary of the Department of Health and Human Services this first Surgeon General's Report on Nutrition and Health. It was prepared under the auspices of the Department's Nutrition Policy Board, and its main conclusion is that overconsumption of certain dietary components is now a major concern for Americans. While many food factors are involved, chief among them is the disproportionate consumption of foods high in fats, often at the expense of foods high in complex carbohydrates and fiber--such as vegetables, fruits, and whole grain products--that may be more conducive to health.

I offer this Report in the context of the obligation of the Surgeon General to inform the American public of developments in the science base that have widespread implications for human health. Perhaps the classic example of such reports is the one issued in 1964 during the tenure of one of my predecessors, Dr. Luther Terry, which summarized the epidemiologic evidence available at the time on the relationship of tobacco to health. This report called attention to the inescapable conclusion that cigarettes were a major source of illness and death for those who smoked--at that time a majority of adult men.

This Surgeon General's Report on Nutrition and Health follows the tradition of the original report on smoking and health. It addresses an area of some controversy and substantial misunderstanding. And the relative magnitude of the associated health concerns is comparable, with dietary factors playing a prominent role in five of the ten leading causes of death for Americans. In addition, the depth of the science base underlying its findings is even more impressive than that for tobacco and health in 1964, with animal and clinical evidence adding to the epidemiologic studies.

On the other hand there are some fundamental differences. Most obvious is the fact that food is necessary for good health. Foods contain nutrients essential for normal metabolic function, and when problems arise, they result from imbalance in nutrient intake or from harmful interaction with other factors. Moreover, we know today much more about individual variation in response to nutrients than we know about possible variations in

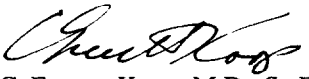
response to tobacco. Some people are clearly more susceptible than others to problems from diets that are, for example, higher in fat or salt.

Also, unlike the experience for tobacco in 1964, people are already making dietary changes, as witnessed by the shift to products lower in saturated fats. Nonetheless, the important effects of the dietary factors underlying problems like coronary heart disease, high blood pressure, stroke, some types of cancer, diabetes, obesity--problems that represent the leading health threats for Americans--indicate the potential for substantial gains to be accrued by the recommendations contained in this Report

It is important to emphasize that the focus of this Report is primarily on the relationship of diet to the occurrence of chronic diseases. The Report is not intended to address the problems of hunger or undernutrition that may occur in the United States among certain subgroups of the population. All Americans should have access to an appropriate diet, but they do not. And even though the size and numbers of problems related to inadequate access to food are proportionately much smaller than those related to dietary excesses and imbalances, the problems of access to food are of considerable concern to me, personally, wherever they may occur.

The apparently sizable numbers of people resorting to the use of soup kitchens and related food facilities, as well as the possible role of poor diet as a contributor to the higher infant mortality rates associated with inadequate income, suggest the need for better monitoring of the nature and extent of the problem and for sustained efforts to correct the underlying causes of diminished health due to inadequate or inappropriate diets.

This report was prepared primarily for nutritional policy makers, although the eventual beneficiaries of better nutritional policy will be the American people. I am convinced that with a concerted effort on the part of policy makers throughout the Nation, and eventually by the public, our daily diets can bring a substantial measure of better health to all Americans. I commend to them the recommendations of this Report.



C. Everett Koop, M.D., Sc.D.
Surgeon General
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Foreword

This first *Surgeon General's Report on Nutrition and Health* marks a key event in the history of public health in the United States. While the Report has been developed for use by policymakers, it offers lessons that can be directly applied to the public. It responds to the increasing interest of scientists, health professionals, and the American people in the role of diet in health promotion. Within recent years, concerns about nutrition and health have expanded beyond the need to prevent deficiencies to encompass the effects of typical American dietary patterns on the incidence of chronic diseases that are leading causes of death and disability in this country. Although scientific research has provided substantial insight into the ways specific dietary factors influence specific diseases, there are still many uncertainties about diet-disease relationships. The Department of Health and Human Services, through the Public Health Service and the Surgeon General, welcomes the responsibility to evaluate the current state of knowledge and to advise the public accordingly.

This Report reviews the scientific evidence that relates dietary excesses and imbalances to chronic diseases. On the basis of the evidence, it recommends dietary changes that can improve the health prospects of many Americans. Of highest priority among these changes is to reduce intake of foods high in fats and to increase intake of foods high in complex carbohydrates and fiber.

The evidence presented here indicates the convergence of similar dietary recommendations that apply to prevention of multiple chronic diseases. The recommendation to reduce dietary fat, for example, aims to reduce the risk for coronary heart disease, diabetes, obesity, and some types of cancer. This advice is not new. But it is now substantiated by a large body of evidence derived from many different kinds of research—a research base that is now even more comprehensive than was the case for the pioneering 1964 *Surgeon General's Report on Smoking and Health.*

The weight of this evidence and the magnitude of the problems at hand indicate that it is now time to take action. In the cause of good health for all our citizens, I urge support for this Report's recommendations by every sector of American society.

Otis R. Bowen, M.D.
Secretary

Preface

The Public Health Service of the Department of Health and Human Services has long maintained an interest in the relationship between food and health. In the 1970's, this interest began to focus on the ways in which dietary excesses and imbalances increase the risk for chronic diseases. With the publication in 1979 of *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention,* attention turned toward environmental and behavioral changes that Americans might make to reduce their risks for morbidity and mortality. Nutrition was one such priority area. The 1980 report *Promoting Health/Preventing Disease: Objectives for the Nation* included 17 specific, quantifiable objectives in nutrition designed to reduce risks and to prevent illness and death. Also in 1980, the Department published, jointly with the U.S. Department of Agriculture, the first edition of *Dietary Guidelines for Americans.* This report, revised in 1985, includes seven recommendations that, taken together, address the relationship between diet and chronic diseases.

Diseases such as coronary heart disease, stroke, cancer, and diabetes remain leading causes of death and disability in the United States. Substantial scientific research over the past few decades indicates that diet can play an important role in prevention of such conditions. The Public Health Service has now reviewed this research and has produced a comprehensive analysis of the relationship between dietary factors and chronic disease risk. This *Surgeon General's Report on Nutrition and Health* summarizes research on the role of diet in health promotion and disease prevention. Its findings indicate the great importance of diet to health. They demonstrate that changes in present dietary practices of Americans could produce substantial gains in the health of the population. The Public Health Service is committed to improving the health of Americans through its programs in education, services, and research.

One mechanism for improving the health of Americans is through the 1990 Health Objectives for the Nation. The role of nutrition in health will continue to be a focus of national health priorities as we develop new objectives for the year 2000. Federal, State, and local governments, the American public, the food industry, and scientists and health professionals can work together to encourage Americans to make healthy food choices and to achieve national health goals.

I am pleased to commend to the American people this review of the scientific evidence that links diet to chronic disease, and I urge that the findings of this important Report be given your careful consideration.

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Summary and Recommendations

This Report addresses the substantial impact of daily dietary patterns on the health of Americans. Good health does not always come easily. It is the product of complex interactions among environmental, behavioral, social, and genetic factors. Some of these are, for practical purposes, beyond personal control. But there are many ways in which each of us can influence our chances for good health through the daily choices we make.

In recent years, scientific investigations have produced abundant information on the ways personal behavior affects health. This information can help us decide whether to smoke, when and how much to drink, how far to walk or climb stairs, whether to wear seat belts, and how or whether to engage in any other activity that might alter the risk of incurring disease or disability. For the two out of three adult Americans who do not smoke and do not drink excessively, one personal choice seems to influence long-term health prospects more than any other: what we eat.

Food sustains us, it can be a source of considerable pleasure, it is a reflection of our rich social fabric and cultural heritage, it adds valued dimensions to our lives. Yet what we eat may affect our risk for several of the leading causes of death for Americans, notably, coronary heart disease, stroke, atherosclerosis, diabetes, and some types of cancer. These disorders together now account for more than two-thirds of all deaths in the United States.

Undernutrition remains a problem in several parts of the world, as well as for certain Americans. But for most of us the more likely problem has become one of overeating—too many calories for our activity levels and an imbalance in the nutrients consumed along with them. Although much is still uncertain about how dietary patterns protect or injure human health, enough has been learned about the overall health impact of the dietary patterns now prevalent in our society to recommend significant changes in those patterns.

This first *Surgeon General's Report on Nutrition and Health* offers comprehensive documentation of the scientific basis for the recommended dietary changes. Through the extensive review contained in its chapters, the Report examines in detail current knowledge about the relationships among specific dietary practices and specific disease conditions and sum-

marizes the implications of this information for individual food choices, public health policy initiatives, and further research. **The Report's main conclusion is that overconsumption of certain dietary components is now a major concern for Americans. While many food factors are involved, chief among them is the disproportionate consumption of foods high in fats, often at the expense of foods high in complex carbohydrates and fiber that may be more conducive to health.** A list of the key recommendations based on the evidence presented in Table 1.

Magnitude of the Problem

Diet has always had a vital influence on health. Until as recently as the 1940's, diseases such as rickets, pellagra, scurvy, beriberi, xerophthalmia, and goiter (caused by lack of adequate dietary vitamin D, niacin, vitamin C, thiamin, vitamin A, and iodine, respectively) were prevalent in this country and throughout the world. Today, thanks to an abundant food supply, fortification of some foods with critical trace nutrients, and better methods for determining and improving the nutrient content of foods, such "deficiency" diseases have been virtually eliminated in developed countries. For example, the introduction of iodized salt in the 1920's contributed greatly to eliminating iodine-deficiency goiter as a public health problem in the United States. Similarly, pellagra disappeared subsequent to the discovery of the dietary causes of this disease. Nutrient deficiencies are reported rarely in the United States, and the few cases of protein-energy malnutrition that are listed annually as causes of death generally occur as a secondary result of severe illness or injury, child neglect, the problems of the house-bound aged, premature birth, alcoholism, or some combination of these factors.

As the diseases of nutritional deficiency have diminished, they have been replaced by diseases of dietary excess and imbalance—problems that now rank among the leading causes of illness and death in the United States, touch the lives of most Americans, and generate substantial health care costs. Table 2, for example, lists the 10 leading causes of death in the United States in 1987.

In addition to the five of these causes that scientific studies have associated with diet (coronary heart disease, some types of cancer, stroke, diabetes mellitus, and atherosclerosis), another three—cirrhosis of the liver, accidents, and suicides—have been associated with excessive alcohol intake.

Table 1
Recommendations

Issues for Most People:

- *Fats and cholesterol:* Reduce consumption of fat (especially saturated fat) and cholesterol. Choose foods relatively low in these substances, such as vegetables, fruits, whole grain foods, fish, poultry, lean meats, and low-fat dairy products. Use food preparation methods that add little or no fat.

- *Energy and weight control:* Achieve and maintain a desirable body weight. To do so, choose a dietary pattern in which energy (caloric) intake is consistent with energy expenditure. To reduce energy intake, limit consumption of foods relatively high in calories, fats, and sugars, and minimize alcohol consumption. Increase energy expenditure through regular and sustained physical activity.

- *Complex carbohydrates and fiber:* Increase consumption of whole grain foods and cereal products, vegetables (including dried beans and peas), and fruits.

- *Sodium:* Reduce intake of sodium by choosing foods relatively low in sodium and limiting the amount of salt added in food preparation and at the table.

- *Alcohol:* To reduce the risk for chronic disease, take alcohol only in moderation (no more than two drinks a day), if at all. Avoid drinking any alcohol before or while driving, operating machinery, taking medications, or engaging in any other activity requiring judgment. Avoid drinking alcohol while pregnant.

Other Issues for Some People:

- *Fluoride:* Community water systems should contain fluoride at optimal levels for prevention of tooth decay. If such water is not available, use other appropriate sources of fluoride.

- *Sugars:* Those who are particularly vulnerable to dental caries (cavities), especially children, should limit their consumption and frequency of use of foods high in sugars.

- *Calcium:* Adolescent girls and adult women should increase consumption of foods high in calcium, including low-fat dairy products.

- *Iron:* Children, adolescents, and women of childbearing age should be sure to consume foods that are good sources of iron, such as lean meats, fish, certain beans, and iron-enriched cereals and whole grain products. This issue is of special concern for low-income families.

Table 2
Estimated Total Deaths and Percent of Total Deaths for the 10 Leading Causes of Death: United States, 1987

Rank	Cause of Death	Number	Percent of Total Deaths
1[a]	Heart diseases	759,400	35.7
	(Coronary heart disease)	(511,700)	(24.1)
	(Other heart disease)	(247,700)	(11.6)
2[a]	Cancers	476,700	22.4
3[a]	Strokes	148,700	7.0
4[b]	Unintentional injuries	92,500	4.4
	(Motor vehicle)	(46,800)	(2.2)
	(All others)	(45,700)	(2.2)
5	Chronic obstructive lung diseases	78,000	3.7
6	Pneumonia and influenza	68,600	3.2
7[a]	Diabetes mellitus	37,800	1.8
8[b]	Suicide	29,600	1.4
9[b]	Chronic liver disease and cirrhosis	26,000	1.2
10[a]	Atherosclerosis	23,100	1.1
. . .	All causes	2,125,100	100.0

[a]Causes of death in which diet plays a part.
[b]Causes of death in which excessive alcohol consumption plays a part.

Source: National Center for Health Statistics, *Monthly Vital Statistics Report*, vol. 37, no. 1, April 25, stics Report, vol. 37, no. 1, April 25, 1988.

Although the precise proportion attributable to diet is uncertain, these eight conditions accounted for nearly 1.5 million of the 2.1 million total deaths in 1987. Dietary excesses or imbalances also contribute to other problems such as high blood pressure, obesity, dental diseases, osteoporosis, and gastrointestinal diseases. Together, these diet-related conditions inflict a substantial burden of illness on Americans. For example:

- *Coronary Heart Disease*. Despite the recent sharp decline in the death rate from this condition, coronary heart disease still accounts for the largest number of deaths in the United States. More than 1.25 million heart attacks occur each year (two-thirds of them in men), and more than 500,000 people die as a result. In 1985, illness and deaths from coronary heart disease cost Americans an estimated $49 billion in direct health care expenditures and lost productivity.
- *Stroke*. Strokes occur in about 500,000 persons per year in the United States, resulting in nearly 150,000 deaths in 1987 and long-term disability for many individuals. Approximately 2 million living Americans suffer from stroke-related disabilities, at an estimated annual cost of more than $11 billion.

- *High Blood Pressure*. High blood pressure (hypertension) is a major risk factor for both heart disease and stroke. Almost 58 million people in the United States have hypertension, including 39 million who are under age 65. The occurrence of hypertension increases with age and is higher for black Americans (of which 38 percent are hypertensive) than for white Americans (29 percent).
- *Cancer*. More than 475,000 persons died of cancer in the United States in 1987, making it the second leading cause of death in this country. During the same period, more than 900,000 new cases of cancer occurred. The costs of cancer for 1985 have been estimated to be $22 billion for direct health care, $9 billion in lost productivity due to treatment or disability, and $41 billion in lost productivity due to premature mortality, for a total cost of $72 billion.
- *Diabetes Mellitus*. Approximately 11 million Americans have diabetes, but almost half of them have not been diagnosed. In addition to the nearly 38,000 deaths in 1987 attributed directly to this condition, diabetes also contributes to an estimated 95,000 deaths per year from associated cardiovascular and kidney complications. In 1985, diabetes was estimated to cost $13.8 billion per year, or about 3.6 percent of total health care expenses.
- *Obesity*. Obesity affects approximately 34 million adults ages 20 to 74 years in the United States, with the highest rates observed among the poor and minority groups. Obesity is a risk factor for coronary heart disease, high blood pressure, diabetes, and possibly some types of cancer as well as other chronic diseases.
- *Osteoporosis*. Approximately 15 to 20 million Americans are affected by osteoporosis, which contributes to some 1.3 million bone fractures per year in persons 45 years and older. One-third of women 65 years and older have vertebral fractures. On the basis of x-ray evidence, by age 90 one-third of women and one-sixth of men will have suffered hip fractures, leading to death in 12 to 20 percent of those cases and to long-term nursing care for many who survive. The total costs of osteoporosis to the U.S. economy were estimated to be $7 to $10 billion in 1983.
- *Dental Diseases*. Dental caries and periodontal disease continue to affect a large proportion of Americans and cause substantial pain, restriction of activity, and work loss. Although dental caries among children, as well as some forms of adult periodontal disease, appear to be declining, the overall prevalence of these conditions imposes a substantial burden on Americans. The costs of dental care were estimated at $21.3 billion in 1985.

- *Diverticular Disease.* Because most persons with diverticular disease do not have symptoms, the true prevalence of this condition is unknown. Frequency increases with age, and up to 70 percent of people between the ages of 40 and 70 may be affected. In 1980, diverticulosis was accountable for some 200,000 hospitalizations.

In assessing the role that diet might play in prevention of these conditions, it must be understood that they are caused by a combination (and interaction) of multiple environmental, behavioral, social, and genetic factors. The exact proportion that can be attributed directly to diet is uncertain. Although some experts have suggested that dietary factors overall are responsible for perhaps a third or more of all cases of cancer, and similar estimates have been made for coronary heart disease, such suggestions are based on interpretations of research studies that cannot completely distinguish dietary from genetic, behavioral, or environmental causes.

We know, for example, that cigarette smoking exerts a powerful influence on the occurrence of both coronary heart disease and some types of cancer. We also know that some people are genetically predisposed to coronary heart disease, stroke, and diabetes and that the interaction of genetic predisposition with dietary patterns is an important determinant of individual risk. For these reasons, it is not yet possible to determine the proportion of chronic diseases that could be reduced by dietary changes. Nonetheless, it is now clear that diet contributes in substantial ways to the development of these diseases and that modification of diet can contribute to their prevention. The magnitude of the health and economic cost of diet-related disease suggests the importance of the dietary changes suggested. This Report reviews these issues in detail.

Nature of the Evidence

Whereas centuries of clinical observations and decades of basic and clinical research prove that dietary deficiencies of single, identifiable nutrients can cause disease, research on the relationship of dietary excesses and imbalances to chronic disease yields results that rarely provide such direct proof of causality. Instead, investigators must piece together various kinds of information from several kinds of sources. Nevertheless, the quantity of current animal, laboratory, clinical, and epidemiologic evidence that associates dietary excesses and imbalances with chronic disease is substantial and, when evaluated according to established principles, compelling.

Scientists must often draw inferences about the relationships between dietary factors and disease from laboratory animal studies or human meta-

bolic and population studies that approach the issues indirectly. Data sources for such human studies include clinical and laboratory measurements of physiologic indicators of nutritional status or risk factors, as well as dietary intake data estimated for populations or individuals. Epidemiologic studies using these data compare dietary intake and disease rates in different countries or in defined groups within the same country.

Interpretations of animal studies are limited by uncertainties about their applicability to people. Clinical, laboratory, and dietary intake studies can provide useful information, but each has limitations. Currently available clinical and laboratory measurements reveal only a small part of the complex physiological responses to diet, and they may reflect past rather than current nutritional status. Dietary surveys depend on accurate recall of the types and portion sizes of consumed foods as well as on the assumption that the food intake during any one period represents typical intake. Reported intake, however, is not always accurate, and intake reported for a given period may differ significantly from that typical of longer time periods. Dietary intake data provide useful indicators for populations, but even when an association or correlation between a dietary factor and a disease is observed, it is often difficult to prove that the dietary factor is an actual or sole cause of that disease.

This difference between association and causation is basic to understanding the scientific evidence that links diet to chronic disease. Uncertainties in the ability to determine causation have sometimes made it difficult to achieve consensus on appropriate public health nutrition policies. Established principles require evaluation of the supporting evidence for a given association between a dietary factor and a disease on the basis of its consistency, strength, specificity, and biological plausibility. The evidence showing that dietary intake of saturated fat raises blood cholesterol, which in turn increases the chance of coronary heart disease, illustrates this point. The similarity in results from laboratory, clinical, and epidemiologic research, the apparent relationship between dose and effect in these studies, the observations that the increase in blood cholesterol level is specific to saturated fatty acids but not to other types, and the biological plausibility of explanations for the observations, when taken together, provide considerable support for concluding that the association is causal, at least for some individuals.

For some of the other diseases reviewed in this Report, the available evidence is less complete and less consistent. Nevertheless, much evidence supports credible associations between a dietary pattern of excesses

and imbalances and several important chronic diseases. These associations, in turn, suggest that the overall health of Americans could be improved by a few specific but fundamental dietary changes.

Key Findings and Recommendations

Even though the results of various individual studies may be inconclusive, the preponderance of the evidence presented in the Report's comprehensive scientific review substantiates an association between dietary factors and rates of chronic diseases. In particular, the evidence suggests strongly that a dietary pattern that contains excessive intake of foods high in calories, fat (especially saturated fat), cholesterol, and sodium, but that is low in complex carbohydrates and fiber, is one that contributes significantly to the high rates of major chronic diseases among Americans. It also suggests that reversing such dietary patterns should lead to a reduced incidence of these chronic diseases.

This *Surgeon General's Report on Nutrition and Health* provides a comprehensive review of the most important scientific evidence in support of current Federal nutrition policy as stated in the *Dietary Guidelines for Americans*. These *Guidelines*, issued jointly by the Department of Agriculture and the Department of Health and Human Services, recommend:

- Eat a variety of foods.
- Maintain desirable weight.
- Avoid too much fat, saturated fat, and cholesterol.
- Eat foods with adequate starch and fiber.
- Avoid too much sugar.
- Avoid too much sodium.
- If you drink alcoholic beverages, do so in moderation.

Evidence presented in this Report expands the focus of these seven guidelines and provides considerable insight into priorities. Clearly emerging as the primary priority for dietary change is the recommendation to reduce intake of total fats, especially saturated fat, because of their relationship to development of several important chronic disease conditions. Because excess body weight is a risk factor for several chronic diseases, maintenance of desirable weight is also an important public health priority. Evidence further supports the recommendation to consume a dietary pattern that contains a variety of foods, provided that these foods are generally low in calories, fat, saturated fat, cholesterol, and sodium.

Taken together, the recommendations in this Report promote a dietary pattern that emphasizes consumption of vegetables, fruits, and whole grain products—foods that are rich in complex carbohydrates and fiber and relatively low in calories—and of fish, poultry prepared without skin, lean meats, and low-fat dairy products selected to minimize consumption of total fat, saturated fat, and cholesterol.

The evidence presented in this Report suggests that such overall dietary changes will lead to substantial improvements in the nutritional quality of the American diet. Consuming a higher proportion of calories from fruits, vegetables, and grains may lead to a modest reduction in protein intake for some people, but this reduction is unlikely to impair nutritional status. Average levels of protein consumption in the United States, 60 grams per day for women and 90 grams per day for men, are well above the National Research Council's recommendations of 44 and 56 grams per day, respectively.

The evidence also suggests that most Americans generally need not consume nutrient supplements. An estimated 40 percent of Americans consume supplemental vitamins, minerals, or other dietary components at an annual cost of more than $2.7 billion. Although nutrient supplements are usually safe in amounts corresponding to the Recommended Dietary Allowances (and such Allowances are set to ensure that the nutrient needs of practically all the population are met), there are no known advantages to healthy people consuming excess amounts of any nutrient, and amounts greatly exceeding recommended levels can be harmful. For example, some nutrients such as selenium have a narrow range of safe level of intake. Toxicity has been reported for most minerals and trace elements, as well as some vitamins, indicating that excessive supplementation with these substances can be hazardous.

Finally, some recommendations for dietary change apply broadly to the general public whereas others apply only to specific population groups. These major findings and recommendations of *The Surgeon General's Report on Nutrition and Health* are noted below.

Issues for Most People

- ***Fats and cholesterol:*** **Reduce consumption of fat (especially saturated fat) and cholesterol. Choose foods relatively low in these substances, such as vegetables, fruits, whole grain foods, fish, poultry, lean meats, and low-fat dairy products. Use food preparation methods that add little or no fat.**

High intake of total dietary fat is associated with increased risk for obesity, some types of cancer, and possibly gallbladder disease. Epidemiologic, clinical, and animal studies provide strong and consistent evidence for the relationship between saturated fat intake, high blood cholesterol, and increased risk for coronary heart disease. Conversely, reducing blood cholesterol levels reduces the risk for death from coronary heart disease. Excessive saturated fat consumption is the major dietary contributor to total blood cholesterol levels. Dietary cholesterol raises blood cholesterol levels, but the effect is less pronounced than that of saturated fat. While polyunsaturated fatty acid consumption, and probably monounsaturated fatty acid consumption, lowers total blood cholesterol, the precise effects of specific fatty acids are not well defined.

Dietary fat contributes more than twice as many calories as equal quantities (by weight) of either protein or carbohydrate, and some studies indicate that diets high in total fat are associated with higher obesity rates. In addition, there is substantial, although not yet conclusive, epidemiologic and animal evidence in support of an association between dietary fat intake and increased risk for cancer, especially breast and colon cancer. Similarly, epidemiologic studies suggest an association between gallbladder disease, excess caloric intake, high dietary fat, and obesity. More precise conclusions about the role of dietary fat await the development of improved methods to distinguish among the contributions of the high-calorie, high-fat, and low-fiber components of current American dietary patterns.

At present, dietary fat accounts for about 37 percent of the total energy intake of Americans—well above the upper limit of 30 percent recommended by the American Heart Association and the American Cancer Society, and above the percent consumed by many societies, such as Mediterranean countries, Japan, and China, for example, where coronary heart disease rates are much lower than those observed in the United States. Consumption of saturated fat and cholesterol is also substantially higher among many Americans than levels recommended by several expert groups.

The major dietary sources of fat in the American diet are meat, poultry, fish, dairy products, and fats and oils. Animal products tend to be higher in both total and saturated fats than most plant sources. Although some plant fats such as coconut and palm kernel oils also contain high proportions of saturated fatty acids, these make minor contributions to total intake of saturated fats in the United States. Dietary cholesterol is found only in foods of animal origin, such as eggs, meat, poultry, fish, and dairy prod-

ucts. To help reduce consumption of total fat, especially saturated fat and cholesterol, food choices should emphasize intake of fruits, vegetables, and whole grain products and cereals. They should also emphasize consumption of fish, poultry prepared without skin, lean meats, and low-fat dairy products. Among vegetable fats, those that are more unsaturated are better choices.

- ***Energy and weight control:*** **Achieve and maintain a desirable body weight. To do so, choose a dietary pattern in which energy (caloric) intake is consistent with energy expenditure. To reduce energy intake, limit consumption of foods relatively high in calories, fats, and sugars and minimize alcohol consumption. Increase energy expenditure through regular and sustained physical activity.**

People are considered overweight if their body mass index, or BMI (a ratio of weight to height described in the Report), exceeds the 85th percentile for young American adults (approximately 120 percent of desirable body weight); they are considered severely overweight if their BMI exceeds the 95th percentile (approximately 140 percent of desirable body weight). Overweight individuals are at increased risk for diabetes mellitus, high blood pressure and stroke, coronary heart disease, some types of cancer, and gallbladder disease. Epidemiologic and animal studies have shown consistently that overall risk for death is increased with excess weight, with risk increasing as severity of obesity increases.

Type II (noninsulin-dependent) diabetes mellitus accounts for approximately 90 percent of all cases of diabetes and is strongly associated with obesity. Clinical studies indicate that weight loss can improve control of Type II diabetes.

Obesity increases the risk for high blood pressure, and consequently for stroke; it also increases blood cholesterol levels associated with coronary heart disease. In addition, it appears to be an independent risk factor for coronary heart disease. Weight reduction has been shown to reduce high blood pressure and high blood cholesterol. Most obese individuals who achieve a more desirable body weight improve their cholesterol profile, achieving a decrease in both total blood cholesterol and LDL (low density lipoprotein) cholesterol.

Some studies have found an association between overweight and increased risk for several cancers, especially cancer of the uterus and breast. In addition, overweight increases the risk for gallbladder disease.

More than a quarter of American adults are overweight. Black women age 45 and above have the highest prevalence, about 60 percent. Although evidence suggests a genetic component to the tendency of many people to become overweight, patterns of dietary caloric intake and energy expenditure play a key role. Sustained and long- term efforts to reduce body weight can best be achieved as a result of improving energy balance by reducing energy consumption and raising energy expenditure through physical activity and exercise.

Maintenance of desirable body weight throughout the lifespan requires a balance between energy (calorie) intake and expenditure. Weight control may be facilitated by decreasing energy intake, especially by choosing foods relatively low in calories, fats, and sugars, and by minimizing alcohol consumption. Energy expenditure can be enhanced through regular physical activities such as daily walks or by jogging, bicycling, or swimming at least three times a week for at least 20 minutes.

- ***Complex carbohydrates and fiber*: Increase consumption of whole grain foods and cereal products, vegetables (including dried beans and peas), and fruits.**

Dietary patterns emphasizing foods high in complex carbohydrates and fiber are associated with lower rates of diverticulosis and some types of cancer. The association shown in epidemiologic and animal studies between diets high in complex carbohydrates and reduced risk for coronary heart disease and diabetes mellitus is, however, difficult to interpret. The fact that such diets tend also to be lower in energy and fats, especially saturated fat and cholesterol, clearly contributes to this difficulty. Some evidence from clinical studies also suggests that water-soluble fibers from foods such as oat bran, beans, or certain fruits are associated with lower blood glucose and blood lipid levels. Consuming foods with dietary fiber is usually beneficial in the management of constipation and diverticular disease.

While inconclusive, some evidence also suggests that an overall increase in intake of foods high in fiber might decrease the risk for colon cancer. Among several unresolved issues is the role of the various types of fiber, which differ in their effects on water-holding capacity, viscosity, bacterial fermentation, and intestinal transit time.

Other food components associated with decreased cancer risk are commonly found in diets high in whole grain cereal products containing complex carbohydrates and fiber. In addition, some epidemiologic evidence

suggests that frequent consumption of vegetables and fruits, particularly dark green and deep yellow vegetables and cruciferous vegetables (such as cabbage and broccoli), may lower risk for cancers of the lung and bladder as well as some cancers of the alimentary tract. However, the specific components in these foods that may have protective effects have not yet been established. Current evidence suggests the prudence of increasing consumption of whole grain foods and cereals, vegetables (including dried beans and peas), and fruits.

- *Sodium:* **Reduce intake of sodium by choosing foods relatively low in sodium and limiting the amount of salt added in food preparation and at the table.**

Studies indicate a relationship between a high sodium intake and the occurrence of high blood pressure and stroke. Salt contains about 40 percent sodium by weight and is used widely in the preservation, processing, and preparation of foods. Although sodium is necessary for normal metabolic function, it is consumed in the United States at levels far beyond the 1.1 to 3.3 grams per day found to be as safe and adequate for adults by the National Research Council. Average current sodium intake for adults in the United States is in the range of 4 to 6 grams per day.

Blacks and persons with a family history of high blood pressure are at greater risk for this condition. While some people maintain normal blood pressure levels over a wide range of sodium intake, others appear to be "salt sensitive" and display increased blood pressure in response to high sodium intakes.

Although not all individuals are equally susceptible to the effects of sodium, several observations suggest that it would be prudent for most Americans to reduce sodium intake. These include the lack of a practical biological marker for individual sodium sensitivity, the benefit to persons whose blood pressures do rise with sodium intake, and the lack of harm from moderate sodium restriction.

Processed foods provide about a third or more of dietary sodium. Because about another third of the sodium consumed by Americans is added by the consumer, much can be done to reduce sodium consumption by using less salt at the table and substituting alternative flavoring such as herbs, spices, and lemon juice in the preparation of foods. In addition, choices can be made of foods modified to lower sodium content and less frequent choices could be made of foods to which sodium is added in processing and preservation.

- *Alcohol:* **To reduce the risk for chronic disease, take alcohol only in moderation (no more than two drinks a day), if at all. Avoid drinking any alcohol before or while driving, operating machinery, taking medications, or engaging in any other activity requiring judgment. Avoid drinking alcohol while pregnant.**

Alcohol is a drug that can produce addiction in susceptible individuals, birth defects in some children born to mothers who drink alcohol during pregnancy, impaired judgment, impaired ability to drive automobiles or operate machinery, and adverse reactions in people taking certain medications. In addition, alcohol abuse has been associated with disrupted family functioning, suicides, and homicides.

Excessive use of alcohol is also associated with liver disease, some types of cancer, high blood pressure, stroke, and disorders of the heart muscle. Extensive epidemiologic and clinical evidence has identified alcohol consumption as the principal cause of liver cirrhosis in the United States, at least in part as a result of the direct toxic effects of alcohol on the liver. Smoking and alcohol appear to act synergistically to increase the risk for cancers of the mouth, larynx, and esophagus. Less conclusive and somewhat conflicting evidence suggests a role of alcohol in other types of cancers such as those of the liver, rectum, breast, and pancreas.

Studies indicate a direct association between increased blood pressure and the consumption of alcohol at levels beyond about two drinks[a] daily. Extremely excessive alcohol consumption is associated with cardiomyopathy. Alcohol consumption by the mother during pregnancy has also been associated with fetal malformations.

Although consumption of up to two drinks per day has not been associated with disease among healthy men and nonpregnant women, surveys suggest that at least 9 percent of the total population consumes two or more drinks per day and those in this group need to reduce their alcohol consumption. A threshold level of safety for alcohol intake during pregnancy has not been established. Thus, pregnant women and women who may become pregnant should avoid drinking alcohol.

[a]One drink is defined as a 12 ounce beer, a 5 ounce glass of wine, or 1½ fluid ounces (one jigger) of distilled spirits, each of which contains about 1 ounce of alcohol.

Other Issues for Some People

- ***Fluoride:*** **Community water systems should contain fluoride at optimal levels for prevention of tooth decay. If such water is not available, use other appropriate sources of fluoride.**

The most efficient means of making fluoride available to the general public to reduce dental disease is through drinking water. Numerous epidemiologic and clinical studies have attested to the efficacy, safety and cost-effectiveness of systemic fluoride in the prevention of tooth decay. Lifetime use of water containing an optimal fluoride concentration of approximately 1 part per million has been shown to reduce the prevalence of dental caries by more than 50 percent. Water fluoridation is considered one of the most successful public health efforts introduced in the United States.

For children living in areas with inadequate concentrations of fluoride in the water, supplementary fluoride sources should be used at dosages that depend on the fluoride content of the local water supply and the age of the child. The effectiveness of prenatal fluoride administration, however, is uncertain because clinical studies of its effects on subsequent caries incidence have been equivocal. Excessive fluoride should be avoided because it may cause mottling of developing teeth.

- ***Sugars:*** **Those who are particularly vulnerable to dental caries (cavities), especially children, should limit their consumption and frequency of use of foods high in sugars.**

Although genetic, behavioral, and other dietary factors also influence dental health, the major role of sugars in promotion of tooth decay is well established from animal, epidemiologic, clinical, and biochemical studies. Newly erupting teeth are generally more vulnerable to decay than mature teeth.

Research has shown that three conditions must exist for the formation of dental caries: the presence of fermentable carbohydrate, acid-producing bacteria, and a susceptible tooth. Caries-producing bacteria metabolize a range of sugars (glucose, fructose, maltose, lactose, and sucrose) to acids that demineralize teeth. The unique role of sucrose (common table sugar) in dental caries is related to its special ability to be converted by these bacteria into long, complex molecules that adhere firmly to teeth and form plaque.

The most important diet-related interventions are fluoridation of drinking water, or the use of other means of fluoride administration, and control of intake of sugars. While fluoride is the most important factor overall in dental caries prevention, reduction in the frequency of consumption and in the quantity of sugar-rich foods in the diet will also help reduce decay. Sticky sweet foods that adhere to the teeth are more cariogenic than those that wash off quickly. The longer cariogenic foods remain in the mouth, the more they are likely to increase the initiation and progression of tooth decay.

- ***Calcium:*** **Adolescent girls and adult women should increase consumption of foods high in calcium, including low-fat dairy products.**

Inadequate dietary calcium consumption in the first three to four decades of life may be associated with increased risk for osteoporosis in later life. Osteoporosis, a chronic disease characterized by progressive loss of bone mass with aging, occurs in both women and men, although postmenopausal women are twice as likely as men to have severe osteoporosis with consequent bone fractures. Evidence shows that chronically low calcium intake, especially during adolescence and early adulthood, may compromise development of peak bone mass. In postmenopausal women, the group at highest risk for osteoporosis, estrogen replacement therapy under medical supervision is the most effective means to reduce the rate of bone loss and risk for fractures. Maintenance of adequate levels of physical activity and cessation of cigarette smoking have also been associated with reduced osteoporosis risk.

Although the precise relationship of dietary calcium to osteoporosis has not been elucidated, it appears that higher intakes of dietary calcium could increase peak bone mass during adolescence and delay the onset of bone fractures later in life. Thus, increased consumption of foods rich in calcium may be especially beneficial for adolescents and young women. Food sources of calcium consistent with other dietary recommendations in this Report include low-fat dairy products, some canned fish, certain vegetables, and some calcium-enriched grain products.

- ***Iron:*** **Children, adolescents, and women of childbearing age should be sure to consume foods that are good sources of iron, such as lean meats, fish, certain beans, and iron-enriched cereals and whole grain products. This issue is of special concern for low-income families.**

Dietary iron deficiency is responsible for the most prevalent form of anemia in the United States. Iron deficiency hampers the body's ability to produce hemoglobin, a substance needed to carry oxygen in the blood. A

principal consequence of iron deficiency is reduced work capacity, although depressed immune function, changes in behavior, and impaired intellectual performance may also result. Because of the serious consequences of iron deficiency, continual monitoring of the iron status of individuals at high risk—particularly children from low-income families, adolescents, and women of childbearing age—is vital, as is treatment of those identified to be iron deficient.

Proper infant feeding—preferably breastfeeding, otherwise use of iron-fortified formula—is the most important safeguard against iron deficiency in infants. Among adolescents and adults, iron intake can be improved by increasing consumption of iron-rich foods such as lean meats, fish, certain kinds of beans, and iron-enriched cereals and whole grain products. Also, consuming foods that contain vitamin C increases the likelihood that iron will be absorbed efficiently.

Policy Implications

Dietary Guidance

General Public

Educating the public about the dietary choices most conducive to prevention and control of certain chronic diseases is essential. Educational efforts should begin in primary school and continue throughout the secondary grades, and should focus on the dietary principles outlined in this Report—the potential health benefits of eating a diet that is lower in fat (especially saturated fat) and rich in complex carbohydrates and fiber. The importance of adequate physical activity should also be stressed. Efforts should continue throughout each stage of life to promote the principles outlined in the *Dietary Guidelines for Americans.*

Special Populations

A disproportionate burden of diet-related disease is borne by subgroups in our population. Black Americans, for example, have higher rates of high blood pressure, strokes, diabetes, and other diseases associated with obesity (but lower rates of osteoporosis) than the general population. Some groups of Native Americans exhibit the highest rates of diabetes in the world. Pregnant and lactating women also have special nutritional needs. Particular effort should be made to identify and remove the barriers to optimal health and nutritional status in such high-risk groups, using methods that take into consideration their diverse cultural backgrounds.

Many older persons suffer from chronic diseases that can reduce functional independence; many take multiple medications that may adversely interact with nutrients. Sound public education directed toward this group—and professional education directed toward individuals who care for older Americans—should focus on dietary means to reduce risk factors for chronic disease, to promote functional independence, and to prevent adverse consequences of use of medications.

Health Professionals

Improved nutrition training of physicians and other health professionals is needed. Training should emphasize basic principles of nutrition, the role of diet in health promotion and disease prevention, nutrition assessment methodologies and their interpretation, therapeutic aspects of dietary intervention, behavioral aspects of dietary counseling, and the role of dietitians and nutritionists in dietary counseling of patients.

Programs and Services

Food Labels

Food labeling offers opportunities to inform people about the nutrient content of foods so as to facilitate dietary choices most conducive to health. Food manufacturers should be encouraged to make full use of nutrition labels. Labels of processed foods should state the content of calories, protein, carbohydrate, fats, cholesterol, sodium, and vitamins and minerals. To the extent permitted by analytical methods, manufacturers should disclose information where appropriate on the content of saturated and unsaturated fatty acids and total fiber in foods that normally contain them. Descriptive terms such as "low calorie" and "sodium reduced" in compliance with the Food and Drug Administration's regulations for food labeling may also be helpful, and the expanded use of these terms should be encouraged.

Nutrition Services

Health care programs for individuals of all ages should include nutrition services such as, when appropriate, nutrition counseling for individuals or groups, interpretation and implementation of prescribed therapeutic diets tailored to individual food preferences and lifestyle, referral to appropriate community services and food assistance programs, monitoring of progress, and appropriate followup. These services should routinely incorporate assessment of nutritional status and needs based on established crite-

ria to identify individuals with nutritional risk factors who would profit from preventive measures and those with nutritional disorders who need remedial care.

Food Services

Lack of access to an appropriate diet should not be a health problem for any American. Wherever food is served to people or provided through food assistance programs, it should reflect the principles of good nutrition stated in this Report. Whether served in hospitals, schools, military installations, soup kitchens, day care centers, or nursing homes, or whether delivered to homes, food service programs offer important opportunities for improving health and providing dietary education. Such programs should pay special attention to the nutritional needs of older people, pregnant women, and children, especially those of low income or other special dietary needs. Because a large proportion of the population takes meals in restaurants and convenience food facilities, improvements in the overall nutritional balance of the meals served in such places can be expected to contribute to health benefits.

Food service programs should also take particular care to ensure that special diets lower in fat, especially saturated fat, are provided to people with elevated blood cholesterol, heart disease, or diabetes; that diets low in sodium are provided to individuals with high blood pressure; and that protein-restricted diets are made available to people with end-stage kidney disease.

Food Products

The public would benefit from increased availability of foods and food products low in calories, total fat, saturated fat, cholesterol, sodium, and sugars, but high in a variety of natural forms of fiber and, perhaps, certain minerals and vitamins. Food manufacturers can contribute to improving the quality of the American diet by increasing the availability of palatable, easily prepared food products that will help people to follow the dietary principles outlined here. Because the public is becoming increasingly conscious of the role of nutrition in health, development of such products should also benefit the food industry.

Research and Surveillance

Impressive evidence already links nutrition to chronic disease. However, much more information is needed to continue to identify changes in the

national diet that will lead to better health for the Nation. Gaps in our knowledge of nutrition suggest future research and surveillance needs. Examples are:

- The role of specific dietary factors in the etiology and prevention of chronic diseases.
- The childhood dietary pattern that will best prevent later development of chronic diseases.
- The effects of maternal nutrition on the health of the developing fetus.
- The nutrient and energy requirements of older adults.
- How nutrient requirements translate into healthful dietary patterns.
- The development of biochemical markers of dietary intake to monitor better the effects of dietary intervention.
- The identification of effective educational methods to translate dietary recommendations into appropriate food choices.
- The establishment of a nutrition surveillance system that will enhance the monitoring of population-specific and State-specific trends in the occurrence of nutrition-related risk factors and conditions.

Chapter 1

Introduction and Background

Power of nutriment reaches to bone and to all the parts of bone, to sinew, to vein, to artery, to muscle, to membrane, to flesh, fat, blood, phlegm, marrow, brain, spinal marrow, the intestines, and all their parts; it reaches also to heat, breath, and moisture.
Hippocrates (460–377 B.C.)

Introduction

It has long been understood that optimal health depends on adequate nutrition, yet knowledge of the ways in which specific dietary factors affect the risk for disease is incomplete. Dietary deficiencies can be manifested in various ways. A deficient intake of energy or nutrients can lead to protein-energy malnutrition or to classic deficiency diseases such as rickets, pellagra, or iron deficiency anemia. Protein-energy malnutrition and diseases due to deficiencies of various nutrients are prominent causes of premature death and disability in developing countries but, with a few exceptions, appear to have been eliminated in the United States.

When nutrient deficiencies are reported in this country, they are most often observed to be associated with poverty, the additional nutrient requirements of pregnancy or infancy (IOM 1985), the abuse or neglect of children or older persons, or some combination of these factors. They also are observed to result from the restricted food intake that sometimes accompanies aging, alcohol or drug abuse, unusually severe and prolonged injury or illness (including prolonged hospitalization), excessive dieting, or restrictive dietary practices. Thus, pregnant women, young infants, children, older persons, alcohol and drug abusers, and chronically ill and disabled individuals are at greatest risk for malnutrition due to dietary deficiencies, especially if their income is low. Whatever its root cause, inadequate nutrition retards normal growth, lowers resistance to infectious disease, impairs maternal and child health, and may adversely affect the ability to function at peak physical and mental capacity. These issues are discussed in detail in the relevant chapters of this Report.

As problems of nutritional deficiency have diminished in the United States, they have been replaced by problems of dietary imbalance and excess. These imbalances and excesses have contributed to the increased prevalence and severity of chronic diseases that are major causes of death and disability among Americans. Table 1-1 lists the 10 leading causes of death in this country. Among them, five—coronary heart disease and generalized atherosclerosis, stroke, some types of cancer, and diabetes—have been associated with dietary excesses or imbalances, and another three—cirrhosis of the liver, accidents, and suicides—are often the result of excessive alcohol intake. Together, these conditions account for as much as 70 percent of annual deaths among Americans (Collins 1986; NCHS 1986). Dietary excesses or imbalances also have been associated with high blood pressure, obesity, dental diseases, osteoporosis, and, perhaps, kidney and gastrointestinal diseases. Such conditions also contribute to much illness, disability, and death in the United States, and thus to substantial human and economic costs to society.

Table 1-1
Estimated Total Deaths and Percent of Total Deaths for the 10 Leading Causes of Death: United States, 1987

Rank	Cause of Death	Number	Percent of Total Deaths
1[a]	Heart diseases	759,400	35.7
	(Coronary heart disease)	(511,700)	(24.1)
	(Other heart disease)	(247,700)	(11.6)
2[a]	Cancers	476,700	22.4
3[a]	Strokes	148,700	7.0
4[b]	Unintentional injuries	92,500	4.4
	(Motor vehicle)	(46,800)	(2.2)
	(All others)	(45,700)	(2.2)
5	Chronic obstructive lung diseases	78,000	3.7
6	Pneumonia and influenza	68,600	3.2
7[a]	Diabetes mellitus	37,800	1.8
8[b]	Suicide	29,600	1.4
9[b]	Chronic liver disease and cirrhosis	26,000	1.2
10[a]	Atherosclerosis	23,100	1.1
. . .	All causes	2,125,100	100.0

[a]Causes of death in which diet plays a part.
[b]Causes of death in which excessive alcohol consumption plays a part.

Source: National Center for Health Statistics 1988.

Much about the ways in which excessive intake of energy and nutrients might affect health remain to be elucidated. Yet despite uncertainties, much has been learned about diet-disease relationships. This first *Surgeon General's Report on Nutrition and Health* examines the current state of knowledge of associations among dietary patterns, nutrients, and certain disease conditions. Its purpose is to review the available research evidence that relates diet to health to establish a basis for policies that promote dietary means to improve health.

Development and Organization of the Report

This *Surgeon General's Report on Nutrition and Health* has been developed in response to the increasing interest of the public, health professionals, and policy leaders in the role of diet in health promotion and prevention of chronic disease. In preparing the Report, the Public Health Service (PHS) reviewed past and current research related to diet and disease as a basis for examination of the implications for public policies on nutrition education, services, and research.

The Report reviews current knowledge of the influence of dietary factors on specific aspects of health. This first chapter introduces the major themes of the Report in their historical context; it also reviews and synthesizes basic information about essential nutrients in the human diet, the levels of intake required for human health, and American dietary patterns, and it explains the criteria used to examine the various kinds of research studies that are reviewed throughout the Report. Chapters 2 through 14 describe the scientific research that has examined associations between specific dietary factors and selected disease conditions in the United States (Coronary Heart Disease, High Blood Pressure, Cancer, Diabetes, Obesity, Skeletal Diseases, Dental Diseases, Kidney Diseases, Gastrointestinal Diseases, Infections and Immunity, Anemia, Neurologic Disorders, and Behavior). Chapters 15 (Maternal and Child Nutrition) and 16 (Aging) review the special nutritional challenges at especially vulnerable stages of the human life cycle. The interactions between nutrients and alcohol and between nutrients and drugs, and the effects of these substances on human nutritional status, are reviewed in chapters 17 and 18, respectively. The Report closes with a final chapter on dietary fads and frauds.

Most of the chapters follow a common format. Each begins with a brief introduction and a section entitled *Historical Perspective* that is designed to establish a historical context for the area under review. A section on

Significance for Public Health contains information currently available on the incidence, prevalence, and cost to the Nation of each of the conditions under review. Many of the chapters contain a further introductory *Scientific Background* section that summarizes technical information needed to understand the research issues reviewed in the Report.

The major part of the chapters is devoted to a review of *Key Scientific Issues* that summarizes current knowledge about possible associations between dietary factors and disease that are most relevant to public policy. Each chapter closes with a section entitled *Implications for Public Health Policy* that summarizes the significance of the research evidence for dietary guidance and education, nutrition programs and services, and nutrition research and surveillance. Finally, *Literature Cited* provides an extensive list of references to support the scientific findings in each chapter.

Historical Perspective

Throughout history, human societies have observed relationships between the consumption of certain foods and the preservation of good health or the prevention or treatment of diseases. Although the word "diet" occurs frequently in writings attributed to Hippocrates and to Galen, the term "nutrition" did not appear as an English word until the mid-1400's and was used infrequently until the second half of the 19th century (Todhunter 1973). The modern concept of nutrition—that human life depends on a steady intake of a variety of specific dietary substances in defined amounts—is less than 200 years old.

Development of Nutritional Science

Conditions related to nutritional deficiency, such as beriberi, rickets, or scurvy, were described in very early writings, but the identification of the specific dietary factors required to prevent or treat these conditions began to occur only in the late 18th century and did not approach completion for another 150 years. Some of the major events in this gradual development of nutrition as a science from the earliest records to 1950 are listed in Table 1-2. The chapters of this Report review the great expansion of nutrition research and knowledge that has occurred since then.

The earliest efforts to establish the scientific basis of nutrition are usually attributed to the French chemist Lavoisier, who demonstrated in 1789 that the oxygen breathed in air was consumed in the body to produce carbon dioxide and water, and that this central metabolic process was measurable, variable, and related to both the level of physical activity and the amount of

Table 1-2
Selected Events in the History of Nutritional Science to 1950

c. 1500 B.C.	*Papyrus Ebers* contains prescription believed to refer to diabetes.
c. 400 B.C.	Hippocrates wrote of relationship of diet to health.
c. 300 B.C.	Beriberi described in ancient Chinese texts.
c. 200 A.D.	Arataeus gave the name diabetes to the condition of "too much passing of urine."
1250	Joinville described scurvy among troops of Louis IX at the siege of Cairo.
1614	Sanctorius published studies relating body weight to food intake.
1650	Glisson described rickets in *De Rachitide*.
1730	Casal described pellagra, calling it "mal de la rosa."
1747	Lind proved that citrus fruits cure scurvy in first controlled human dietary experiment. Menghini established presence of iron in blood.
1752	Reaumur published experiments on digestion in birds.
1780	Spallanzani produced evidence that digestion was the chemical action of gastric juices.
1789	Lavoisier and Seguin make first measurements relating oxygen consumption to human energy metabolism. Cod liver oil used as treatment for rickets.
1796	Lemon juice officially introduced in British Navy to prevent scurvy.
1807	Davy isolated sodium, potassium, calcium, magnesium, sulphur, and boron.
1810–23	Chevreul studied chemistry of animal fats.
1810	Wollaston isolated cystic oxide (later named cystine) from urine—first amino acid discovered.
1816	Magendie identified dietary nitrogen requirements in dogs.
1827	Prout classified food constituents as saccharine, oily, and albuminous (sugar, fat, and protein).
1833	Beaumont reported observations and experiments on digestion in his patient St. Martin.
1838	Mulder introduced the term "protein."
1839	Boussingault conducts first nitrogen balance studies in animals.
1840	Liebig published *Animal Chemistry*, stating basic principles of metabolism.

Table 1-2 (continued)

1843	Chossat studied the effect of starvation on the body using pigeons.
1848	Addison described pernicious anemia.
1849–57	Bernard elucidated digestive action of pancreatic juices and glycogenic function of liver.
1850	Livingstone described xerophthalmia (due to vitamin A deficiency) in Africa.
1850–52	Chatin in France used iodine to prevent goiter.
1866–81	Voit and Pettenkofer explained protein metabolism.
1867	Boussingault recognized iron as essential nutrient.
1877	Pavlov began classic studies on digestion in dogs.
1885	Takaki demonstrated in controlled dietary experiments with Japanese Navy sailors that beriberi could be prevented.
1896	Atwater and Bryant introduced their basic reference, *Chemical Composition of American Food Materials.*
1897	Eijkman published his work on causes of beriberi.
1902	Rubner showed that food components increased metabolism by different amounts.
1909–28	Osborne and Mendel studied the nutritive value of protein.
1912	Funk coined the term "vitamine."
1914	Goldberger established dietary cause of pellagra.
1916	McCollum and Davis and Osborne and Mendel discovered accessory dietary factors "fat-soluble A" and "water-soluble B."
1918	Mellanby showed that experimental rickets in dogs is due to lack of fat-soluble vitamin.
1919–22	Water-soluble B factor shown to be more than one factor.
1921–24	Blindness in children shown to be result of lack of vitamin A.
1922	McCollum identified vitamin D in cod liver oil.
1928	Goldberger identified pellagra-preventing factor in yeast.
1929	Role of intrinsic and extrinsic factors in pernicious anemia discovered.
1931–37	Fluoride content of drinking water identified as cause of mottled enamel of teeth and prevention of tooth decay.
1932	Vitamin C isolated from lemon juice. Warburg and Christian identified riboflavin and defined its molecular function.
1933	Williams identified kwashiorkor as a nutritional disease.

Table 1-2 (continued)

1938	Rose classified amino acids as essential and nonessential.
1941	Evidence provided for the influence of prenatal diet on the health of the newborn infant.
1944–46	Keys and coworkers studied effects on young men of experimentally induced semistarvation and methods of dietary rehabilitation.
1945	Grand Rapids, Michigan, becomes the first city in the world to fluoridate its drinking water to prevent tooth decay.
1948–49	Crystalline vitamin B_{12} isolated from liver extract and shown to contain cobalt.
1949	Framingham Study of coronary heart disease risk factors begins.

Sources: Darby 1985; McCollum 1957; Murlin 1948; Olson 1978; Todhunter 1962, 1973, 1976.

food ingested (Lusk 1933). In the 19th century, European and American scientists isolated and began to identify the major groups of nutrients in the diet, to develop the first estimates of nutrient requirements, and to explore the basics of energy metabolism. For example, in 1816, Magendie of France established that nitrogen-containing compounds were essential in the diet of dogs; in 1838, these compounds were given the name protein (from the French word for "primary substance"). In 1814, the French chemist Chevreul discovered that fats consisted of fatty acids attached to a glycerol molecule. By 1834, the London physician Prout was able to introduce the idea that food consists of substances called saccharine, oily, and albuminous—today called carbohydrates, fats, and proteins (Todhunter 1959). Later in the century, Rubner of Germany and Atwater of the United States established the energy values of these substances as approximately 4, 9, and 4 kcal/g, respectively (McCollum 1957).

Thus, from the time of Lavoisier to the end of the 19th century, knowledge of nutritional science grew to encompass the metabolic basis of energy production from food, the classification of nutrients and sources of energy, the dependence of energy requirements on physical activity, the influence of diet on body weight and of fevers on metabolism of food substances, the principles of metabolic homeostasis, and the roles of specific essential nutrients in human physiology (Murlin 1948). During this period, lemon juice was found to prevent scurvy, iodine to prevent goiter, and incompletely milled rice to prevent beriberi. Despite these advances, the most fundamental concepts about nutrition were still poorly developed at the beginning of the 20th century. It was not until the first half of this

century that scientists identified human nutritional requirements, characterized the nutritional value of proteins, and identified the amino acids, vitamins, fatty acids, and minerals essential in the human diet (Todhunter 1976). For example, Osborne and Mendel of Yale University elucidated the differences between complete and incomplete proteins during the first decades of this century. Later, Rose of the University of Illinois established which of the amino acids were essential and estimated how much of each was required each day.

The diseases of scurvy, beriberi, rickets, and pellagra had been described in very early writings, but their specific causes were not identified until after 1900. In 1906, Hopkins of Cambridge University suggested that food contained certain accessory factors necessary for prevention of these conditions. In 1912, Funk named these factors "vitamines," later called vitamins as more was learned about their chemical structure (Rosen 1958).

Early in the century, the dietary cause of pellagra was established by Goldberger, a PHS physician, and fat- and water-soluble vitamins were isolated and characterized (McCollum 1957). Also during this period, kwashiorkor was identified as a nutritional disease and the importance of prenatal diet on the health of newborn infants began to be appreciated (Darby 1985). Over the next three decades, all of the vitamins were identified, starting with the isolation of a fat-soluble substance in egg yolk by McCollum at the University of Wisconsin, now known as vitamin A, and continuing with the discoveries of folic acid, vitamin B_{12}, and other B vitamins in the 1930's and 1940's (McCollum 1957). The essential nature of trace elements such as selenium and zinc were finally recognized in the 1950's and 1960's (Darby 1985).

After World War II, the major focus of attention in nutrition began to shift away from acute nutrient deficiency diseases. The advent of improved transportation systems and home refrigeration and frozen foods expanded the year-round availability of fresh and wholesome foods, and food fortification helped to increase the availability of previously scarce nutrients. At the same time, vaccines, antibiotics, and other advances in medicine and health prevented and controlled many of the infectious diseases that had previously shortened the human lifespan. Thus, chronic degenerative diseases became more important as causes of illness and death. Nutrition scientists began to examine the relationship of modern dietary patterns and practices to these chronic diseases—cardiovascular disease, cancer, and diabetes, for example—that were becoming increasingly prevalent among

Americans in middle and late life, and attention shifted to the effects of specific nutrients and dietary factors on the long, slow development of these conditions.

Evolution of Federal Nutrition Policy

As knowledge developed in the nutrition sciences and on the health effects of food, and as food availability and consumption patterns became more apparent, nutrition assumed an increasingly visible role in public policy. By 1979, the Federal Government was involved in efforts to ensure an adequate, safe, and nutritious food supply for Americans through sponsorship of more than 350 programs in key areas of nutrition policy: agricultural support, food safety and regulation, food fortification, food assistance, nutrition services and training, food intake and nutritional status monitoring, food and nutrition research, and food and nutrition education (Comptroller General 1979). Some of these programs had roots that reached back to the turn of the century, but since World War II the Government's efforts have increasingly focused on meeting the needs of high-risk groups and on the role of diet in health promotion and disease prevention. Table 1-3 presents a chronological listing of selected events in the development of Federal domestic nutrition policies; the history of Federal initiatives in the major areas of nutrition policy is reviewed below.

Table 1-3
Selected Federal Domestic Nutrition Policy Initiatives, 1862–1988

1862	U.S. Department of Agriculture (USDA) created. Morrill Act establishes land grant colleges.
1867	Office of Education established with responsibilities for nutrition education within public schools.
1887	Hatch Act establishes agricultural experiment stations. Federal research laboratory established at Staten Island. Name is changed to the National Institute of Health in 1930.
1889	U.S. Public Health Service Commissioned Corps authorized for duty on communicable, nutritional, and other diseases.
1893	USDA authorized by Congress to conduct research on agriculture and human nutrition.
1906	The Pure Food and Drug (Wiley) Act prohibits interstate commerce and misbranded and adulterated foods, drinks, and drugs. Federal Meat Inspection Act passed.
1914	Cooperative Extension Service created as part of USDA.
1916	USDA publishes *Food for Young Children*, first dietary guidance pamphlet.

Table 1-3 (continued)

1917	U.S. Food Administration established to supervise World Wa I food supply. First dietary recommendations issued by USDA—*Five Food Groups*.
1921–29	Maternity and Infancy Act enabled State health departments to employ nutritionists.
1924	Addition of iodine to salt to prevent goiter is first U.S. food fortification program.
1927	Food, Drug, and Insecticide Administration established. Name is changed to Food and Drug Administration (FDA) in 1932.
1930	USDA and Federal Emergency Relief Administration buy and distribute surplus agricultural commodities as food relief. Public Health Service Hygienic Laboratory designated as National Institute of Health (later changes to National Institutes of Health).
1933	Agricultural Act amendments permit purchase of surplus commodities for donation to child nutrition and school lunch programs.
1935	Food Distribution Program established. Social Security Act authorizes grants to States for nutrition services to mothers and children.
1936–37	USDA conducts first Nationwide Food Consumption Survey (NFCS).
1938	The Food, Drug and Cosmetic (FD&C) Act includes provisions for food standards. FDA nutrition research program established. Social Security Act provides support for role of nutrition in health.
1939	Federal Surplus Commodities Corporation initiates experimental Food Stamp Program.
1940	National Defense Advisory Commission draws attention to malnutrition in the United States.
1941	President Roosevelt calls National Nutrition Conference, with announcement of the first Recommended Dietary Allowances by the Food and Nutrition Board. FDA promulgates standards for enrichment of flour and bread with B-complex vitamins and iron.
1946	National School Lunch Program established.
1947	Laboratories of Nutrition, Chemistry, and Pathology of the National Institutes of Health incorporated into Experimental Biology and Medicine Institute.
1954	Special Milk Program established.

Table 1-3 (continued)

1955	Interdepartmental Committee on Nutrition for National Defense established (discontinued 1967).
1956	Title VII of the Public Health Service Act authorizes funds to support graduate training in public health nutrition.
1958	Food Additives Amendment to FD&C Act prohibits use of a food additive until safety established by manufacturer. Delaney Clause prohibits carcinogenic additives. GRAS (Generally Recognized As Safe) list established.
1961	President Kennedy expands the use of surplus food for needy people at home and abroad and announces a new pilot Food Stamp Program.
1963 and 1965	Maternal and Child Health and Mental Retardation Planning Amendments to the Social Security Act allow for an expanded number of nutritionists in health care programs.
1965	Food Stamp Act passed by Congress. Nationwide Food Consumption Survey collects first data on dietary intake of individuals.
1966	Child Nutrition Act passed. School Breakfast Program established. President Johnson outlines Food for Freedom Program, the "war on hunger." Allied Health Professions Personnel Training Act includes support for training of dietitians.
1966–70	The Department of Health, Education, and Welfare (DHEW), which later becomes the Department of Health and Human Services (DHHS), sponsors a National Academy of Sciences study, Maternal Nutrition and the Course of Pregnancy, which makes major recommendations related to the role of nutrition in human reproduction.
1968	U.S. Senate Select Committee on Nutrition and Human Needs established.
1968–70	DHEW sponsors Preschool and Ten-State Nutrition Surveys that report evidence of hunger and malnutrition in poverty groups in the United States.
1969	President Nixon calls White House Conference on Food, Nutrition, and Health. Secretary of Agriculture establishes the Food and Nutrition Service to administer Federal food assistance programs.
1971–74	The National Center for Health Statistics conducts the first National Health and Nutrition Examination Survey (NHANES) to measure the nutritional status of the U.S. population. This is followed by NHANES II in 1976–80, Hispanic HANES in 1982–84, and NHANES III in 1988.

Table 1-3 (continued)

1972	USDA establishes Special Supplementary Food Program for Women, Infants, and Children (WIC). Agriculture and Consumer Protection Act provides price supports to farmers. Amendments to the Older Americans Act of 1965 establish a congregate and home-delivered meals program for older Americans.
1974	U.S. Senate Select Committee on Nutrition and Human Needs issues *Guidelines for a National Nutrition Policy*, prepared by the National Nutrition Consortium. Safe Drinking Water Act passed.
1975	National Institutes of Health establishes Nutrition Coordinating Committee.
1977	U.S. Senate Select Committee on Nutrition and Human Needs issues two editions of *Dietary Goals for the United States*. Food and Agricultural Act and Child Nutrition and National School Lunch Amendments passed.
1978	Joint Subcommittee on Human Nutrition Research established in Office of Science and Technology Policy (in 1983 becomes Interagency Committee on Human Nutrition Research under joint direction of USDA and DHHS). DHEW and USDA submit proposal to Congress for National Nutrition Monitoring System.
1979	DHEW establishes Department-wide Nutrition Policy Board and issues *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention.*
1980	USDA and DHHS jointly issue *Nutrition and Your Health: Dietary Guidelines for Americans*. A second edition follows in 1985. DHHS issues *Promoting Health/Preventing Disease: Objectives for the Nation*, which contains 17 nutrition objectives to be achieved by the year 1990. The Surgeon General's Workshop on Maternal and Infant Health makes recommendations about improving nutrition for these vulnerable groups.
1981	DHHS and USDA issue *Joint Implementation Plan for a Comprehensive National Nutrition Monitoring System*, revised in 1987 as the *Operational Plan for the National Nutrition Monitoring System*. The Select Panel for the Promotion of Child Health, created by Public Law 95-626, submits to Congress and the Secretary of DHHS its report, which includes recommendations on nutrition.
1984	The Surgeon General's Workshop on Breastfeeding and Human Lactation develops strategies for promoting breastfeeding.
1985	USDA initiates Continuing Survey of Food Intakes by Individuals, repeated in 1986.

Table 1-3 (continued)

1986	DHHS and USDA issue *Nutrition Monitoring in the United States*, the report of the Joint Nutrition Monitoring Evaluation Committee.
1988	DHHS publishes *The Surgeon General's Report on Nutrition and Health.*

Agricultural Support. The earliest Federal nutrition policies in this area were designed to strengthen the agricultural production system and to ensure a consistent and adequate food supply. In 1862, the U.S. Department of Agriculture (USDA) was created, and the Morrill Act established land grant universities as sites for agricultural training and research. The Hatch Act of 1887 authorized the creation of agricultural experiment stations. As a result of these and other policies, food production increased and farmers began to produce more food than could be consumed. Eventually, a system of commodity price and income supports was developed to stabilize the economic condition of the farm sector. The Agricultural and Consumer Protection Act of 1973 and the Food and Agriculture Act of 1977 established the basis for current agricultural support policies (Stucker and Boehm 1978; Boehm 1979).

Food Safety and Regulation. The pure food movement of the late 1800's, led by Dr. Harvey Wiley, chief of the Government's Bureau of Chemistry, and popularized by the publication of Upton Sinclair's novel of 1906, *The Jungle*, led Congress to pass the Pure Food and Drug Act of 1906—then known as the Wiley Act—which prohibited interstate transport and sale of misbranded or adulterated foods (Ziporyn 1985). This Act and the Federal Meat Inspection Act, also passed that year, extended Federal responsibility into the arena of food safety. Significant revisions to the legislation occurred in 1938 when the Food, Drug, and Cosmetic Act established standards of identity and quality for certain foods, required ingredient listings on food labels, and prohibited sales of foods that were determined to be harmful to health. In 1958, the Food Additives Amendment to the 1938 Act shifted the burden of proof of safety to the manufacturer, required that additives known to cause cancer in either humans or animals be deemed unsafe (the Delaney Clause), and established the list of ingredients in common use that were "Generally Recognized As Safe" (GRAS) for human consumption. A 1960 Color Additives Amendment applied the Delaney Clause to all chemical food coloring agents. Since 1969, a major review has been under way of the safety of substances on the GRAS list (Smith and Rulis 1981). Regulation of food safety is a shared responsibility

of several Federal agencies, primarily the USDA for plant, animal, poultry production; the Food and Drug Administration (FDA) for all c foods and additives; and the Environmental Protection Agency pesticide contaminants.

The food labeling provisions of the 1906 and 1938 Acts were designe protect consumers against fraudulent misbranding of foods, and this pc was extended by the Fair Packaging and Labeling Act of 1966, which ca for accurate ingredient labeling on foods in interstate commerce (Pc 1987). More recently, interest has grown in the use of food labels to edu consumers about the nutritional quality of food and the role of nutritic health. Regulations published in 1973 authorized voluntary nutrition la ing and required nutrition labeling for fortified foods and those for wl nutritional claims were made (Hutt 1981). In 1987, the FDA proposed a policy for public health messages on food labels to permit health claim package labels when the information is true and certain criteria are (FDA 1987). Responsibility for regulating labeling and marketing pr dures related to foods is shared by the USDA (meat, poultry, eggs), F (all other foods) and, for advertising, the Federal Trade Commission (ter 1987).

Food Fortification. The onset of World War I brought new nutriti concerns and focused attention on the need for an overall improvemer the availability of nutrients to the general population. The first food tification program, instituted in 1924, was the addition of iodine to sal prevent goiter. During the Second World War, this program was extende include enrichment of wheat flour with iron and the vitamins thian niacin, and riboflavin. Also during the 1940's, milk was fortified v vitamin D and margarine with vitamin A.

Food Assistance. As early as 1918, the idea of targeting food assistanc vulnerable population groups was proposed in the Children's Bureau p lication *Milk—The Indispensable Food for Children.* Milk supplies l decreased and prices increased due to the effects of World War I, and Children's Bureau advocated that children be given priority in allocat milk supplies. Charitable organizations established milk stations and cc munity kitchens to provide food supplements to the poor and to help peo with limited income choose and prepare an adequate diet (Egan 1980

Widespread unemployment and poverty during the 1930's stimulated t development of new Federal programs to provide food assistance to t poor. At first, these programs focused exclusively on distribution of surp agricultural commodities. In 1930, for example, the USDA and the Fede

Emergency Relief Administration began a distribution program as food relief. The donation of surplus foods to child nutrition and school lunch programs was authorized by amendments to the Agricultural Act in 1933. The more formally organized Food Distribution Program was established in 1935. An experimental Food Stamp Program was initiated by the Surplus Commodities Corporation in 1939. The National School Lunch Program was established in 1946, and the Special Milk Program was added in 1954 (U.S. Senate 1976).

In the early 1960's, as a result of surveys and assessments indicating special needs among low-income populations (Citizens' Board 1968), the Federal Government expanded its involvement in income support and direct delivery of food services. A pilot study in 1961 led to the Food Stamp Act of 1965, which authorized a small-scale program to meet limited needs for food assistance. The Child Nutrition Act of 1966 established the School Breakfast Program. Following the 1969 White House Conference on Food, Nutrition, and Health (White House Conference 1970), eligibility and benefits were enlarged for the Food Stamp, School Lunch, School Breakfast, Special Milk, and Summer Food Programs; the Special Supplemental Food Program for Women, Infants, and Children (WIC) was created; general assistance reimbursements were increased (for the School Breakfast and School Lunch Programs); and the Nutrition Program for the Elderly was established through an amendment to the Older Americans Act. From 1969 to 1977, Federal expenditures for these programs increased from about $1.2 to $8.3 billion (U.S. Senate 1977a). By 1986, as many as 50 million Americans (the exact number is uncertain due to overlapping benefits) were served by food assistance programs administered by the USDA. The cost of these programs exceeded $18.8 billion in 1986 and $20 billion in 1987 (Matsumoto 1987).

Nutrition Services and Training. In the 1920's under the Federal Maternity and Infancy Act, nutrition services were launched in nine State departments of public health. Enactment of the Social Security Act in 1935, authorizing grants-in-aid to the States for health services for mothers and children, was a major impetus for the further development of nutrition services in State health agencies. By 1945, all but three States had one or more nutrition consultant positions included in their budgets. Nutrition services began to extend beyond maternal and child health during the late 1950's and early 1960's in response to new mental retardation, chronic disease control, home health service, and nursing home and other extended care programs. Initiatives in primary health care, family planning, and comprehensive health planning during the 1970's further expanded the availability of nutrition services (Nutrition Services Project Committee

1983), as did establishment of the Community Food and Nutrition Program (CFN) in the 1980's to provide nutrition services to low-income populations (Office of Community Services 1987).

To ensure an adequate supply of health professionals to serve the population, the Federal Government also supports health professions education in primary care as well as public health practice. Since the 1940's, funds have been available from Title V of the Social Security Act for nutrition training of health professionals, and since 1957, various authorities under Title VII of the Public Health Service Act have supported health professions students and curriculum development in applied nutrition, including capitation grants to schools of public health that support traineeships for public health nutrition students.

Food Intake and Nutrition Status Monitoring. The involvement of the Federal Government in monitoring of food intake dates back to 1893 when the USDA received an appropriation for this purpose (Porter 1986). The USDA first began to collect data on the wholesale availability or "disappearance" of food commodities in 1909. The subsequent annual collection of such data has provided an important source of information on trends in the availability of food, an indirect indicator of food use by the population (Bunch 1987). Attempts to estimate actual food intake by the population began in the 1930's. For example, household food purchases were examined by the USDA in 1936–37 through the first Nationwide Food Consumption Survey (NFCS); such surveys have been conducted about every 10 years since, most recently in 1987–88 (USDA 1986, 1987a, 1987b). Estimations of the per capita nutrient content of the food supply began in the 1940's and are now reported annually (Marston and Raper 1986). The first collections of data on the food consumption habits of individuals in sampled households were performed by the USDA in 1965 (NRC 1984). Examples of food intake and availability data are given later in this chapter in the section on dietary patterns.

Assessment of nutritional status emerged as a concern as early as 1918 when infants and children were weighed and measured during the opening event of the Children's Year Campaign (initiated to "protect children from the effects of war"). The impetus for this activity was the high percentage of Selective Service rejections in World War I caused by conditions that might have been prevented or corrected by adequate nutrition in early childhood. The first studies of nutrition and child health were conducted by the Children's Bureau in a mountainous section of Kentucky in 1920 and in the industrial area of Gary, Indiana, in 1922 (Egan 1980).

Much of the recent expertise in measuring human nutritional status was developed through the work of the Interdepartmental Committee on Nutrition for National Defense, which conducted nutrition surveys in more than 30 countries during the 1950's and 1960's. Attempts to evaluate the nutritional status of the U.S. population began in 1956 when Congress authorized the Department of Health, Education, and Welfare (DHEW) to conduct periodic national health examination surveys; with the addition in 1971 of additional status measures, including a dietary intake component, these surveys evolved into the National Health and Nutrition Examination Surveys (NHANES). The first NHANES was conducted from 1971–74, the second from 1976–80, and the Hispanic HANES from 1982–84 (DHHS/USDA 1986). The third NHANES started in 1988. In 1968–70, in response to increasing concern about the nutritional status of low-income populations, DHEW sponsored the Preschool (Owen et al. 1974) and Ten-State (DHEW 1972) Nutrition Surveys and identified evidence of malnutrition in these populations.

The dietary intake, health, and nutritional status surveys and surveillance systems listed in Table 1-4 and described above are components of the National Nutrition Monitoring System—a complex assortment of interconnected activities that provide regular information about dietary intake and nutritional status to the health of the American people and about factors that affect diet and nutritional status (DHHS/USDA 1987). The present system was proposed in 1978 in response to a congressional request in the 1977 Food and Agriculture Act that the Secretaries of Agriculture and of Health, Education, and Welfare, now Health and Human Services (DHHS), develop a joint proposal for a comprehensive system that would monitor the nutritional status of the American people. In 1981, a *Joint Implementation Plan* (revised in 1987) committed the two Departments to close coordination of survey methods and to submission of reports to Congress every 3 years on information gained from monitoring activities. The National Nutrition Monitoring System includes efforts by several Federal agencies to provide information about health and nutritional status, food consumption, food composition, dietary knowledge and attitudes, and food safety and quality.

Food and Nutrition Research. The Federal role in nutrition research began in 1887 with the development of the forerunner of the National Institutes of Health (NIH) as a one-room laboratory on Staten Island. In 1893, the USDA was authorized to perform agricultural and human research. The PHS Hygienic Laboratory developed into the first National Institute of Health in 1930; subsequently, it was joined by other laboratories to create

Table 1-4
National Nutrition Surveillance Activities

Category	Activity	Department[a]	Agency[a]	Population	Timing
Health and Nutritional Status Measurements	National Health and Nutrition Examination Surveys	DHHS	CDC/NCHS	U.S. population, special groups	
	NHANES I			1–74 yrs	1971–74
	NHANES II			6 mo–74 yrs	1976–80
	Hispanic HANES			6 mo–74 yrs	1982–84
	NHANES III			2 mo+	1988–94
	National Health Interview Survey	DHHS	CDC/NCHS	U.S.	Annual
	NHIS Special Topics	DHHS	CDC/NCHS	U.S.	Selected topics
	NHANES I Epidemiologic Followup	DHHS	CDC/NCHS	NHANES I older persons	1982–84, 1986, 1987
	National Survey of Family Growth	DHHS	CDC/NCHS	Women 15–44 yrs	1976, 1983, 1987
	National Maternal and Infant Health Survey	DHHS	CDC/NCHS		Planned 1988
	National Mortality Survey	DHHS	CDC/NCHS		Annual 1961–68, 1986
	Vital Statistics	DHHS	CDC/NCHS	U.S. States, counties, local areas	Annual

Health and Nutritional Status Measurements (continued)	Coordinated State Surveillance System	DHHS	CDC/CHPE	Pregnant women, children	Continuous
	Behavioral Risk Factor Surveillance System	DHHS	CDC/CHPE	Adults	Continuous
	Nutrition Research in Support of Nutrition Monitoring[b]	DHHS USDA	NIH ARS CDC/CHPE FDA	Varies	Ongoing
Food Consumption Measurements	Nationwide Food Consumption Survey (NFCS)	USDA	HNIS	U.S., low-income sample	Every 10 years, current 1987–88
	Continuing Survey of Food Intakes by Individuals (CSFII)	USDA	HNIS		
	1985 and 1986			Women 19–50, their children, men, low-income sample	Annual
	1989 and beyond			U.S. population, low-income sample, other	Annual (planned)
	NHANES	DHHS	CDC/NCHS	U.S. population	1971–74, 1976–80, 1982–84, 1988–94

Table 1-4 (continued)

Food Consumption Measurements (continued)	Total Diet Study	DHHS	FDA	Specific age-sex groups	Annual
	Vitamin/Mineral Supplement Adverse Reactions	DHHS	FDA	U.S.	Continuous
Food Composition Measurements	Nutrient Data Bank	USDA	HNIS		Continuous
	Nutrient Composition Laboratory	USDA	ARS		Continuous
	Food Labeling and Package Survey	DHHS	FDA		Annual and biennial parts
	Total Diet Study	DHHS	FDA		Annual
	Fiber, Carotenoid, and Vitamin A Comp. Studies;	DHHS	NIH/NCI		Ongoing
	Taurine and Biotin Comp. Studies		NIH/ NIDDK		Ongoing
Dietary Knowledge and Attitude Assessment	Health and Diet Survey	DHHS	FDA	U.S. adults	• 18–22 mo intervals
	Survey of Infant Feeding Practices	DHHS	FDA	Pregnant women	1988 or 1989
	Survey of Weight-Loss Practices	DHHS	FDA NIH/ NHLBI	U.S. adults	1987 or 1988
	Cholesterol Awareness Survey	DHHS	NIH/ NHLBI + FDA	Physicians Adults	1986

Dietary Knowledge and Attitude Assessment (continued)	Nursing and Dietitian Survey	DHHS	NIH/ NHLBI	Nurses, dietitians	1986, 1987
	NHIS Special Topics	DHHS	CDC/NCHS	U.S. adults	
	Health Promotion/ Disease Prevention				1985
	Vit/Min Supplement				1986
	Cancer Control		+NIH/NCI		1987
	CSFII Followup (Consumer Perceptions Survey)	USDA/DHHS	HNIS FSIS FDA	U.S. population	Planned 1989–96
	Physician Knowledge Survey on Hypertension	DHHS	NIH/NHLBI	Physicians	1978–88
	Cancer Prevention Awareness Program	DHHS	NIH/NCI	U.S. adults	1984 + ongoing
Food Supply Determinations	Demand Studies	USDA	ERS	U.S. population	Continuous

[a]ARS = Agricultural Research Service, CDC = Centers for Disease Control, CHPE = Center for Health Promotion and Education, DHHS = Department of Health and Human Services, ERS = Economic Research Service, FDA = Food and Drug Administration, FSIS = Food Safety and Inspection Service, HNIS = Human Nutrition Information Service, NCHS = National Center for Health Statistics, NCI = National Cancer Institute, NHIS = National Health Interview Survey, NHLBI = National Heart, Lung, and Blood Institute, NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases, NIH = National Institutes of Health, USDA = U.S. Department of Agriculture.

[b]Includes research on nutritional status assessment and requirements throughout the life cycle. The nutritional status research focuses on (1) indices of nutritional status, (2) micromethods to measure nutrient concentrations in various tissues and plasma, and (3) methods that improve accuracy of dietary intake data.

Source: U.S. Department of Health and Human Services and U.S. Department of Agriculture 1987.

the present research enterprise of NIH (Simopoulos 1986). In 1975, the NIH Nutrition Coordinating Committee was established to address NIH nutrition issues that span the goals and purposes of 12 Institutes, 2 Divisions, and 2 Centers within the agency. The FDA began conducting nutrition research in 1938. By 1976, Federal expenditures for nutrition research and research training exceeded $73 million (U.S. Senate 1976). The amount was reported as nearly $200 million by 1979 (JSHNR 1980) and $270 million in 1984, of which nearly $200 million represented research supported by NIH (ICHNR 1986; NIH 1987). In 1987, NIH expended a total of $261 million, reinforcing its longstanding position as the major Federal agency in biomedical and behavioral nutrition research and training support. This nutrition research encompasses a broad range of topics, including health maintenance, human development throughout the life cycle, disease prevention, and disease treatment.

The Interagency Committee on Human Nutrition Research (ICHNR) was established by the Secretaries of DHHS and USDA to succeed the Joint Subcommittee on Human Nutrition Research that operated out of the White House Office of Science and Technology Policy to coordinate all Federal nutrition research activities. The ICHNR produced a 5-year plan for human nutrition research that reviewed the research activities of eight Federal agencies, listed research priorities, and identified six areas for expanded research investigation: nutritional requirements at various stages of the life cycle, nutrition interactions and bioavailability, nutrition and chronic diseases, energy regulation and eating disorders, nutrition monitoring, and nutrition education methodology (ICHNR 1986).

Dietary Guidance and Nutrition Education. The Federal Government has supported efforts to teach the public about nutrition since 1867 when the Office of Education was established with responsibility for nutrition education within the public schools. The Children's Bureau of the Department of Labor published *Prenatal Care* in 1913 and *Infant Care* in 1914 to provide dietary guidance to mothers. These books have been in publication ever since and are all-time best sellers of the U.S. Government Printing Office.

The USDA also had an early role and published its first food selection guide, designed to help parents meet the nutritional needs of young children, in 1916 (Hunt 1916). Since that time, federally supported dietary guidance materials have been issued and revised regularly to meet the needs of specific target audiences and to reflect emerging knowledge of nutritional science. A list of Federal dietary guidance publications for the general public since 1917 is presented in Table 1-5.

Table 1-5
Federal Dietary Recommendations for the General Public, 1917–1988

Year	Agency[b]	Publication	Recommendation[a]							
			Variety	Maintain Ideal Body Weight	Include Starch and Fiber	Limit Sugar	Limit Fat	Limit Cholesterol	Limit Salt	Limit Alcohol
1917	USDA	What the Body Needs—Five Food Groups	+		+	*	*			
1942	USDA	Food for Freedom—Daily Eight	+		+		*			
1943	USDA	National Wartime Nutrition Guide—Basic Seven	+		+		*			
1946	USDA	National Food Guide—Basic Seven	+		+		*			
1946	USDA	Food for Growth—Four Food Groups	+		+					
1958	USDA	Food for Fitness—Four Food Groups	+		+					
1977	U.S. Senate	Dietary Goals for the U.S.		+	+	+	+	+	+	
1979	USDA	Building a Better Diet—Five Food Groups	+	+	+	+	+	+	+	+
1979	DHEW	Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention	+	+	+	+	+	+	+	+
1979	DHEW/NCI	Statement on Diet, Nutrition, and Cancer—Prudent Interim Principles	+	+	+		+			+

Table 1-5 (continued)

Year	Agency[b]	Publication	Recommendation[a]							
			Variety	Maintain Ideal Body Weight	Include Starch and Fiber	Limit Sugar	Limit Fat	Limit Cholesterol	Limit Salt	Limit Alcohol
1980	USDA/DHHS	Dietary Guidelines for Americans	+	+	+	+	+	+	+	+
1980	DHHS	National 1990 Nutrition Objectives	+	+	+	+	+	+	+	+
1984	DHHS/NHLBI	Recommendations for Control of High Blood Pressure		+			+		+	+
1985	USDA/DHHS	Dietary Guidelines for Americans, 2nd edition	+	+	+	+	+	+	+	+
1986	DHHS/NCI	Cancer Control Nutrition Objectives for the Nation: 1985–2000		+	+		+			+
1987	DHHS/NHLBI	National Cholesterol Education Program Guidelines	+	+	+		+	+		+
1988	DHHS/NCI	Dietary Guidelines for Cancer Prevention	+	+	+		+		+	+

*Recommended for *inclusion* in the daily diet, as opposed to subsequent recommendations to *limit* intake.

[a]Other recommendations include: increased consumption of foods containing vitamins and minerals (USDA 1917–1958; NCI 1986), increased physical activity (USDA/DHHS 1980, 1985; DHHS 1980), and reduced intake of salt-cured or smoked foods (NCI 1988).

[b]USDA = U.S. Department of Agriculture, U.S. Senate = U.S. Senate Select Committee on Nutrition and Human Needs, DHEW = Department of Health, Education, and Welfare, DHHS = Department of Health and Human Services, NCI = National Cancer Institute, NHLBI = National Heart, Lung, and Blood Institute.

The earliest federally sponsored guidelines advised the public to consume portions from a variety of food groups every day to obtain sufficient energy and to avoid nutritional deficiencies. As more was learned about nutrients essential in the diet, recommendations began to emphasize consumption of foods containing vitamins, minerals, and other "protective" dietary components (Hertzler and Anderson 1974). In response to the economic crisis of the 1930's, the USDA began to develop meal plans for consumers at different levels of income to address issues of cost (Haughton, Gussow, and Dodds 1987).

The first Recommended Dietary Allowances (RDA's) for intake of energy and eight nutrients were developed by the National Research Council and adopted at the wartime National Nutrition Conference in 1941 (Roberts 1958). RDA's have been published periodically since; the most recent (ninth) edition appeared in 1980 (NRC 1980). Its recommendations are reviewed later in this chapter. Also in 1941, the USDA, in cooperation with the Office of Education and the PHS, published the first Federal guide to incorporate information on specific vitamins and minerals and the first to use the term "enriched." Meal plans and dietary guidelines published since the 1940's have been designed increasingly to translate the RDA's into terms usable by consumers (Hertzler and Anderson 1974). The USDA's 1958 *Food for Fitness—A Daily Food Guide*, written in terms of four food groups, was the first to promote intake of specific nutrients—calcium, vitamin A, and vitamin C—that were commonly consumed in amounts substantially below RDA levels (Haughton, Gussow, and Dodds 1987).

Typically, an adequate diet has been defined as providing the basic food groups that would contain amounts of essential nutrients—protein, vitamins, and minerals—sufficient to prevent deficiency diseases. In the mid-1970's, however, the focus of national policy objectives expanded to encompass the role of overconsumption of fat, cholesterol, salt, sugar, and alcohol as dietary factors associated with chronic disease. The increasing scientific interest in these relationships led the U.S. Senate to hold hearings on diet and health from 1973 through 1977 (U.S. Senate 1977a). Expanding knowledge of the role of diet in health maintenance also led to the development in 1975 of a DHEW Policy Statement on Health Aspects of Nutrition (U.S. Senate 1976). Thus, dietary adequacy began to include consideration of the most reasonable proportions of dietary factors for prevention of chronic—rather than deficiency—diseases.

This new perspective was reflected in the two editions of the 1977 report *Dietary Goals for the United States*, produced by the Senate Select Committee on Nutrition and Human Needs (U.S. Senate 1977b, 1977c). These

reports recommended significant changes in average dietary intake patterns to improve protection against the principal chronic diseases. To accomplish this goal, they established quantitative targets for consumption of complex carbohydrates and naturally occurring sugars (greater than 48 percent of energy), refined and processed sugars (10 percent of energy), total fats (less than 30 percent of energy), saturated fat (less than 10 percent of energy), cholesterol (less than 300 mg/day), and salt (less than 5 g/day) (U.S. Senate 1977c).

These principles, although not the quantitative targets, were supported and expanded in the 1979 report *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention* (DHEW 1979) and by the 1980 publication *Nutrition and Your Health: Dietary Guidelines for Americans*, jointly issued and revised in 1985 by the Departments of Agriculture and of Health and Human Services (USDA/DHHS 1985). The *Guidelines* recommend:

- Eat a variety of foods.
- Maintain desirable weight.
- Avoid too much fat, saturated fat, and cholesterol.
- Eat foods with adequate starch and fiber.
- Avoid too much sugar.
- Avoid too much sodium.
- If you drink alcoholic beverages, do so in moderation.

This approach reflects the increase in interest in the relation between nutrition and prevention of chronic diseases, a development that has shaped and mandated Federal nutrition education activities of the past decade (see Table 1-4) and is the principal focus of the discussion, conclusions, and recommendations of this Report.

Scientific Background

Human Nutritional Requirements

Essential nutrients must be obtained from the diet in the proper amounts and proportions to maintain good health and to prevent deficiency diseases. A deficiency of an essential nutrient causes signs and symptoms that can be prevented or cured by an increased intake of the nutrient. Such deficiencies may be due to inadequate dietary intake, or they may be

induced by either inherited or acquired inabilities to absorb, transport, store, or metabolize nutrients or by excessive losses of nutrients from the body (for example, from vomiting, bleeding, or diarrhea).

Just as a deficiency of a nutrient can cause disease, too much of a nutrient can also lead to disease. For example, as discussed throughout this Report, the excessive consumption of energy, fat (especially saturated fat), and alcohol have been associated with the development of specific chronic disease conditions in some individuals. Excessive intake of some vitamins and most of the minerals also has been shown to result in either acute or long-term disorders. For most nutrients, there appears to be a safe and adequate range of dietary intake that satisfies nutritional requirements but does not cause untoward symptoms. This concept is illustrated in Figure 1-1. Ideally, the diet should contain energy and all of the essential nutrients in amounts that fall within these ranges of intake.

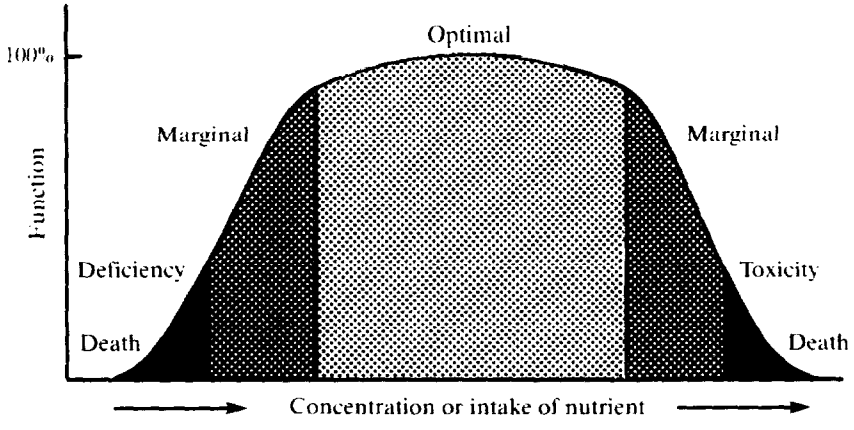

Figure 1-1. Dependence of biologic function or tissue concentration on intake of a nutrient. For nutrients and energy sources, there is a range of intake that confers optimal physiologic function. Below this range, deficiencies can cause disease or death. Excessive intake also can lead to increasing symptoms of toxicity. The optimal range varies for each nutrient and is affected by many individual and environmental factors.

Source: Mertz, W. 1981. The essential trace elements. *Science* 213:1332-38. Copyright 1981 by the American Association for the Advancement of Science, reprinted with permission.

Recommended Dietary Allowances

The need to establish goals for good nutrition in the United States was recognized in the 1930's and led to the establishment in 1940 of the Committee on Food and Nutrition, now called the Food and Nutrition Board, of the National Research Council, National Academy of Sciences. The Committee's initial purpose was to make sure that the population was adequately nourished during World War II, and one of its early functions was to recommend quantities of nutrients that should be provided to the Armed Forces and the general population. These recommendations led to the development of goals for intake of nine specific nutrients that would meet the known nutritional requirements of men, women, and children of varying ages. These first RDA's were adopted in 1941 (Roberts 1958), and they have been published at 5- to 10-year intervals since 1943. Although the original purpose of the RDA's was to promote nutritional health during wartime, their purpose has expanded over the years to include use for development of standards for food assistance programs, food labels, and evaluation of dietary adequacies.

Because research on human nutritional requirements is often incomplete or inconsistent, and because of variability in individual nutrient requirements, the RDA's represent an estimated, rather than an absolute, standard of dietary adequacy, and they are revised periodically to reflect current scientific evaluation of the available nutrition research. The most recent revision was published in 1980 and is presented in Table 1-6 (NRC 1980). The RDA's are defined as ". . . the levels of intake of essential nutrients considered, in the judgment of the Committee on Dietary Allowances of the Food and Nutrition Board on the basis of available scientific knowledge, to be adequate to meet the known nutritional needs of practically all healthy persons." Thus, each RDA is deliberately set higher than the actual requirement for that nutrient in most individuals.

Specific RDA's have been established for protein, 10 vitamins, and 6 minerals; they are presented in categories that vary according to body size, gender, and energy consumption (NRC 1980). RDA's are usually higher for males than for females, except for women who are pregnant or lactating. For 12 additional nutrients, research has been too limited to establish specific RDA's and the Food and Nutrition Board has proposed ranges of daily intake that are considered "safe and adequate." These are presented in Table 1-7. The RDA's are designed to exceed the nutrient requirements of most individuals, but the allowances for energy are designed to reflect average needs for people of different heights and weights, ages, and activity levels.

Table 1-6
Food and Nutrition Board, National Academy of Sciences-National Research Council Recommended Daily Dietary Allowances,[a] Revised 1980
Designed for the maintenance of good nutrition of practically all healthy people in the U.S.A.

	Age (years)	Weight (kg)	Weight (lb)	Height (cm)	Height (in)	Protein (g)	Fat-Soluble Vitamins: Vitamin A (μg RE)[b]	Fat-Soluble Vitamins: Vitamin D (μg)[c]	Fat-Soluble Vitamins: Vitamin E (mg α-TE)[d]
Infants	0.0–0.5	6	13	60	24	kg × 2.2	420	10	3
	0.5–1.0	9	20	71	28	kg × 2.0	400	10	4
Children	1–3	13	29	90	35	23	400	10	5
	4–6	20	44	112	44	30	500	10	6
	7–10	28	62	132	52	34	700	10	7
Males	11–14	45	99	157	62	45	1000	10	8
	15–18	66	145	176	69	56	1000	10	10
	19–22	70	154	177	70	56	1000	7.5	10
	23–50	70	154	178	70	56	1000	5	10
	51+	70	154	178	70	56	1000	5	10
Females	11–14	46	101	157	62	46	800	10	8
	15–18	55	120	163	64	46	800	10	8
	19–22	55	120	163	64	44	800	7.5	8
	23–50	55	120	163	64	44	800	5	8
	51+	55	120	163	64	44	800	5	8
Pregnant						+30	+200	+5	+2
Lactating						+20	+400	+5	+3

[a]The allowances are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods to provide other nutrients for which human requirements have been less well defined.

[b]Retinol equivalents; 1 RE = 1 μg retinol or 6 μg β carotene.

[c]As cholecalciferol; 10 μg cholecalciferol = 4000 IU of vitamin D.

[d]α-tocopherol equivalents; 1 mg *d*-α tocopherol = 1 α-TE.

Table 1-6 (continued)

	Age (years)	Weight (kg)	Weight (lb)	Height (cm)	Height (in)	Water-Soluble Vitamins: Vitamin C (mg)	Thiamin (mg)	Riboflavin (mg)	Niacin (mg NE)[e]	Vitamin B_6 (mg)	Folacin[f] (μg)	Vitamin B_{12} (μg)
Infants	0.0–0.5	6	13	60	24	35	0.3	0.4	6	0.3	30	0.5[g]
	0.5–1.0	9	20	71	28	35	0.5	0.6	8	0.6	45	1.5
Children	1–3	13	29	90	35	45	0.7	0.8	9	0.9	100	2.0
	4–6	20	44	112	44	45	0.9	1.0	11	1.3	200	2.5
	7–10	28	62	132	52	45	1.2	1.4	16	1.6	300	3.0
Males	11–14	45	99	157	62	50	1.4	1.6	18	1.8	400	3.0
	15–18	66	145	176	69	60	1.4	1.7	18	2.0	400	3.0
	19–22	70	154	177	70	60	1.5	1.7	19	2.2	400	3.0
	23–50	70	154	178	70	60	1.4	1.6	18	2.2	400	3.0
	51+	70	154	178	70	60	1.2	1.4	16	2.2	400	3.0
Females	11–14	46	101	157	62	50	1.1	1.3	15	1.8	400	3.0
	15–18	55	120	163	64	60	1.1	1.3	14	2.0	400	3.0
	19–22	55	120	163	64	60	1.1	1.3	14	2.0	400	3.0
	23–50	55	120	163	64	60	1.0	1.2	13	2.0	400	3.0
	51+	55	120	163	64	60	1.0	1.2	13	2.0	400	3.0
Pregnant						+20	+0.4	+0.3	+2	+0.6	+400	+1.0
Lactating						+40	+0.5	+0.5	+5	+0.5	+100	+1.0

[e]Niacin equivalent; 1 NE = 1 mg of niacin or 60 mg of dietary tryptophan.

[f]The folacin allowances refer to dietary sources as determined by *Lactobacillus casei* assay after treatment with enzymes (conjugates) to make polyglutamyl forms of the vitamin available to the test organism.

[g]The recommended dietary allowance for vitamin B_{12} in infants is based on average concentration of the vitamin in human milk. The allowances after weaning are based on energy intake (as recommended by the American Academy of Pediatrics) and consideration of other factors, such as intestinal absorption.

Table 1-6 (continued)

	Age (years)	Weight (kg)	Weight (lb)	Height (cm)	Height (in)	Minerals: Calcium (mg)	Phosphorus (mg)	Magnesium (mg)	Iron (mg)	Zinc (mg)	Iodine (μg)
Infants	0.0–0.5	6	13	60	24	360	240	50	10	3	40
	0.5–1.0	9	20	71	28	540	360	70	15	5	50
Children	1–3	13	29	90	35	800	800	150	15	10	70
	4–6	20	44	112	44	800	800	200	10	10	90
	7–10	28	62	132	52	800	800	250	10	10	120
Males	11–14	45	99	157	62	1200	1200	350	18	15	150
	15–18	66	145	176	69	1200	1200	400	18	15	150
	19–22	70	154	177	70	800	800	350	10	15	150
	23–50	70	154	178	70	800	800	350	10	15	150
	51+	70	154	178	70	800	800	350	10	15	150
Females	11–14	46	101	157	62	1200	1200	300	18	15	150
	15–18	55	120	163	64	1200	1200	300	18	15	150
	19–22	55	120	163	64	800	800	300	18	15	150
	23–50	55	120	163	64	800	800	300	18	15	150
	51+	55	120	163	64	800	800	300	10	15	150
Pregnant						+400	+400	+150	[h]	+5	+25
Lactating						+400	+400	+150	[h]	+10	+50

[h]The increased requirement during pregnancy cannot be met by the iron content of habitual American diets nor by the existing iron stores of many women; therefore, the use of 30–60 mg of supplemental iron is recommended. Iron needs during lactation are not substantially different from those of nonpregnant women, but continued supplementation of the mother for 2–3 months after parturition is advisable to replenish stores depleted by pregnancy.

Source: National Research Council 1980.

Table 1-7
Estimated Safe and Adequate Daily Intakes of Selected Vitamins and Minerals[a]

		Vitamins		
	Age (years)	Vitamin K (μg)	Biotin (μg)	Pantothenic Acid (mg)
Infants	0–0.5	12	35	2
	0.5–1	10–20	50	3
Children and	1–3	15–30	65	3
Adolescents	4–6	20–40	85	3–4
	7–10	30–60	120	4–5
	11+	50–100	100–200	4–7
Adults		70–140	100–200	4–7

		Trace Elements[b]					
	Age (years)	Copper (mg)	Manganese (mg)	Fluoride (mg)	Chromium (mg)	Selenium (mg)	Molybdenum (mg)
Infants	0–0.5	0.5–0.7	0.5–0.7	0.1–0.5	0.01–0.04	0.01–0.04	0.03–0.06
	0.5–1	0.7–1.0	0.7–1.0	0.2–1.0	0.02–0.06	0.02–0.06	0.04–0.08
Children and	1–3	1.0–1.5	1.0–1.5	0.5–1.5	0.02–0.08	0.02–0.08	0.05–0.1
Adolescents	4–6	1.5–2.0	1.5–2.0	1.0–2.5	0.03–0.12	0.03–0.12	0.06–0.15
	7–10	2.0–2.5	2.0–3.0	1.5–2.5	0.05–0.2	0.05–0.2	0.10–0.3
	11+	2.0–3.0	2.5–5.0	1.5–2.5	0.05–0.2	0.05–0.2	0.15–0.5
Adults		2.0–3.0	2.5–5.0	1.5–4.0	0.05–0.2	0.05–0.2	0.15–0.5

		Electrolytes		
	Age (years)	Sodium (mg)	Potassium (mg)	Chloride (mg)
Infants	0–0.5	115–350	350–925	275–700
	0.5–1	250–750	425–1275	400–1200
Children and	1–3	325–975	550–1650	500–1500
Adolescents	4–6	450–1350	775–2325	700–2100
	7–10	600–1800	1000–3000	925–2775
	11+	900–2700	1525–4575	1400–4200
Adults		1100–3300	1875–5625	1700–5100

[a]Because there is less information on which to base allowances, these figures are not given in the main table of RDA and are provided here in the form of ranges of recommended intakes.

[b]Because the toxic levels for many trace elements may be only several times usual intakes, the upper levels for the trace elements given in this table should not be habitually exceeded.

Source: National Research Council 1980.

The fact that most RDA's are intentionally established to exceed the nutrient requirements of most people means that a dietary intake below the RDA is not necessarily inadequate for an individual whose requirement for a nutrient is average or even above average (NRC 1980). It also means that the small percent of persons who have unusually high nutrient requirements may not meet nutritional needs even when they consume nutrients at RDA levels. The RDA's are estimates of the nutrient requirements for populations rather than for individuals. In addition, RDA's may need to be modified for people who are ill or injured.

Translating the RDA's into a single, universally applicable, ideal pattern of food choices that best supports health and longevity is, for many reasons, difficult. As noted above, individual nutrient requirements depend upon complex interactions between genetic and environmental factors and the stage of physiologic development. The nutritional needs of infants, young adults, and older persons vary, and dietary habits and preferences differ markedly from culture to culture and from individual to individual.

A definition of the food choices that best fulfill nutrient requirements has been a goal of the many Federal agencies and private health organizations that have developed sets of dietary recommendations during the past decade (Dwyer 1983; McNutt 1980). Some of these recommendations are noted in Table 1-5; the evidence on which they are based is presented throughout this Report. Most current recommendations emphasize that it is the overall dietary pattern that determines whether or not nutrient intakes are likely to fall within desirable ranges. Public health concerns about specific nutrients, therefore, usually are directed to the kinds and amounts of foods consumed and to the genetic, behavioral, and environmental factors that affect food choices.

The diet must contain adequate energy, all essential nutrients, and certain other dietary factors to sustain normal growth, development, and health. The nutrients and dietary factors discussed in this Report include carbohydrates, fats, and proteins—the macronutrients—which are sources of energy as well as of essential fatty acids and amino acids that either cannot be synthesized or are synthesized in amounts inadequate to meet body needs; micronutrients—vitamins and mineral elements—which are necessary in small amounts; and substances such as fiber, which does not fall into either category but is nonetheless beneficial for good health. This section defines these nutrients as background for this Report. Basic information on essential nutrients has been reviewed extensively (see, for example, Nutrition Reviews 1984; Passmore and Eastwood 1986; Schneider, Anderson, and Coursin 1983; Shils and Young 1988).

Energy

The diet must supply sufficient energy to support growth and development, maintain basic physiologic functions, meet the demands of muscle activity, and repair damage caused by illness or injury. In the United States, energy intake and expenditure are measured in kilocalories, abbreviated as kcal, and referred to as Calories or, commonly, calories. In international usage, the term is kilojoules, abbreviated kJ (1 kcal = 4.184 kJ). In this Report, the terms energy and calories are used interchangeably to refer to the general concept of energy; specific measures of energy intake or expenditure or the energy value of food are given in kilocalories.

The body obtains chemical energy from food from the oxidation (chemical burning) of protein, fat, carbohydrate, and, when it is consumed, alcohol. The oxidation within the body of 1 g each of these substances in pure form yields about 4, 9, 4, and 7 kcal, respectively. Thus, fat contains more than twice the caloric value of either protein or carbohydrate. The health significance of the relatively high energy value of alcohol is discussed in the chapter devoted to this topic.

Body weight depends on complex physiologic controls of the balance between energy intake and energy expenditure. Both intake and expenditure are equally important in regulation of body weight. Weight increases when more energy is consumed than expended. Over time, such an imbalance can lead to obesity. The physiologic controls of that balance and the ways in which diet and exercise affect body weight are reviewed in the chapter on obesity.

Carbohydrates

Carbohydrates are sources of energy for vital metabolic processes and also are constituents of cellular substances such as nucleic acids, glycoproteins, and enzyme cofactors and structural components of cell walls and cell membranes. Carbohydrates are classified as monosaccharides, disaccharides, and polysaccharides. Monosaccharide and disaccharide sugars are referred to as simple carbohydrates and the polysaccharides (starches and fibers) as complex carbohydrates.

Monosaccharides. Monosaccharides are simple sugars that do not need to be further digested to be absorbed. The most important dietary monosaccharides are glucose, fructose, and galactose. Glucose and fructose are found in fruits, vegetables, and honey. They are also products of the digestion of sucrose (table sugar) and, in the case of glucose, other disaccharides. The glucose obtained from corn starch can be converted by

enzymatic processes to fructose to produce high fructose corn sweeteners. As discussed below, galactose is a subunit of the disaccharide lactose.

Disaccharides. Sugars formed from two monosaccharides are called disaccharides. Sucrose, common table sugar, is composed of glucose and fructose. It is found in many fruits and vegetables but occurs in especially high concentrations in sugar beets and sugar cane. Maltose is a disaccharide of two glucose molecules and is found in beer, glucose syrups, and cereals. Lactose, the sugar of milk, is composed of one molecule of glucose and one of galactose.

Polysaccharides. Starch, glycogen, and most types of fiber are large, high-molecular weight polysaccharides. Starch and glycogen are composed of glucose molecules. Fiber includes a variety of carbohydrates and other components. These molecules differ from each other in the ways their monosaccharide units are linked to each other and, therefore, in their ability to be digested to sugars that can be absorbed into the body. The chemical linkages in starch and glycogen can be split by human intestinal enzymes, but those of polysaccharides found in fiber are, by definition, indigestible although some fiber components can be broken down by enzymes released by bacteria in the digestive tract to short-chain fatty acids that can be reabsorbed and furnish small amounts of energy.

Fiber. Dietary fiber is a term used to describe a heterogeneous group of plant food components that are resistant to human digestive enzymes (LSRO 1987). Not all are fibrous in the usual sense of the word, and some are even soluble. Dietary fiber includes some of the structural components of plant cell walls (e.g., cellulose and noncellulosic polysaccharides such as hemicellulose) and certain nonstructural components of cells such as pectins, gums, brans, mucilages, algal polysaccharides, and modified cellulose.

Specific types of dietary fiber are often classified as soluble or insoluble on the basis of their response to extraction methods. In general, the soluble fibers include gums, mucilages, and some pectins and hemicelluloses, while insoluble fibers include cellulose, lignin, and other pectins and hemicelluloses. Although all fruits, vegetables, and grains contain these fiber components, some are especially good sources of one or another type. Oat bran and beans, for example, contain relatively large proportions of soluble fibers whereas wheat bran is a good source of insoluble fiber. In general, diets that contain large amounts of fiber add bulk and may confer greater feelings of satiety.

The effects of the various fiber types on intestinal function differ, however. Insoluble fibers that adsorb water increase stool weights. Some soluble fibers have been found in short-term studies to reduce blood cholesterol, enhance glucose tolerance, and increase insulin sensitivity (LSRO 1987). These issues are reviewed in appropriate chapters of this Report.

Lipids

Dietary fats or lipids include a variety of substances soluble in organic solvents, such as chloroform or benzene, but insoluble in water. Food lipids include triglycerides (composed of fatty acids and glycerol), phospholipids, and cholesterol. Any excess of energy in the body, whether derived from carbohydrate, fat, protein, or alcohol, can be converted to fatty acids and stored in adipose tissue triglyceride, but dietary fat is essential because it supplies linoleic acid (an essential fatty acid) and it is a vehicle for absorption of fat-soluble substances such as the vitamins A, D, E, and K (NRC 1980).

Lipids are concentrated sources of energy as well as structural components of cell membranes and are molecular precursors for the synthesis of hormones and other substances. In adults, these functions usually can be met by a daily intake of 15 to 25 g of fat (NRC 1980), a level well below that typical of current American diets. In addition, fats impart characteristic mouth-feel and flavors to foods and increase the feeling of satiety after meals by delaying the passage of food from the stomach to the small intestine. The reservoirs of fat stored in the body protect the body's organs, provide insulation from heat loss, and maintain energy production during long periods of reduced food consumption, such as in starvation, dieting, or serious illness or injury.

Fatty Acids. Fatty acids are molecules containing carbon, hydrogen, and oxygen with chain lengths ranging from 4 to about 25 carbon atoms. A small amount of food fat occurs as phospholipid. Most fat in food, however, occurs as triglycerides, three fatty acid chains attached to a glycerol molecule. Triglycerides are called fats or oils depending on whether they are solid or liquid at room temperature. Both provide concentrated sources of metabolizable energy, about 9 kcal/g, more than twice the level of either proteins or carbohydrates. Recent studies suggest that the caloric value of fat may appear even higher in growing rats, reflecting greater efficiency of utilization under certain circumstances (Donato and Hegsted 1985; Donato 1987).

The fatty acids commonly found in food are usually composed of an even number of carbon atoms, usually 12 to 22, and contain from 0 to 6 double bonds—sites where additional hydrogen atoms can be attached. The number of double bonds determines the degree of saturation of fats. Fatty acids with no double bonds are saturated, those with one double bond are monounsaturated, and those with two or more double bonds are polyunsaturated.

Although all dietary fats consist of a mixture of saturated, monounsaturated, and polyunsaturated fatty acids, fatty acids in foods of animal origin are more often saturated, while those in plants are more likely to be monounsaturated and polyunsaturated. There are some important exceptions to this generalization. Coconut oil and palm kernel oil contain a high proportion of saturated fatty acids even though they are derived from plants, and as discussed below, certain fish are good sources of polyunsaturated fatty acids.

The location of double bonds along the carbon chain is also of physiologic importance. The site of the double bonds is used to categorize unsaturated fatty acids into three groups—the omega-3, omega-6, and omega-9 fatty acids. In the metabolism of fatty acids, the end of the carbon chain containing the methyl group (whose carbon atom is known as the omega carbon) tends to remain unchanged, whereas enzymes can add or subtract carbon atoms or double bonds starting from the end of the molecule that contains the carboxyl group. For convenience, the chemical features of fatty acids are usually described in terms of the structure at the methyl end of the chain. Oleic acid has nine carbon atoms between its methyl omega carbon atom and its closest double bond, so it belongs to the omega-9 family of fatty acids. Linoleic acid and the compounds to which it is connected in the body have six carbons between their omega carbons and closest double bonds, and they are omega-6 fatty acids. Linolenic acid and its derivatives have three carbons between the omega carbon and the closest double bond and are omega-3 fatty acids.

Monounsaturated omega-9 fatty acids such as oleic and palmitoleic acids are not essential in the human diet because they can be synthesized biochemically within the body. Linoleic acid, an omega-6 fatty acid, cannot be synthesized by the human body and must be consumed in the diet. It is a component of cell membranes and is required for the synthesis of arachidonic acid, the major precursor of prostaglandins, prostacyclins, thromboxanes, and leukotrienes that influence many physiologic pro-

cesses, including blood vessel dilation, platelet aggregation, smooth muscle contraction, inflammation, and reproduction. Linoleic acid is widely distributed in the fatty portion of both plant and animal foods. Vegetable seed oils are especially rich sources. Symptoms of its deficiency have been reported among infants restricted to skim milk and among children and adults fed intravenous solutions lacking fat (Rivers and Frankel 1981). Linoleic acid deficiency can be prevented by consuming about 3 to 5 g of linoleic acid a day, an amount considerably less than that consumed by the average adult in the United States. Thus, essential fatty acid deficiencies are reported rarely in the United States (NRC 1980).

The role of omega-3 fatty acids, particularly eicosapentaenoic acid and docosahexaenoic acid, in human nutrition and health is under active investigation. Omega-3 fatty acids are present in the human brain, retinal lipids, and phosphoglycerides of synaptic membranes. Of current interest are the potential health effects of these highly polyunsaturated fatty acids derived from linolenic acid (omega-3).

Recent epidemiologic, clinical, and experimental data suggest that omega-3 fatty acids may have important physiologic effects that cannot be met by omega-6 or omega-9 fatty acids. Some of these effects are reviewed in the chapter on coronary heart disease.

Cholesterol. Cholesterol is a fatty substance required for synthesis of sex hormones, bile acids, and vitamin D, and it is an important constituent of all cell membranes. It is both synthesized in the body (endogenous) and obtained from the diet (exogenous) and is not, therefore, an essential nutrient. In normal individuals, endogenous synthesis of cholesterol is reduced when blood cholesterol levels are high. When the physiologic mechanisms that regulate this feedback mechanism are insufficient, blood cholesterol levels can rise and increase the risk for coronary heart disease (see that chapter). Dietary cholesterol is found only in foods derived from animals (meat, poultry, fish, eggs, and dairy products); it is not present in plants.

Protein

Body proteins serve many functions; they include structural components of cells and tissues, enzyme catalysts of biochemical reactions, peptides and hormone messengers, and components of the immune system. The amino acids in proteins can also serve as sources of energy, and most can be used to synthesize glucose when dietary carbohydrate is inadequate. Some amino acids are needed for the synthesis of special compounds;

tryptophan, for example, is required for synthesis of serotonin (a neurotransmitter) and niacin (a vitamin).

Proteins are formed from various combinations of amino acids that are linked together in chains ranging from several to hundreds in length. Each plant and animal species has its own characteristic proteins that are distinguished by the sequence of amino acids. Plants can synthesize all of their amino acids from the elements carbon, oxygen, hydrogen, nitrogen, and sulfur, but humans lack the ability to synthesize at least eight amino acids and must obtain them from the diet. The rest are called nonessential amino acids because, although needed for protein synthesis, they are not required in the diet. Essential amino acids include isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. The amino acid cystine can replace part of the requirement for methionine, and tyrosine can replace part of the requirement for phenylalanine. Histidine is an essential amino acid for infants, but its essentiality for adults has not been conclusively demonstrated (NRC 1980).

The proteins in different foods vary in their biologic value due to their content and balance of amino acids. When the concentration of one essential amino acid is low relative to the others, that amino acid is considered limiting and the protein is said to be incomplete. The presence of limiting amino acids in incomplete proteins can be compensated for at least partially by dietary intake of complementary proteins, those with different limiting amino acids. When consumed together or within a short time (the exact length of time has not been defined), such proteins can meet requirements for essential amino acids. This explains, in part, why strict vegetarians can maintain good health without eating foods derived from animals. The addition of even a small amount of protein from animal foods can improve amino acid intake. The RDA's for protein intake of men, women, and children of different ages are given in Table 1-6.

Vitamins

Vitamins are organic (carbon-containing) compounds that are essential in very small amounts for health, growth, and reproduction. They must be obtained from the diet either because they cannot be synthesized at all by the body or because the amounts made are insufficient to meet requirements. Vitamins are classified according to their solubility in fat or water, and this property affects their occurrence in foods as well as their absorption, transport, storage, and metabolism.

Fat-Soluble Vitamins. The fat-soluble vitamins are vitamins A, D, E, and K. These vitamins are generally found in high concentrations in the fatty portions of food and are absorbed, transported, metabolized, and stored along with fat. Their absorption requires bile and dietary fat. They are transported in the body by the same mechanisms by which fat is transported, are bound to lipoproteins or specific transport proteins, and are stored in liver and fat tissue. Fat-soluble vitamins are excreted into the intestine in bile and are either reabsorbed or are eliminated in feces. They are not excreted to any appreciable extent in urine. Because excretion of fat-soluble vitamins is minimal, excess intake is more likely to cause toxicity symptoms. For the same reason, deficiencies are reported rarely among healthy adults, although they are observed among children who are growing rapidly and who lack adequate fat stores and among children or adults who have disease conditions that interfere with fat metabolism, such as malabsorption, biliary obstruction, or renal or liver disease. The RDA's for vitamins A, D, and E are given in Table 1-6; the estimated safe and adequate intake of vitamin K is shown in Table 1-7.

Vitamin A is present in the diet both as the vitamin and its precursor. Retinol, or preformed vitamin A, is found in foods derived from animals (milk, butter, egg yolks, liver) and, when bound to a fatty acid, is used to fortify many foods. Retinol occurs in foods primarily in the ester form. Certain carotenoids (pigments found in many dark green, yellow, and orange vegetables, fruits, and egg yolks) can be converted by the body into retinol. The conversion of beta-carotene into retinol occurs mainly in the intestinal mucosa. Retinol circulates in the plasma bound to a specific transport protein called retinol-binding protein. Excess amounts are stored in the liver. Excessive intake of retinol has caused toxic symptoms (headache, skin and bone disorders, and renal failure) among people consuming abnormally large amounts of vitamin supplements, or—less commonly—liver from animals with high vitamin A levels (Selhorst et al. 1984; Mahoney et al. 1980). High intakes of retinol supplements have also been associated with birth defects (Rosa 1986); synthetic retinoid analogs, used to treat a variety of skin disorders (Bollag 1983), can cause fetal malformations. They are hazardous to pregnant women or women planning to become pregnant (Lammer et al. 1985) and should be used only under medical supervision. Excess amounts of beta-carotene are stored in body fat deposits. Excessive intake of foods rich in beta-carotene, such as carrots, is not known to cause toxic effects. It raises levels of carotene in the blood and can cause the skin to take on an orange color that disappears when the carotene consumption declines. Vitamin A is essential for visual processes, for the normal differentiation of epithelial tissue, for the regulation of cell membrane structure and function, and for the maintenance of

immunocompetence. Vitamin A deficiency, through adverse effects on eye epithelial tissues, is a major cause of blindness among children in many developing countries, and it is also responsible for substantial additional illness. Recent studies of children consuming inadequate levels of retinol or carotenes suggest that retinol supplementation may improve their survival (Sommer et al. 1986; Tarwotjo et al. 1987).

Vitamin D_3 (cholecalciferol or calciol) is synthesized from a precursor (7-dehydrocholesterol) in skin that becomes activated by exposure to ultraviolet light from the sun. It is essential in the diet only when exposure to sun is inadequate. The vitamin is converted by the liver to 25-dihydroxyvitamin D (calcidiol) and then further converted by the kidney to 1,25-dihydroxyvitamin D (calcitriol), the metabolically active form. Excess vitamin D can be toxic, especially to children and adults who have kidney disease or certain metabolic disorders. The metabolism and functions of vitamin D are reviewed in detail in the skeletal diseases chapter.

Vitamin E functions as an antioxidant. Its principal dietary sources are vegetable seed oils. Its deficiency has been associated with a hemolytic anemia in premature infants and with neurologic symptoms in adults. Vitamin K functions as an activator of blood clotting proteins, proteins in bone and kidney, and the formation of other proteins that contain gamma-carboxyglutamic acid (GLA). It is synthesized by intestinal bacteria. Thus, deficiencies generally occur only in infants whose intestinal flora has not yet been established, in children and adults receiving antibiotic or anticoagulant therapy (see chapter on drug-nutrient interactions), and in individuals with disease conditions that interfere with intestinal absorption. Vitamins E and K are less toxic than vitamins A or D.

Water-Soluble Vitamins. The water-soluble vitamins include vitamin C (ascorbic acid) and those of the B-complex group: biotin, folate, niacin, pantothenic acid, riboflavin, thiamin, vitamin B_6, and vitamin B_{12}. The RDA's for vitamin C, thiamin, riboflavin, niacin, vitamin B_6, folacin, and vitamin B_{12} are presented in Table 1-6; the safe and adequate ranges of intake of biotin and pantothenic acid are given in Table 1-7. These vitamins are generally found in whole grain cereals, legumes, leafy vegetables, and meat and dairy foods. The two exceptions are vitamin C, which can be obtained in adequate amounts only from fruits and vegetables, and vitamin B_{12}, which is made by bacteria and found only in foods of animal origin. Water-soluble vitamins are absorbed from the intestine, and most are stored in a form that is bound to enzymes or transport proteins and excreted in urine. Thus, they should be supplied in adequate amounts in the daily diet even though tissue depletion may take as long as weeks or months.

Water-soluble vitamins are essential components of enzymes and enzyme systems that catalyze a wide variety of biochemical reactions in cellular energy production and biosynthesis. Thus, deficiencies of these vitamins particularly affect tissues that grow or metabolize rapidly, such as skin, blood, and the cells of the digestive tract and nervous system. Common deficiency symptoms are skin disorders, anemia, malabsorption and diarrhea, neurologic disorders, and defects in tissues of the mouth. Specific vitamin deficiencies infrequently occur in the United States. When deficiencies occur, they usually are found along with other deficiencies and are due to diseases or to consumption of highly restricted diets or excessive amounts of alcohol or drugs that interfere with vitamin metabolism. The risk for deficiencies is greater in growing infants (see maternal and child nutrition chapter) and, perhaps, in older persons (see chapter on aging). Substantial intake of these vitamins causes toxicity infrequently, although severe toxic reactions have been reported from very excessive intakes of niacin and vitamin B_6.

Minerals

Minerals perform a number of roles in the body. They function as inorganic components of enzyme systems that catalyze the metabolism of protein, carbohydrate, and lipids. Some act to regulate fluid and electrolyte balance, to provide rigidity to the skeleton, and to regulate the function of muscles and nerves. Minerals also work together with vitamins, hormones, peptides, and other substances to regulate the body's metabolism.

Essential minerals are often classified as macrominerals, required in amounts from several hundred milligrams to 1 or more grams a day (calcium, phosphorus, magnesium, sodium, potassium, and chloride), or as trace elements—iron, zinc, iodine, copper, manganese, fluoride, chromium, selenium, molybdenum, and cobalt (as a component of vitamin B_{12})—which are required in small amounts (Underwood 1977). Other minerals such as nickel, vanadium, silicon, or boron have been shown to be essential under rigorous conditions for experimental animals but do not have well-established functions in humans. Still others, such as lead or mercury, are potentially toxic. RDA's for six minerals are given in Table 1-6. Ranges of dietary intake considered safe and adequate are given for nine others in Table 1-7.

Minerals are distributed in a variety of foods, but they usually are present in limited amounts. Thus, diets must contain enough of a variety of foods to meet daily requirements. People consuming diets low in energy for pro-

longed intervals are at risk of developing mineral deficiencies. Deficiencies can also result from therapy with medications that interfere with mineral absorption and metabolism; alcoholism, renal disease, or gastrointestinal diseases (see relevant chapters); and causes of mineral loss such as bleeding or diarrhea. Toxic symptoms can result from consumption of excessive amounts of almost any mineral or as a result of defective regulation of absorption or inadequate excretion.

Dietary Patterns

There are two types of data for monitoring dietary patterns: food availability and dietary intake. Food availability data are derived from annual estimates of per capita availability of selected commodities in the food supply. These data are useful in examining changes over time in the availability of agricultural commodities. Estimates of dietary intake come from periodic national food consumption surveys of individuals.

Time Trends in the Availability of Foods

Food availability data are produced by the USDA and are derived from annual production and marketing estimates of food products that are then usually adjusted for imports, exports, and stock changes. Such data have been collected since 1909 and have been published as a historical series from 1909 to the mid-1960's (USDA 1968). Data for the most recent 20 years are published annually (Bunch 1987). Per capita estimates of food availability are derived by dividing the total amount of food available by the total U.S. population. These data represent economic rather than physiologic consumption because they estimate the amount of food available at wholesale and retail levels rather than actual intake by individuals. Certain limitations restrict use of such data as proxies for consumption—for example, the difficulty in correcting for wastes and losses that occur before consumption by individuals, for inedible food components and food for human consumption fed to pets, or for variabilities in intakes of population subgroups.

Nonetheless, food availability data provide useful information when used within their appropriate limits of interpretation. Time trend changes in availability of foods are best estimated from these data because the data have been available on an annual basis for many years. At the current time, these data are also the best source of information for tracking changes in the use of commodities or products that can be substituted for one another (e.g., partial substitution of high-fructose corn syrup for refined sugar).

A summary of the recent trends is noted below, taken mainly from the data of the last two decades as presented in Table 1-8 (Bunch 1987), but in part from the early data series as well (USDA 1968).

Overall, total per capita availability of *meat, poultry, and fish* increased by about 10 percent since 1965–67, primarily due to increases in poultry and fish and shellfish. Availability of red meat increased substantially after World War II (USDA 1968) but, after peaking in about 1970, has since declined to approximately 1965–67 levels.

Egg availability reached its peak about 1950. During the past 20 years, it has declined by about 18 percent; this is approximately equivalent to a decrease of one egg per week per person (from about six to five eggs per week).

The availability of fluid whole *milk* declined by 48 percent from 1965–67, while available levels of low-fat milk and milk products (including yogurt) more than doubled from 1965–67 to 1983–85. Cheese availability also more than doubled during this period.

Availability of *fats and oils* increased by approximately 23 percent since 1965–67, primarily due to a 77 percent increase in salad and cooking oil and a 36 percent increase in shortening. Butter availability was about 18 lb per capita per year in 1909 (USDA 1968) and has declined to about 5 lb, including about a 20 percent decline since 1965–67 (Bunch 1987). Availability of total animal fat also declined by 1983–85, to levels approximately 80 percent of those in 1965–67, but with a slight recent increase. Over the two decades, vegetable sources increased from 67 percent to 79 percent of all fats and oils—in marked contrast to the first half of the century when animal sources provided most of the fats and oils (USDA 1968).

As noted earlier, these data represent availability of commodities and thus do not necessarily reflect changes in actual intakes of fats and oils by the U.S. population. For example, there is no correction for losses of fats and oils used for deep fat frying, which are discarded after use rather than consumed. Second, the bulk data represent only fats and oils that are added to foods or used in table spreads; they do not include "hidden" fats in foods such as marbled fat in meats or the fats in nuts.

Vegetable and fruit availability increased from 1965–67 by 19 percent and 7 percent, respectively, primarily due to increases in availability of fresh produce. There was, however, no consistent change in availability of legumes (beans, peas, and nuts) or starchy vegetables (potatoes and sweet potatoes).

Table 1-8
Annual Per Capita Availability of Selected Commodities in the U.S. Food Supply, 1965–1985[a]
(pounds)

	Meat, Poultry, and Fish[b]					Dairy Products[d]			
Year	Meat	Poultry	Fish and Shellfish	Total	Eggs[c]	Fluid Whole Milk	Low-fat Milk[e] and Milk Products (fluid)	Cheese[f]	Totals[g]
1965–67	123.6	30.6	10.8	165.0	40.0	240.3	41.7	9.8	343.9
1968–70	130.8	33.0	11.3	175.1	39.5	219.5	54.6	11.0	334.6
1971–73	129.5	35.1	12.3	176.9	38.2	199.2	69.3	12.9	327.7
1974–76	128.7	35.5	12.4	176.6	35.1	176.0	82.9	14.9	317.1
1977–79	126.2	40.1	13.0	179.3	34.6	155.9	95.3	16.8	310.2
1980–82	120.9	44.2	12.7	177.8	33.9	138.1	101.7	18.7	299.7
1983–85	120.9	47.6	13.8	182.3	32.8	125.3	111.4	21.5	301.7

[a]Totals may include more categories than the selected commodities.
[b]Meat (beef, veal, pork, lamb), poultry, and fish, edible weight. Fish excludes game fish (Bunch 1987, Table 9, p. 15).
[c]Eggs, retail weight. Weight of a dozen eggs is assumed to be 1.57 lb (Bunch 1987, Table 8, p. 14).
[d] Dairy products are for civilian population, except fluid milk and cream data, which use U.S. resident population (Bunch 1987, Table 10, p. 16).
[e]Low-fat and other milk products include low-fat, skim, buttermilk, flavored drinks, and yogurt.
[f]Cheese is whole and part-whole milk cheese, excluding pot, baker's, and cottage cheese.
[g]Total dairy products calculated as total retail product weight minus butter (Bunch 1987, Table 10, p. 16). Includes frozen dairy products, cottage cheese, and other products not indicated in table. The amount of calcium contributed by this food group has actually increased slightly during the 20-year period shown, as a result of increases in products such as dry milk powder.

Table 1-8 (continued)

	Fats and Oils[h]								Fruits[i]		
	Animal			Vegetable							
Year	Butter	Lard	Total Animal	Margarine	Shortening	Salad and Cooking Oil	Total Vegetable	Total	Fresh	Processed	Total
1965–67	5.9	5.7	16.9	10.3	15.4	12.6	35.2	52.1	79.0	35.3	114.3
1968–70	5.5	5.0	16.0	10.7	16.9	14.4	38.8	54.9	77.1	37.6	114.7
1971–73	4.9	3.7	14.1	11.0	17.2	16.7	41.9	56.0	75.5	39.4	114.9
1974–76	4.5	2.9	11.6	11.4	17.2	18.5	44.8	56.4	79.9	40.6	120.5
1977–79	4.4	2.3	11.6	11.3	17.9	20.0	46.3	57.9	80.4	39.8	120.2
1980–82	4.4	2.5	12.8	11.2	18.4	21.6	48.1	60.9	84.8	37.1	121.9
1983–85	4.9	2.0	13.5	10.5	20.9	22.3	50.6	64.1	87.9	34.8	122.7

[h]Food fats and oils calculated on a total population basis except butter, which is based on civilian population (Bunch 1987; animal and vegetable fats are from Table 2, p. 7; butter, lard, margarine, shortening, and salad and cooking oil are from Table 12, p. 18). The animal and vegetable categories are not strictly distinct because some margarines and shortenings include animal fats.

[i] Selected fruits, retail weights. Include fruits for which data are available for the entire series: oranges, tangerines, tangelos, lemons and limes, grapefruit, apples, avocados, bananas, cherries, grapes, nectarines, peaches, pears, pineapples, plums and prunes, strawberries, minor fruits, and a variety of canned, frozen, and chilled fruit and juices (Bunch 1987, Table 2, p. 7).

Table 1-8 (continued)

Year	Vegetables[j]			Beans, Peas, and Nuts	Potatoes[k] and Sweet Potatoes	Flour and Cereal Products	Sugar and Sweeteners[l]			Coffee, Tea and Cocoa
	Fresh	Processed	Total				Refined Cane and Beet	Corn Sweeteners	Total Caloric Sweeteners	
1965–67	62.6	41.4	104.0	14.8	84.5	143.8	97.6	15.5	114.8	15.1
1968–70	65.2	45.4	110.6	14.8	85.1	141.9	100.6	18.2	120.4	14.5
1971–73	66.1	45.9	112.0	14.2	80.6	138.5	101.7	21.8	125.0	14.2
1974–76	68.9	46.1	115.0	15.1	81.5	143.6	92.7	27.3	121.4	13.1
1977–79	71.7	46.1	117.7	14.3	81.5	145.8	91.7	33.8	126.8	11.1
1980–82	74.3	44.2	118.6	14.0	76.3	150.2	78.9	44.4	124.6	11.3
1983–85	79.7	44.7	123.3	14.6	79.5	150.5	67.4	58.3	127.1	11.6

[j] Selected vegetables: fresh vegetables for which data are available for entire series include broccoli, carrots, cauliflower, celery, corn, lettuce, onions and shallots, and tomatoes; 1985 data for processed vegetables are unavailable (Bunch 1987, Table 2, p. 7).

[k] Potatoes and sweet potatoes: data not comparable to pre-1960 figures. Data revised to reflect conversion from processed weight to fresh-weight equivalent to dehydrated potatoes, frozen potatoes, chips, and shoestrings (Bunch 1987, Table 2, p. 8).

[l] Sugars and sweeteners, dry weight basis (Bunch 1987, Table 27, p. 33).

Availability of *flour and cereal products* showed both decreasing and increasing fluctuations during the 20-year period; 1983–85 levels were approximately 5 percent higher than 1965–67 levels. Availability of grains was at its lowest point this century in 1971–73, but has since increased by about 9 percent.

Availability of *sugars and sweeteners* increased by about 11 percent since 1965–67. It should be noted that the availability data for sugars and sweeteners are for bulk commodity forms only; they do not include estimates of sugars that are consumed as a natural constituent of food products, for example, lactose in milk or sugars naturally present in fruits.

Availability of *coffee, tea, and cocoa* decreased approximately 25 percent since 1965–67.

Current Dietary Intakes

Food consumption surveys can be used to estimate food and nutrient intakes of populations and population subgroups. The most recent nationally representative survey is the first Continuing Survey of Food Intakes by Individuals (CSFII), conducted by the USDA in 1985. Data are limited to three subgroups: children 1 through 5 years and adult men and women 19 through 50 years of age. Results are presented based on 1 day of intake (Table 1-9). When applicable, estimated mean intakes are compared with recommendations in the latest report on RDA's (NRC 1980). In interpreting results, it should be noted that the RDA's (except for energy) have a margin of safety above average requirements. Thus, diets that do not meet the RDA's do not by themselves provide conclusive evidence of nutritional deficiencies. Corroborating health data are needed.

Food Energy. Men and children had estimated mean intakes of more than 90 percent of the Recommended Energy Intakes (REI); for women, the estimated mean intake was 82 percent of the REI.

Total Fat, Fatty Acids, and Cholesterol. Fat contributed 34 percent of total energy intake for children and 36 to 37 percent for men and women. The relative fatty acid contributions were approximately 40 percent saturated, 40 percent monounsaturated, and 20 percent polyunsaturated. Cholesterol intakes ranged from a mean of 254 mg/day for children to 304 and 435 mg for women and men, respectively.

Protein. For men, women, and children, estimated mean intakes were 140 percent or more of the RDA. Protein contributed approximately 16 percent of total energy intakes.

Table 1-9
Mean Daily Intake[a] of Food Energy, Nutrients, and Food Components for Men, Women, and Young Children From the Continuing Survey of Food Intakes by Individuals (CSFII), 1985[b]

	Men	Women	Children
Total Food Energy (% REI)[c]	(94)	(82)	(100)
Fat [% total energy]	[36]	[37]	[34]
Total fat	[13]	[13]	[14]
Saturated fatty acids	[14]	[14]	[12]
Monounsaturated fatty acids	[7]	[7]	[6]
Polyunsaturated fatty acids	435	304	254
Cholesterol mg			
Protein	[16]	[16]	[16]
[% total energy]	(175)	(144)	(222)
(% RDA)[d]	[45]	[46]	[52]
Carbohydrates [% total energy]	18	12	10
Dietary Fiber g			
Vitamins (% RDA)	(122)	(127)	(215)
Vitamin A	(98)	(97)	(108)
Vitamin E	(182)	(133)	(186)
Vitamin C	(124)	(110)	(153)
Thiamin	(129)	(115)	(197)
Riboflavin	(146)	(130)	(151)
Niacin	(85)	(61)	(127)
Vitamin B_6	(245)	(156)	(192)
Vitamin B_{12}	(76)	(51)	(157)
Folacin			
Minerals (% RDA)	(115)	(78)	(105)
Calcium	(192)	(126)	(132)
Phosphorus	(159)	(61)	(88)
Iron	(94)	(60)	(84)
Zinc	(94)	(72)	(121)
Magnesium			
Minerals (ESADDI)[e]	(exceeds)	(within)	(exceeds)
Sodium	(within)	(within)	(1–3 years exceeds)
Potassium			(4–5 years within)
Copper	(below)	(below)	(below)

[a]Estimated mean daily intake is expressed in several ways: amount of intake, percent of total energy intake, percent of Recommended Dietary Allowance, or comparison with Estimated Safe and Adequate Daily Dietary Intake.
[b]Data based on 1-day dietary recalls obtained by personal interview for 658 men 19 to 50 years of age, for 1,459 women 19 to 50 years of age, and for 489 of their children 1 to 5 years of age in 1985 (unweighted numbers). Nutrient intakes do not include vitamin and mineral supplements or sodium from salt added at the table.
[c]Recommended Energy Intake (NRC 1980); Source of percentages: NFCS, CSFII Report Nos. 85–1 and 85–3 (USDA 1985, 1986).
[d]Recommended Dietary Allowance (NRC 1980); Source of percentages: NFCS, CSFII Report Nos. 85–1 and 85–3 (USDA 1985, 1986).
[e]Estimated Safe and Adequate Daily Dietary Intake (NRC 1980).

Dietary Fiber. Estimated mean intakes were 10 g/day for children, 12 g for women, and 18 g for men. For all three groups, these intake values corresponded to levels of about 7 g/1,000 kcal.

Calcium. Children and men had estimated mean intakes of 105 and 115 percent of the RDA, respectively. For women, estimated mean intakes were 78 percent of the RDA.

Iron. For women and children, estimated mean intakes were 61 percent and 88 percent of the RDA, respectively. For men, the estimated mean intake was 159 percent of the RDA.

Sodium and Potassium. For men and children, estimated mean intakes of sodium from foods alone (excluding salt added at the table) exceeded the upper limit of the Estimated Safe and Adequate Daily Dietary Intake (ESADDI) (Table 1-7). For women, the estimated mean intake of sodium was within the ESADDI. For children 1 to 3 years, the estimated mean intake of potassium exceeded the ESADDI. For children 4 to 5 years, men, and women, the estimated mean intake of potassium was within the ESADDI.

Other Nutrients. The estimated mean intakes for the following nutrients were close to or above 100 percent of the RDA for men, women, and children: vitamin A, vitamin E, vitamin C, thiamin, riboflavin, niacin, vitamin B_{12}, and phosphorus.

Nutrients for which estimated mean intakes were below recommended levels for one or more groups were vitamin B_6 (women had a mean intake of less than 70 percent of the RDA; men had mean intake of less than 90 percent of the RDA), folacin (women had a mean intake of less than 60 percent of the RDA; men had a mean intake of less than 90 percent of the RDA), zinc (women had a mean intake of less than 70 percent of the RDA; children had a mean intake of less than 90 percent of the RDA), and copper (men, women, and children had mean intakes below the lower limit of the ESADDI).

Use of Nutrient Supplements

Between 35 and 40 percent of the U.S. population took vitamin or mineral supplements in the late 1970's and early 1980's (Koplan et al. 1986; Stewart et al. 1985). In the 1985 CSFII, 58 percent of women and 60 percent of children reported using supplements on a regular or occasional basis, levels that are 19 and 12 percentage points higher, respectively, than those for comparable age and gender groups in the 1977–78 NFCS (USDA 1985).

An FDA telephone survey on the levels of 21 nutrients consumed from supplements indicated that median intake ranged from the RDA level to about six times the RDA. For some nutrients, intake levels for some people were as much as 60 times the RDA. The most commonly consumed nutrient (91 percent of users) was vitamin C, either used alone or as a component of other supplements (Stewart et al. 1985).

Supplement use is higher among females than among males, higher in the West than in other regions of the United States, and higher in whites than in nonwhites (Koplan et al. 1986; Read et al. 1981; Read et al. 1986; Schutz et al. 1982; Stanton 1983; Worthington-Roberts and Breskin 1984; Block et al. 1988). Higher use of vitamin supplements is also associated with older ages, higher incomes, and higher educational levels (Koplan et al. 1986; Garry et al. 1982; Read and Graney 1982). Limited information is available on supplement use by children. The National Health Interview Survey reported that 36 percent of children to age 17 took a vitamin/mineral supplement during a 2-week period in 1981. Use of supplements was highest among younger children (46 percent of children to age 2 and 49 percent of children ages 3 to 6) and was higher in the winter than in any other season (Kovar 1985).

NHANES II data show a correlation between dietary intake of nutrients and nutrient supplementation. Persons with higher nutrient intakes from foods alone are more likely to take supplements than those with deficient intakes, even after adjusting for the effects of other variables (Koplan et al. 1986). Analysis of types of foods consumed by people who take nutrient supplements showed similar results. Supplement users tended to consume more of all types of fruits and vegetables and, therefore, more dietary vitamin C (Looker et al. 1987). A recent review of surveys of supplement usage in the United States concluded further that use of supplements is frequently inappropriate, that exceptionally high intake among certain population groups raises concerns about the potential for toxicity, and that nutrition education and research are needed to combat supplement abuse (McDonald 1986).

Criteria for Scientific Judgment

Research on the relationship of dietary factors to disease is often complicated by the complexity of the variables, the intricacy of the interactions, and the disparate nature of the analytical tools. Thus, for many nutritional research questions, proof of causality in the classic scientific sense (i.e., uniform causality or absolute protection) is often not attainable. Whereas

classic nutritional disorders such as beriberi, pellagra, or scurvy could be clearly and directly demonstrated to be deficiencies of single identifiable nutrients, it has proved far more difficult to demonstrate that associations between specific dietary factors and chronic diseases are causally related.

Development of the major chronic disease conditions—coronary heart disease, stroke, diabetes, or cancer—is affected by multiple genetic, environmental, and behavioral factors among which diet is only one—albeit an important—component. These other factors interact with diet in ways that are not completely understood. In addition, foods themselves are complex; they may contain some factors that promote disease as well as others that are protective. The relationship of dietary fat intake to causation of atherosclerotic heart disease is a prominent example. An excess intake of total fat, if characterized by high saturated fat, is associated with high blood cholesterol levels and therefore an increased risk for coronary heart disease in many populations. A higher proportion of mono- and polyunsaturated fats in relation to saturated fats is associated with lower blood cholesterol levels and, therefore, with a reduced risk for coronary heart disease.

Because of these complexities, definitive scientific proof that specific dietary factors are responsible for specific chronic disease conditions is difficult—and may not be possible—to obtain, given available technology. An ideal study to demonstrate a causal association between a specific dietary factor and cancer, for example, would feed otherwise identical diets varying only in that factor to two large groups of children with comparable family histories, environments, and behavioral patterns. The study would then compare cancer rates in each group for the 30 to 50 years or more that it might take the disease to develop. Although this study would constitute a direct test of the hypothesis, it is evident that such research would be impractical and prohibitively expensive, as well as slow in yielding results.

For these reasons, researchers generally identify a relationship between a dietary factor and disease from studies in laboratory animals and from observations in humans. Data sources for human studies include laboratory measurements of blood nutrient levels or other biochemical measures of nutritional or risk status, population estimates of dietary intakes, and estimates of individual dietary intake based on recall. Epidemiologic studies using these data sources can compare dietary intake and disease rates in different countries or in defined groups within the same country (ecologic correlation studies). Another approach compares levels of dietary or biochemical indicators in persons with a specific condition to those observed

in persons without the condition (case-control studies). And it is sometimes possible to conduct prospective studies that compare dietary intake and disease rates in defined groups over time.

Biochemical, epidemiologic, and dietary intake studies can provide useful information, but each has important limitations. Interpretation of animal studies is always limited by uncertainties about their applicability to humans. Laboratory measurements reveal only a small part of the complex physiologic processes involved and do not always reflect current nutritional status. Dietary surveys depend on recall of the types and portion sizes of consumed foods (Basiotis et al. 1987). Epidemiologic studies can only demonstrate an association or correlation between a dietary risk factor and a disease; they cannot prove that the dietary factor causes the disease. For example, a study might show that populations consuming high-fat diets have higher rates of breast cancer than populations consuming low-fat diets. Although such a study demonstrates an association between fat and breast cancer, it may be that some genetic, environmental, or other dietary factor might be the true cause of the apparent relationship between fat and breast cancer. Prospective studies must be conducted with precisely comparable populations under strictly controlled conditions that may be difficult to achieve or to maintain for a sufficiently long period of time to observe significant differences in disease rates.

For these reasons, the relationship between diet and disease is usually inferred from the totality of existing laboratory, animal, dietary, genetic, metabolic, and epidemiologic evidence. Such inferences must be based on the application of established principles for making determinations of the quality of scientific evidence (Lilienfeld and Lilienfeld 1980). These principles include:

Consistency of the Association. Evidence gathered from a range of biochemical, animal, epidemiologic, and clinical studies should all produce results that support the possibility that a dietary factor is causally associated with increased disease risk. Repeated findings in different population groups and in different countries should consistently yield similar results.

Strength of the Association. The more powerful the correlation between dietary intakes and a health outcome, the more convincing the evidence. A causal relationship between dietary fat and coronary heart disease, for example, would be more credible if all individuals with coronary heart disease—but no healthy individuals—routinely consumed high-fat diets. Most diseases, however, are caused by multiple factors, and perfect corre-

spondence cannot be expected. Instead, the strength of association is expressed as a correlation between levels of exposure and disease rates in a population. The greater the correlation between dietary fat and coronary heart disease in a population, the more that correlation supports an inference that dietary fat increases coronary risk. Strength of association also can be expressed as a relative risk—the ratio of disease rates in the population exposed to the dietary factor (e.g., consuming high-fat diets) to the population that has not been exposed (e.g., consuming low-fat diets). A high relative risk supports an inference that a dietary factor increases disease risk.

Specificity of the Association. Demonstration of specificity in an association makes a causal hypothesis more convincing. Complete specificity only occurs, however, when a single cause is totally responsible for one—and only one—disease or condition and is, therefore, both necessary and sufficient. Because few nutritional factors act in complete independence of other factors, and many have roles in more than one disease, this criterion has limited applicability to evaluation of nutritional evidence.

Degree of Exposure to a Factor. If a dietary factor causes a disease, the risk for developing the disease should increase with the degree of exposure to the factor. The higher the fat intake in a population, for example, the greater should be the rate of coronary heart disease. While evidence of such dose-response relationships increases the plausibility of associations between dietary factors and disease, dose responses are often difficult to demonstrate because of variations in dietary intake and uncertainties in evaluating food and nutrient consumption.

Biological Credibility. There should be a reasonable physiologic explanation for the relationship between the dietary factor and the health outcome. Exposure to the dietary factor should precede the onset of disease, with appropriate latent or induction periods.

Experimentation and elucidation of physiologic and molecular mechanisms provide the most direct evidence for a causal relationship between a dietary factor and a specific disease condition. Epidemiologic studies provide evidence in support of such associations. Although this evidence usually is indirect, it can accumulate in quantity and quality to the point where a causal relationship appears sufficiently probable to provide a reasonable basis for public health action.

Application of these principles to development of a dietary recommendation for reduction of risk for a given disease must consider the effect of that

recommendation on the risk for other chronic diseases and on requirements for energy and nutrients. The evidence presented in this Report suggests that similar dietary patterns affect the risk for several chronic diseases. For example, diets containing a large proportion of calories from foods high in fat but low in complex carbohydrates and fiber are associated not only with increased risk for coronary heart disease, but also with increased risk for some types of cancer, diabetes, and obesity. Evidence also suggests that potentially competing risks can be accommodated within recommended changes in such patterns. For example, the recommendations to consume adequate calcium yet reduce overall fat intake can be accommodated by advice to select low-fat dairy products. Consequently, the interdependent nature of dietary changes to reduce disease risk have been considered along with the criteria described above in developing the overall findings and recommendations of this Report.

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Chapter 2

Coronary Heart Disease

The heart in itself is not the beginning of life;
but it is a vessel formed of thick muscle,
vivified and nourished by the artery and vein
as are the other muscles.
Leonardo da Vinci (1452–1519)
The Notebooks of Leonardo

Introduction

Coronary heart disease (CHD) is a term used to identify several cardiac disorders resulting from inadequate circulation of blood to local areas of heart muscle. This deficiency is nearly always a consequence of focal narrowing of the coronary arteries by atherosclerosis. Atherosclerosis is a progressive disease that often begins in childhood. The earliest lesions probably arise in the lining of the coronary arteries or in the aorta, often by ages 10 to 15. They appear first as fatty streaks, some of which may later progress to fatty or fibrous plaques and, eventually, large complicated lesions (Berenson 1986). The result of the progressive narrowing of the vessels may be angina pectoris, myocardial infarction (heart attack), or sudden death. These are the most common manifestations of CHD. Elsewhere in the body, the same process may lead to serious and sudden decrease of the blood supply to the brain (ischemic stroke), peripheral vascular disease, or serious problems caused by weakening of the lower abdominal aorta. The development of CHD is a silent process generally lasting decades before the onset of symptoms. Of the half-million heart attack deaths that occur annually, approximately 60 percent occur suddenly or outside of a hospital before treatment can be administered (Kannel and Thom 1984). Thus, much attention is directed at the prevention of CHD by identifying and modifying risk factors before clinical disease develops.

The causes of CHD are multifactorial. It is generally accepted that high blood cholesterol, high blood pressure, and cigarette smoking play causal roles in the development of atherosclerosis, which leads in turn to narrowing of the arteries and development of CHD. Diet plays an important role in

the regulation of blood cholesterol levels and influences other risk factors for CHD as well. For millions of Americans, the most effective CHD preventive strategies are to avoid smoking cigarettes, to control high blood pressure, and to lower high blood cholesterol.

This chapter focuses on the influence of diet on the development, treatment, and prevention of CHD. The role of diet in hypertension is reviewed in the chapter on high blood pressure.

Historical Perspective

Interest in atherosclerosis and its relationship to dietary factors can be traced to observations made in 18th and 19th century medicine. During that period, the fatty nature of the plaque was described and cholesterol was identified in the blood (see historical review, Stamler 1967). In the early 20th century, atheromatous aortas were found to contain excessive amounts of cholesterol (Windaus 1910). These observations led to a series of experiments to induce atherosclerosis in animals by feeding them a diet rich in fats and cholesterol. In 1912–13, typical arterial atherosclerosis was produced in rabbits by feeding pure cholesterol dissolved in vegetable oil (Anitschkow 1967).

At that time, another line of investigation was based on the theory that atherosclerosis was caused by toxic products of protein metabolism. Nutritional experiments, in which large amounts of foods rich in animal protein were fed to rabbits, produced changes in the aorta similar to those in humans. The observed effects were later attributed to the high cholesterol content of the experimental diets (Anitschkow 1967).

Early observations by clinicians and pathologists working in the colonies of British India, Indonesia, Africa, and Latin America were consistent with the pathologic and experimental findings. More than 50 years ago, these workers observed the relative rarity of CHD among the native populations compared with European and North American populations and associated this finding with the nature of the habitual diets. Whereas native groups consumed diets composed mainly of vegetable products, the Westernized population consumed large quantities of eggs and butter (Raab 1932).

Subsequent epidemiologic studies, including long-term prospective studies, of CHD mortality among many national, occupational, racial, and

religious subgroups have established three major modifiable risk factors for developing CHD: cigarette smoking, high blood pressure, and high levels of blood cholesterol.

Significance for Public Health

Deaths from CHD are declining in this country, and this decline has been attributed both to improved medical care and changes in lifestyle. Thus, from 1964 to 1985, the age-corrected CHD death rate has dropped by more than 42 percent, resulting in 350,000 fewer deaths in 1986 than would otherwise have occurred. A recent analysis of the effects of changes in medical intervention and changes in lifestyle attributes 30 percent of this decline to reductions in plasma cholesterol (Goldman and Cook 1984).

Despite this decline, however, CHD still accounts for more deaths annually than any other disease or group of diseases. More than 1.25 million heart attacks occur each year (two-thirds occur in men), and more than 500,000 people die as a result (NHLBI 1984). Death rates for CHD in men under age 65 and in women under age 75 are higher among blacks than among whites, the reverse being true in older persons (Tables 2-1 and 2-2). Available data show lower rates for CHD in the Hispanic population than in non-Hispanic whites (Heckler 1985).

Table 2-1
Death Rate for Coronary Heart Disease by Age, Race, and Sex, United States, 1985

	Death Rate per 100,000 Population[a]			
Age (years)	White Men	Black Men	White Women	Black Women
Total	180.8	164.9	82.9	100.8
Under 45	8.2	13.2	1.7	4.3
45–64	294.5	317.8	85.1	161.1
65–74	1,132.6	990.6	506.0	645.9
75 and over	3,071.8	2,205.0	2,010.2	1,717.5

[a]Age-adjusted to the U.S. population, 1940.

Source: National Center for Health Statistics. In press.

Table 2-2
Prevalence of Coronary Heart Disease by Age, Race, and Sex, United States, 1985

	Prevalence per 1,000 Persons			
Age (years)	Men	Women	White	Black
Total	32.9	24.7	31.8	11.3[a]
Under 45	0.9[a]	1.6[a]	1.3[a]	1.1[a]
45–64	80.9	44.4	65.1	46.3
65–74	175.6	107.0	143.9	62.2
75 and over	169.0	124.6	154.7	[a]

[a]Figure does not meet standards of reliability or precision.

Source: National Center for Health Statistics 1986a.

CHD ranks first as the reason for Social Security disability (Social Security Administration 1982), third after arthritis and hypertension for limitation of activity (Collins 1986), and third after mental illness and all forms of cancer for total hospital bed days (NCHS 1987). According to information from the National Heart, Lung, and Blood Institute (NHLBI), morbidity and mortality from CHD cost the United States an estimated $49 billion a year in 1985 in direct health care expenditures and lost productivity. Furthermore, it has been estimated that unless there are reductions in risk factors or improvements in the efficacy of therapies, CHD prevalence and incidence will increase in the future because of the aging of the population, especially with maturation of the post World War II baby boom generation (Weinstein et al. 1987).

High Blood Cholesterol (Hypercholesterolemia) and CHD Risk

An extensive body of clinical evidence supported by animal, epidemiologic, and metabolic studies has established the relationship between high blood cholesterol and increased CHD risk (Grundy 1986). The relationship is strong, continuous, and graded.

Until recently, it was unclear whether this relationship held only for blood cholesterol levels above a threshold value of about 200 to 220 mg/dl. However, data from the 361,000 men ages 35 to 57 screened for the Multiple Risk Factor Intervention Trial indicate that the association is apparent at even lower levels—about 180 mg/dl (Stamler, Wentworth, and Neaton 1986; Martin et al. 1986).

Average blood cholesterol levels for adult American men and women are 211 and 215 mg/dl, respectively (NCHS 1986b). Individuals whose cholesterol levels are within the top 25 percent of the cholesterol distribution

(above 240 mg/dl) have been defined as being hypercholesterolemic and at substantially higher risk (Consensus Development Panel 1985).

Scientific Background

The effects of dietary factors on circulating lipids in blood were among the earliest observations of factors influencing lipid metabolism and the atherogenic process. A voluminous literature has accumulated over the past 75 years on the relationship between diet, lipoproteins, atherogenesis, and CHD. The primary conclusions of this research are (1) that the higher the total blood cholesterol level, the greater the severity of atherosclerosis and the greater the risk for CHD, (2) that dietary saturated fat and cholesterol raise total blood cholesterol and low density lipoprotein (LDL) cholesterol levels, and (3) polyunsaturated fat lowers total blood cholesterol and LDL cholesterol levels (Levy et al. 1979). Monounsaturated fat also appears to lower blood cholesterol (Grundy et al. 1986).

Atherogenesis

Atherosclerosis is a combination of changes in the inner lining of arteries that occur in response to vessel injury and repair. These changes, as well as elevations in the blood lipids, including cholesterol, permit the excessive entry of proteins and lipoproteins, especially LDL, from the blood into focal regions of the artery wall. In general, LDL is thought to enter intact, but some may have been modified by oxidation or by glycosylation (as in diabetes). They may also undergo alteration, which makes them more atherogenic, after entering the artery wall. Some evidence suggests that very low density lipoproteins (VLDL) may also injure the vessel wall in some individuals with hyperlipidemia (Bradley, Gotto, and Gianturco 1985).

Injury of the blood vessel may also allow certain cells from the blood to adhere to its lining or to enter it, causing low-grade chronic inflammation, which helps to stimulate the proliferation of the arterial cells. The resulting arterial plaque is made up mostly of these modified and rapidly dividing arterial smooth muscle cells, proteins from the blood (especially lipoproteins and their transported fats, including cholesterol), and other cells such as platelets and monocyte/macrophages from the blood. Smooth muscle cells multiply in the plaque, apparently partly in response to growth factors carried to them by blood platelets and released at the site where the platelets adhere when they aggregate. The proliferating cells produce an excessive amount of collagen, elastin, and intercellular matrix. Thrombotic processes probably also participate in the progression of the plaque, especially when endothelial injury becomes more severe.

Figure 2-1 illustrates the microscopic appearance of arterial plaque created as a result of the interaction of these various mechanisms. The smooth muscle cell proliferation in conjunction with cellular accumulations of cholesterol and fat-filled macrophages or foam cells results in a tissue mass with a fibrous layer, or cap, on the lumen (interior) side of the artery. Within the plaque, dead cells and lipid debris, which represent the breakdown of earlier stages of plaque growth, form a central core. This is the soft cholesterol ester-rich component from which the lesion derives its name (athero-"gruel") (Wissler 1985).

Lipoprotein Metabolism

The link between high blood cholesterol and atherogenesis has been elucidated through studies of lipoprotein metabolism. Lipoproteins are the protein carriers of lipids in the blood. Four classes of plasma lipoproteins are generally recognized. They are designated according to their density, which depends on their relative proportions of protein and lipid; those that contain the greatest proportion of lipid are the lightest. Chylomicrons, the lightest lipoproteins, contain mostly triglyceride (90 percent) and originate when dietary fats are delivered to the blood stream via the intestinal lymph. Very low density lipoproteins mainly manufactured by the liver, are also rich in triglyceride (65 percent). The low density lipoproteins normally carry 60 to 70 percent of the circulating cholesterol. High density lipoproteins (HDL) are the heaviest lipoprotein particles because they contain a

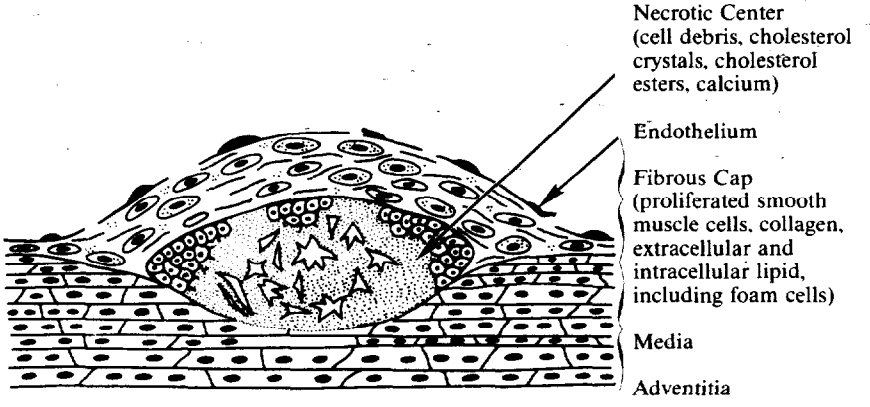

Figure 2-1. Diagram of an atherosclerotic plaque. The advanced atherosclerotic plaque has two important components—the cholesterol- and cholesterol ester-rich necrotic core and the fibrous cap.

Source: Conner, W.E., and Bristow, J.D., eds. 1985. *Coronary heart disease: Prevention, complications and treatment,* p. 194. Philadelphia, PA: Lippincott. Reprinted with permission.

relatively higher proportion of protein (approximately 50 percent by weight) (Rifkind 1982). All of these lipoproteins contain cholesterol but in varying amounts. All contribute to the total blood cholesterol level. An increase in any of them therefore contributes to high blood cholesterol. Lipoproteins are generally measured in the blood as the cholesterol fraction, for example, HDL cholesterol.

The metabolism of lipoproteins is largely determined by the composition of their protein components, or apoproteins. Some apoproteins serve primarily a structural role in lipid transport; others serve as functional units that are recognized by and bind to cell receptors. Still other apoproteins appear to act as cofactors for enzyme systems involved in catalyzing the intravascular changes in lipoproteins or their entry or exit from cells. Advances in techniques for measuring the composition and structure of lipoproteins are providing new insights into mechanisms controlling lipid metabolism and the process of atherogenesis. Although much information is available on how diet affects circulating levels of lipoproteins and the process of atherogenesis, less is known about its effects on the underlying mechanisms.

Low Density Lipoproteins. Low density lipoprotein is the major atherogenic lipoprotein and usually accounts for most of the CHD risk associated with elevated plasma total cholesterol (Gordon et al. 1977b). The level of LDL in the blood is an important determinant of the rate at which cholesterol is deposited in the artery walls. Low density lipoprotein levels are also influenced by other risk factors such as diabetes, cigarette smoking, and obesity (Schwarz et al. 1982).

The level of circulating LDL is determined by specialized proteins called LDL receptors, located on the surface of cells in the liver and other tissues (Goldstein, Kita, and Brown 1983). The number of receptors is determined by the cholesterol needs of the cell. Although cells are capable of making their own cholesterol, their receptors can also bind cholesterol-rich LDL particles and remove them from the circulation, leading to the incorporation of their cholesterol into the cell. If uptake of cholesterol by this route is decreased, as when the number of receptors is deficient, the cell increases its own synthesis of cholesterol. When the cholesterol is not withdrawn by the cells, LDL accumulates in the plasma and may be taken up by the arterial wall cells by mechanisms that do not involve LDL receptors.

Although the synthesis of cholesterol by the liver is under feedback regulation from dietary cholesterol, a reduction in dietary cholesterol intake to lower levels (<300 mg/day) will cause a net plasma cholesterol decrease

despite increased endogenous synthesis (Ernst and Levy 1980). The ability with which dietary cholesterol suppresses endogenous cholesterol synthesis varies greatly among individuals (Quintao, Grundy, and Ahrens 1971). Dietary cholesterol appears to suppress LDL receptor function in humans (Appelbaum-Bowden et al. 1984).

Much information about the consequences of diminished LDL receptor production has come from studies of individuals with familial hypercholesterolemia (FH) (Goldstein, Kita, and Brown 1983). This disease is caused by a genetic inability to synthesize normally functioning LDL receptor protein, causing very high circulating levels of LDL cholesterol, severe atherosclerosis, and often death in early adulthood from heart attack. In the most severe form of FH, accelerated and clinically catastrophic CHD occurs in early childhood in the absence of any other risk factors and is caused solely by elevated LDL cholesterol. Although the receptor defect in FH is genetically determined, other factors, such as increasing age and high-fat diets, may also lead to diminished receptor function in normal individuals (Brown, Kovanen, and Goldstein 1981).

Baboons, rabbits, and dogs maintained on low-fat diets have a high number of LDL receptors, and their circulating LDL levels are much lower than those of humans. When dogs and rabbits are fed high-fat diets, receptor activity is decreased by as much as 90 percent and circulating LDL levels rise (Brown and Goldstein 1984). At birth, infants have blood LDL concentrations similar to newborns of other species, apparently because of their ability to produce LDL receptors. In Western societies, LDL levels rise threefold to fourfold by adulthood. Clinical studies have suggested that this increase is attributable to a decrease in the number of receptors (Brown and Goldstein 1984). The cause of this receptor deficiency is not known, but a high-fat diet may be an important contributing factor. Diets high in saturated fat and cholesterol cause cholesterol to accumulate in cells and the liver, which could lead to a reduction in the number of LDL receptors. In some animals, dietary cholesterol has been reported to inhibit LDL receptor function by 30 percent, even in the presence of added polyunsaturated fat, and saturated fat may depress receptor function by as much as 90 percent (Spady and Dietschy 1985).

Experiments with cultured cells suggest that LDL receptor activity operates optimally at an LDL blood concentration of 25 mg/dl (Brown and Goldstein 1986). Average LDL cholesterol levels of 120 mg/dl in adult Western populations far exceed optimal levels (Goldstein and Brown 1977). This suggests that the human LDL receptor system evolved to function at low LDL levels and that a substantial portion of humanity may not be

genetically adapted to the relatively recent introduction of high dietary fat intake (Tiger 1980). This hypothesis is consistent with epidemiologic findings relating elevated LDL cholesterol to dietary fat intake (Brown and Goldstein 1984).

High Density Lipoproteins. High density lipoprotein is considered to protect against CHD. Numerous epidemiologic studies have shown that the higher the HDL cholesterol level, the lower the risk for CHD (Heiss et al. 1980). Female sex, estrogen use, exercise, moderate alcohol consumption, and weight loss have been associated with higher levels of HDL; in contrast, obesity and cigarette smoking have been associated with lower levels (Heiss et al. 1980). Some components of the HDL fraction may be involved in removing cholesterol from cells (reverse cholesterol transport) and inhibiting deposition of cholesterol in arteries, but the precise role of HDL is not well understood.

Very Low Density Lipoproteins. Very low density lipoprotein consists primarily of triglyceride of endogenous origin. The relationship between triglyceride and CHD is complex (NIH 1983). Although triglyceride levels are positively associated with an increased risk of CHD in most prospective population studies, they are closely associated with attributes such as obesity, total cholesterol, HDL levels, hypertension, and cigarette smoking and generally not independently predictive of CHD risk (Hulley et al. 1980). Elevated triglyceride may be an independent risk factor in older women (Gordon et al. 1977a).

However, almost all case-control studies of survivors of myocardial infarction have shown higher triglyceride levels in the affected patients, and many diseases associated with high triglyceride levels, such as diabetes mellitus, chronic renal disease, and certain primary hyperlipidemias, are associated with an increase in risk for cardiovascular disease (NIH 1983). Moreover, plasma triglyceride levels between 250 and 500 mg/dl may be a marker of lipoprotein abnormalities that are more directly associated with atherosclerosis, such as low HDL cholesterol. Alternatively, elevated triglycerides may reflect the presence of abnormal, triglyceride-rich lipoprotein particles or their metabolic products that may enhance atherogenesis. Whether or not triglycerides are directly involved in the atherogenic process, the identification of elevated levels may help to identify persons with increased CHD risk.

Expert Reports and Recommendations

Numerous expert bodies have examined the evidence relating diet to CHD and its implications for public health. Although there are many determi-

nants of blood cholesterol levels, no modifiable factor has been shown to influence cholesterol and LDL more profoundly than diet. The average adult American currently consumes a diet in which about 37 percent of the total calories is contributed by fat and 13 percent of calories by saturated fat. Dietary cholesterol is estimated to be about 300 to 400 mg/day (USDA 1985a, 1985b). These levels of saturated fat and cholesterol, the major determinants of blood cholesterol, exceed those in countries with low CHD rates, indicating the need for vigorous promotion and dissemination of appropriate dietary guidance.

Federal recognition of this need is demonstrated in the USDA/DHHS *Dietary Guidelines for Americans* issued in 1980 and revised in 1985 (USDA/DHHS 1985). The guidelines, which are being widely distributed and promoted in the public and private sectors, emphasize the reduction of fat, saturated fat, and cholesterol in diets for healthy Americans and suggest some ways to reduce these components through appropriate food selection.

A national preventive strategy to reduce the risk of CHD was enunciated in the 1980 DHHS report *Promoting Health, Preventing Disease: Objectives for the Nation* (DHHS 1981). Specific objectives are aimed at controlling high blood pressure, stopping smoking, lowering blood cholesterol levels, and reducing the prevalence of obesity. By 1990, the report states, the mean cholesterol level in the adult population ages 18 to 74 should be at or below 200 mg/dl.

In 1984, the NHLBI and the National Institutes of Health Office of Medical Applications of Research convened a consensus development conference on *Lowering Blood Cholesterol to Prevent Heart Disease* (Consensus Development Panel 1985). After reviewing much of the available data, the consensus panel of lipoprotein experts, cardiologists, primary care physicians, epidemiologists, nutrition scientists, biostatisticians, experts in preventive medicine, and lay representatives unanimously concluded, despite consideration of some dissenting views (Ahrens 1985), that elevated blood cholesterol is a major cause of CHD and that the risk for heart attacks due to CHD should be reduced by lowering elevated blood cholesterol levels, specifically, blood levels of LDL cholesterol. The panel members suggested that although the benefits of blood cholesterol reduction had been demonstrated most conclusively in men with elevated levels, the evidence justified the conclusion that women with elevated levels would be afforded similar protection. The panel further recommended designation of individuals with blood cholesterol levels above the 75th percentile (the upper 25 percent of values) as being at special risk and requiring vigorous treatment

with dietary measures. It also recognized that dietary treatment of elevated blood cholesterol in children requires special consideration to ensure adequate nutrients for growth and development and to meet energy needs. Older persons, who are at increased risk for malnutrition, may also require special care to ensure adequate intake of essential nutrients.

The panel members asserted that the average blood cholesterol level in the United States is too high, largely because of high intakes of calories, saturated fat, and cholesterol. They recommended that all Americans, except children under age 2, adopt a diet with total dietary fat intake of 30 percent of total calories, with less than 10 percent of calories from saturated fatty acids; limit polyunsaturated fat intake to a maximum of 10 percent of calories; and limit daily cholesterol intake to 250 to 300 mg or less. These dietary recommendations are compatible with food intakes of countries with low CHD prevalence. The panel further advised that caloric intake be reduced if necessary to correct for obesity and that it be adjusted to maintain ideal body weight (Consensus Development Panel 1985).

Although the consensus panel considered the moderate-fat, moderate-cholesterol diet recommended for the general public to be suitable for all members of the family over 2 years of age, special concern was expressed about promotion of cholesterol-lowering diets for children because such diets might inadvertently compromise their nutritional needs (Ahrens 1985). The American Academy of Pediatrics has recommended moderation with respect to decreases in saturated fat and cholesterol, noting that 30 to 40 percent of calories from fat seems sensible for adequate growth and development (AAP Committee on Nutrition 1986; see chapter on maternal and child nutrition). Diets that avoid extremes, it states, are safe for children for whom there is no evidence of specific vulnerability.

National Cholesterol Education Program

The NHLBI is providing the focus for a national effort to reduce cholesterol levels through the National Cholesterol Education Program (NCEP), initiated in 1985. The NCEP has issued detailed guidelines for treatment of adults with high blood cholesterol (NCEP 1988a) and recommendations for improvements in the measurement of blood cholesterol (NCEP 1988b). Future panel reports will provide recommendations for the general public and for treatment of high blood cholesterol in children and adolescents (Lenfant 1987).

The report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP 1988a) defined categories of risk according to measurement of total cholesterol and, when

indicated, subsequent evaluation of LDL cholesterol (Table 2-3). Patients with borderline high blood cholesterol (200 to 239 mg/dl) and no other risk factors should be given cholesterol-lowering dietary information and should be reevaluated annually. Lipoprotein analysis is recommended for patients either with high blood cholesterol (240 mg/dl or greater) or with borderline high blood cholesterol and CHD, or with two other risk factors (one of which can be male sex). The LDL cholesterol is the basis for initiating treatment. Persons with borderline high LDL cholesterol levels (130 to 159 mg/dl) and CHD or two other risk factors and persons with LDL cholesterol levels of 160 mg/dl or greater should be treated to lower their cholesterol.

The report recognized that diet is the cornerstone of therapy to reduce borderline and high-risk blood cholesterol levels whether or not drug therapy is eventually added to the regimen; in general, drug therapy is not recommended without at least 6 months on optimal diet. The advent of highly effective drugs for the treatment of elevated blood cholesterol levels may stimulate widespread use as an alternative to diet therapy. Concerns have been raised about this potential trend because all lipid-lowering drugs have potential side effects, and adverse effects may not become manifest for many years (Grundy 1986). Many patients can reduce their cholesterol levels substantially with diet alone (see Dietary Guidance, Special Populations section). When drugs are required, concomitant modification of the diet may reduce their dosage requirements, cost, and potential side effects. Based on the NCEP adult treatment guidelines (NCEP 1988a), it is estimated that over 40 million adult Americans could be candidates for dietary education or treatment.

Other Reports

A compilation of 47 major reports addressing the public health issues of habitual diet and CHD risk issued since 1968 reveals a common theme—recommendations for less total fat, less saturated fat, and control of

Table 2-3
National Cholesterol Education Program
Adult Treatment Panel Classification

	Total Cholesterol	LDL Cholesterol
	mg/dl	mg/dl
Desirable	<200	<130
Borderline high	200–239	130–159
High	≥240	≥160

Source: National Cholesterol Education Program 1988a.

obesity—and most of the reports also recommend a reduction in dietary cholesterol and partial replacement of saturated with polyunsaturated fat (Truswell 1983).

In response to a congressional directive, DHHS and USDA jointly sponsored an assessment of the existing evidence relating dietary cholesterol to blood cholesterol and human health, as well as recommendations for further research. Their report to Congress, *The Relationship Between Dietary Cholesterol and Blood Cholesterol and Human Health and Nutrition* (1986), concluded that high blood cholesterol is one of the major risk factors for CHD and that cholesterol in the diet, but even more the amount and types of fat in the diet, affect blood cholesterol; dietary cholesterol raises blood cholesterol in most people; in some there is a small response and in others the increase is more pronounced. The prevalence of different degrees of response in the population is not known. A broad program of research was recommended.

The National Research Council of the National Academy of Sciences recently conducted a 3-year review of the role of animal products in the American diet (NRC 1988). Its report, *Designing Foods. Animal Product Options in the Marketplace,* concluded that nutrition-related health problems affect nearly every American family and recommended measures to reduce the quantity of animal fat in the diet and to increase consumers' access to fat and cholesterol information.

Key Scientific Issues

- Role of Dietary Fat and Cholesterol in CHD
- Role of Other Dietary Factors in CHD
- Efficacy of Dietary Interventions in CHD

Role of Dietary Fat and Cholesterol in CHD

Of the many dietary factors that have been studied, the strongest and most consistent evidence relates to dietary fat. Systematic examination of the diet-blood cholesterol-CHD link through clinical, epidemiologic, and animal research implicates both the amount and nature of dietary fats as important determinants of plasma cholesterol levels.

Clinical Studies

Clinical studies have addressed the role of dietary fat and cholesterol upon CHD through their effects upon blood cholesterol and by their effects upon

development and severity of heart disease. The latter type of clinical studies is summarized in the section on Efficacy of Dietary Interventions in CHD, while studies on blood cholesterol are summarized below.

A variety of clinical studies carried out over the past several decades have shown that the type of fat and amount of cholesterol in the diet affect blood cholesterol levels. In these studies, the composition of the diet is controlled so that the effects of single constituents can be tested. Fatty acid sources examined include butter fat, olive oil, cottonseed oil, sunflower oil, hydrogenated coconut oil, sardine oil, safflower oils, margarines, and cocoa butter (Keys, Grande, and Anderson 1974). Typically, saturated fatty acids were shown to raise and polyunsaturated fatty acids to lower plasma cholesterol levels in comparison with monounsaturated fatty acids, which were considered to be neutral. The degree of response to saturated fatty acids depends on the individual fatty acid content. Myristic (14 carbon atoms, C:14) and lauric acids (C:12) have a more powerful effect than palmitic acid (C:16), but palmitic acid is more abundant in the food supply. Saturated fatty acids with more than 18 or fewer than 10 carbon atoms appear to have little or no effect on plasma cholesterol levels (Keys 1967). Likewise, stearic acid (C:18) has been reported not to raise blood cholesterol levels or, when substituted for palmitic acid, to lower blood cholesterol levels (Bonanome and Grundy 1988). *Trans* fatty-acids are isomers of naturally occurring *cis* unsaturated fatty acids. They are produced in fats as a result of commercial hydrogenation of cooking oils and also occur in ruminant fats, including milk fat, beef fat, and lamb fat. *Trans* fatty acids as consumed in hydrogenated vegetable oil appear to be the equivalent of oleic acid in their cholesterolemic properties in humans. In this respect, they are similar to stearic acid, but dissimilar to palmitic, myristic, and lauric acids (LSRO 1985).

Equations to estimate the change in serum cholesterol from changes in dietary fats and cholesterol (Keys, Anderson, and Grande 1965; Hegsted et al. 1965) derived from such clinical experiments are presented in Table 2-4. They show that saturated fatty acids are about twice as powerful in raising plasma cholesterol levels as polyunsaturated fatty acids are in lowering them, while dietary cholesterol has a smaller effect (Blackburn 1979). It has been estimated that increasing the dietary cholesterol intake by 100 mg/1,000 kcal increases the plasma total cholesterol by about 10 mg/dl (Grundy et al. 1988). Thus, if a person consuming 2,000 calories per day increases his or her dietary cholesterol from 300 to 500 mg/day, plasma cholesterol will rise about 10 mg/dl.

Table 2-4
Estimates of Serum Cholesterol Change From Given Changes in Dietary Lipids Based on Isocaloric Controlled Experiments in Humans

Keys (Minnesota) equation:

$$\Delta \text{ CHOL} = 1.35 (2 \Delta \text{ S} - \Delta \text{ P}) + 1.52 \Delta \text{ Z}$$

Hegsted (Harvard) equation:

$$\Delta \text{ CHOL} = 2.16 \Delta \text{ S} - 1.65 \Delta \text{ P} + 0.0677 \Delta \text{ C} - 0.53$$

Where Δ CHOL = estimated change in serum cholesterol in mg/dl; Δ S = change in percent daily calories from saturated fat; Δ P = change in percent daily calories from polyunsaturated fat; Δ Z = change in the square root of daily dietary cholesterol in mg/1,000 calories; and Δ C = dietary cholesterol in mg/day.

Source: Blackburn, H. 1979. Diet and mass hyperlipidemia: public health considerations—a point of view. In *Nutrition, lipids, and coronary heart disease*, ed. R. Levy, B. Rifkind, B. Dennis, and N. Ernst, pp. 309–47. New York: Raven. Reprinted with permission from Raven Press, New York.

Numerous studies have predicted group mean plasma cholesterol levels on the basis of the dietary content of saturated and polyunsaturated fatty acids and cholesterol alone (Keys, Grande, and Anderson 1974). Other clinical studies have shown that although saturated fat raises and polyunsaturated fat lowers plasma cholesterol levels, the magnitude of the change differs from that predicted by the equations. Results of six European experiments were compared with those predicted by equations such as those shown in Table 2-4 (Grande 1983). The predicted changes in serum cholesterol were generally in agreement with the observed changes, with some variability. For example, in the Finnish Mental Health Study, a dietary change that was predicted to raise cholesterol 33 mg/dl produced an average elevation of 49 mg/dl. In another experiment, the cholesterol-lowering effect of corn oil and olive oil were compared with a control diet. Mean serum cholesterol reductions were 50 mg/dl and 38 mg/dl, respectively, whereas the equations predicted the same decrease for both diets, 43 mg/dl. In another experiment, the effect of dietary cholesterol added to a diet rich in polyunsaturated fat was in agreement with the predicted value but was underestimated when cholesterol was added to a diet high in saturated fat.

More recently, the effects of high-oleic safflower oil (monounsaturated), high-linoleic safflower oil (polyunsaturated), and palm oil (saturated) on

blood cholesterol levels were compared in normal and hypertriglyceridemic patients. Both the high monounsaturated and high polyunsaturated fatty acid oils achieved similar lowering of total cholesterol (35 mg/dl), compared with 78 mg/dl predicted for the high polyunsaturated and 45 mg/dl predicted for the high monounsaturated fat diets (Mattson and Grundy 1985).

In another study, beef fat, coconut oil, and safflower oil were isocalorically exchanged in the diets of healthy normal volunteers (Reiser et al. 1985). Mean plasma total cholesterol was 21 mg/dl lower on the safflower oil diet compared with the habitual diet. Mean plasma total cholesterol on the beef fat diet was 14 mg/dl higher than on the diet containing safflower oil and 13 mg/dl lower than on the diet containing coconut oil. The authors suggested that the relatively higher proportion of stearic acid in the beef fat might contribute to these differences.

Despite some inconsistencies in the degree of plasma cholesterol responses, clinical studies have generally shown a fall in response to polyunsaturated fat and a rise in response to saturated fat. However, the above two experiments suggest that the interaction of dietary factors in regulating blood cholesterol levels may be more complex than can be accounted for solely by the amount of saturated and polyunsaturated fats and dietary cholesterol. Other factors that might contribute to inconsistencies across studies include differences in baseline plasma cholesterol levels, composition and form (food vs. liquid formula) of the diet, age, metabolic status of the participants, and duration of the experiment (Mattson and Grundy 1985).

Most clinical studies have noted a high degree of individual variability in response to dietary cholesterol, a characteristic also noted among some animal species (Jokinen, Clarkson, and Prichard 1985). Humans are generally less sensitive to dietary cholesterol than most animal species, and the high degree of individual variability in plasma cholesterol responses to dietary cholesterol suggests that some people may be overly sensitive to dietary cholesterol while others are relatively resistant. The proportion of the population that might be cholesterol-sensitive and the factors that contribute to that sensitivity are not well understood. The response to dietary cholesterol may be affected by such factors as previous diet, age, or genetic makeup (McGill 1979) and the relative proportions of other nutrients in the diet. For example, one controlled clinical study compared the effects of adding three or six eggs to basal diets containing 40 percent fat and 300 mg of cholesterol and differing ratios of polyunsaturated to saturated fat (P/S). At P/S ratios of 0.25 and 0.4, the addition of three and six eggs raised LDL cholesterol by 16 mg/dl and 25 mg/dl, respectively. At P/S

ratios of 0.8 and 2.5, the addition of three eggs had little effect, but the addition of six eggs at the P/S ratio 0.8 raised LDL cholesterol 17 mg/dl. On the diet with a P/S of 2.5, neither three nor six eggs produced significant changes. Thus, both the cholesterol content and the P/S ratios were important in determining LDL level (Schonfeld et al. 1982). Another example suggests that type of protein may influence response to dietary cholesterol. In a controlled dietary study in Type II hypercholesterolemia patients, substitution of soybean for animal protein caused a reduction in serum cholesterol concentrations, and the decrease was about the same with or without the addition of 500 mg of cholesterol to the diet (Sirtori, Gatti, and Mantero 1979).

A total of 75 studies were carried out in 50 male outpatient volunteers fed high cholesterol (approximately 800 mg/dl) versus low cholesterol (approximately 250 mg/dl) in a diet containing 35 percent of calories as either polyunsaturated or saturated fat. In 69 percent of the studies, participants compensated for the increased dietary cholesterol by decreasing cholesterol absorption or endogenous synthesis. The type of dietary fat had a larger and more consistent effect on plasma cholesterol (McNamara et al. 1987).

The main effect of dietary cholesterol on lipoproteins is to raise LDL levels, but it also affects other lipoprotein fractions. For example, human volunteers who ate three to six eggs per day showed increased binding activity of an HDL subfraction that might be associated with increased risk for the development of atherosclerosis (Mahley et al. 1978). It is hypothesized that dietary cholesterol might increase the cholesterol content of chylomicron and VLDL remnants, making them more atherogenic; these changes would not be detected in fasting blood samples, indicating the need for information on postprandial lipoproteins (Grundy et al. 1988).

Epidemiologic Studies

Extensive evidence relating diet to high blood cholesterol has been amassed in a variety of observational-epidemiologic studies. These investigations involve comparisons of different populations, comparisons of migrant with native populations, and comparisons of groups within populations.

Between-Population Studies (International Comparisons). In one type of international analysis, nutrient and food commodity data from Food and Agriculture Organization food balance sheets have been compared with World Health Organization CHD mortality data for sets of countries (Stamler 1983). Univariate analyses consistently showed statistically sig-

nificant positive associations of CHD mortality with calories, total fat, animal fat, saturated fat, dietary cholesterol, total protein, animal protein, animal products (dairy products, meat, poultry, and eggs), and refined sugars. Similar analyses have also shown an inverse association between vegetable products and CHD mortality. Since many of these variables occur together, the independent effect of a single nutrient cannot be determined in such analyses. When the data were reanalyzed, combining the saturated and polyunsaturated fatty acids and dietary cholesterol into a single score based on defined equations (see Table 2-4) and using analysis of variance to control separately for the influence of sugar, vegetable products, and fat, the significant effects of dietary fats persisted while sugar and vegetable products no longer related to CHD mortality (Liu et al. 1982).

In a second type of international comparison, autopsy records were used to compare the degree of atherosclerosis with dietary data. The most systematic study was the International Atherosclerosis Project (McGill 1968), in which severity of atherosclerosis was quantified in autopsies of 23,000 people in 12 countries. The percent of calories consumed as fat ranged from 10 to 15 percent in Costa Rica and Guatemala to nearly 50 percent in the United States. Dietary composition was estimated from available survey data and subjective judgment. The countries were ranked on the basis of severity of disease, dietary indices, and serum cholesterol. The results showed that the percentage of calories from dietary fat was related to the severity of the atherosclerosis ($r = 0.67$) and to population levels of blood cholesterol ($r = 0.74$).

A third type of international comparison involves the direct measurement of cardiovascular risk factors and dietary assessment. These epidemiologic surveys provide further descriptive data on dietary factors associated with the prevalence of heart disease in the populations studied. For example, the Seven Countries Study (Keys 1970) has involved 12,000 men from 18 populations sampled in Finland, Greece, Italy, Japan, the Netherlands, the United States, and Yugoslavia. Fourfold differences in prevalence and incidence of CHD were shown among these populations. The highest incidence rates were recorded for Finland and the United States and the lowest for Japan and three populations in Greece (Corfu, Crete, and Dalmatia). Seven-day food records supplemented by chemical analyses of the diets consumed by study participants showed wide variability across population samples in both amount and type of fat. Saturated fat intake was highest in Finland, the United States, and the Netherlands (17 to 22 percent of calories, compared with 5 to 9 percent of calories in the other countries). Saturated fat intakes and 5-year CHD incidence rates for these populations were highly and significantly correlated ($r = 0.84$), as were saturated fat and

serum cholesterol levels ($r = 0.89$) and serum cholesterol levels and CHD incidence rates ($r = 0.81$) (Keys 1972). Followup after 10 years still supported these findings (Stamler 1979).

International migration studies are yet another type of cross-country comparison. The movement of population groups from less affluent to more affluent societies provides a special opportunity to evaluate changes in risk factors among persons sharing the same genetic and cultural background. Such observations have helped to dispel the view that atherosclerosis and CHD essentially represent an immutable aging process, with most of the variations representing the inherited population pattern, or that the cholesterol levels encountered in most people in the United States can be regarded as normal. They indicate that as populations move and show a rise in dietary fat and saturated fat intake, they move from areas with low incidence of CHD to high incidence. They also display concurrent elevations in serum cholesterol. For example, the Ni-Hon-San Study, initiated in 1965 with middle-aged men of Japanese ancestry residing in Japan, Honolulu, and the San Francisco Bay area, showed intakes of saturated fat to be about 7 percent, 12 percent, and 14 percent, respectively. Average dietary cholesterol intakes were 464, 545, and 533 mg/day, and mean body weights were 55, 63, and 66 kg for the respective populations. Compared with Japan, serum cholesterol was 12 percent higher in Hawaii and 21 percent higher in San Francisco, and CHD mortality was 1.7 times higher in Hawaii and 2.8 times higher in San Francisco (Kato et al. 1973; Marmot et al. 1975; Robertson, Kato, Gordon, et al. 1977; Robertson, Kato, Rhoads, et al. 1977; Worth et al. 1975).

Within-Population Studies. The existence of groups within populations who consume diets different from the rest of the population provides another opportunity to examine the relationship between diet, serum cholesterol, and CHD. For example, studies in the United States comparing serum cholesterol levels in communities of omnivores (consuming animal and vegetable products), vegans (consuming only vegetable products), and lacto-ovo vegetarians (consuming milk, egg, and vegetable products) showed that vegans, who habitually consume a low saturated fat and cholesterol-free diet, had mean serum cholesterol levels 29 percent lower than omnivores, and those of lacto-ovo vegetarians were 16 percent lower (Hardinge and Stare 1954). Seventh-day Adventists who consume lacto-ovo vegetarian diets have lower mean serum cholesterol levels than the general American population. A 6-year prospective study of 20,044 Seventh-day Adventists in California showed that CHD mortality rates among those 35 to 64 years of age and over age 65 were 72 percent lower and 50 percent lower, respectively, than rates found in the general population.

Among Seventh-day Adventists, risk for CHD in nonvegetarian males 35 to 64 years of age was threefold greater than in vegetarian males (Phillips, Lemon, and Kuzma 1978).

All these types of epidemiologic studies involve analysis of data for groups. Despite the strength and consistency of results of group comparisons across and within populations, it has been difficult in studies of individuals within a given population to demonstrate similar relationships of dietary fat with either the plasma cholesterol level or CHD. While studies of individuals have revealed strong relationships between plasma cholesterol and CHD, only weak associations of dietary factors with plasma cholesterol levels or CHD have been shown.

In the Puerto Rico Heart Study, for example, baseline serum cholesterol levels in the urban sample were positively related to percent of calories from protein, fat, and saturated fat, and serum cholesterol was negatively related to percent of calories from total carbohydrate and complex carbohydrate (Garcia-Palmieri et al. 1977). In the Honolulu Heart Study, baseline serum cholesterol was positively related to dietary cholesterol, animal protein, and saturated fat and to percent of calories from total protein, total fat, animal protein, and saturated fat; it was negatively associated with percent of calories from complex carbohydrate and total carbohydrate (Kato et al. 1973). Multivariate analysis controlling for age, relative weight, systolic blood pressure, serum cholesterol, and cigarette smoking showed CHD incidence after 6 years to be inversely related to alcohol, starch, and caloric intake per kilogram of body weight (Gordon et al. 1981). Followup of the Honolulu cohort after 10 years showed that percentage of calories from fat, saturated fat, and dietary cholesterol was related directly to CHD mortality, although percentage of calories from fat was inversely related to total mortality, cancer mortality, and stroke mortality (McGee et al. 1985).

The Western Electric Study examined diet, serum cholesterol, and other variables in 1,900 middle-aged men, who were examined at entry, 1 year later, and 20 years later. Changes in the intake of saturated fat and dietary cholesterol between entry and 1-year visits were positively related to change in the level of serum cholesterol. The dietary data collected at the first two visits were averaged to provide baseline estimates of intake for the followup study analysis. Results showed that the 19-year risk for death from CHD was inversely related to polyunsaturated fat intake and positively related to dietary cholesterol intake. These correlations persisted after adjustment for baseline serum cholesterol, body mass index, systolic pressure, cigarette smoking, monthly alcohol intake, and age (Shekelle et al. 1981). After 25 years of followup, dietary cholesterol was

still positively and independently related to risk for death from CHD (Shekelle and Stamler 1988).

The Ireland-Boston Heart Study reported within-population analyses showing that individuals who died of CHD had a higher intake of saturated fatty acids and cholesterol and a lower intake of polyunsaturated fatty acids. Mean total fat intake was higher (39.4 percent vs. 38.5 percent) in the group who died of CHD, but the difference was not statistically significant. Fiber intake was significantly lower among those who died of CHD (Kushi et al. 1985).

Although these epidemiologic studies have shown that diet, particularly the amount and type of fat in the diet, influences the level of plasma cholesterol, other studies of individuals within populations, such as Framingham, Tecumseh, and Evans County, have failed to find any association of diet with plasma cholesterol or CHD (Kannel and Gordon 1970; Nichols et al. 1976; Cassel 1971; Gordon et al. 1981).

Difficulties in establishing a consistent correlation between diet and plasma cholesterol in individuals within a given population (short of such extremes as comparing vegetarians with the general public) have been attributed to several factors. First, most methods used for measuring habitual dietary patterns in free-living populations have a high degree of technical error (Bingham 1982). Daily variability in dietary intakes of individuals is greater than the variability among individuals. Hence, methods that measure dietary intake only over 1 day, as was done in Puerto Rico (Garcia-Palmieri et al. 1980), Honolulu (Kato et al. 1973), and Tecumseh (Nichols et al. 1976), can result in considerable misclassification of individuals on the basis of long-term dietary patterns (Liu et al. 1978).

Intake of fat, especially saturated fat, and cholesterol tends to be uniformly high in Western industrialized countries. Under such circumstances, possible fallacies may arise (Rose 1985). If nearly everyone in a population is exposed to a causal agent such as smoking or high saturated fat intake, then the presence of disease in an individual will appear to be attributable to individual genetic and personal characteristics, and traditional case-control and cohort methods will fail to identify the causal agents. Under these circumstances, causal agents are better revealed by differences between populations or by contrasting changes within populations over time (Rose 1985).

Other problems arise from the variability and error in measurement of factors such as plasma cholesterol. These difficulties weaken considerably

any attempt to correlate diet with other CHD indices (Liu et al. 1978). Conversely, epidemiologic correlations based on group averages of populations, such as the international comparisons cited earlier, tend to overestimate the true effect (McGill, McMahn, and Wene 1981). Thus, the true contribution of diet to plasma cholesterol levels probably lies somewhere between the estimates obtained in comparisons between groups and between individuals within a group.

Animal Studies

Animal models extend the observations made in humans by providing opportunities to explore directly mechanisms by which dietary factors mediate the development, progression, and regression of atherosclerotic lesions. Such studies often cannot be done in humans because the disease develops slowly over a long period of time, and techniques to measure the severity of the disease carry risk and have technical limitations. The advantages and disadvantages of the use of various animal models in atherosclerosis research have been reviewed (Jokinen, Clarkson, and Prichard 1985). Because no single animal model can duplicate the range of human arterial lesions that develop over long periods of time, several animal species have been used, depending on the mechanism to be investigated. These species vary in the natural occurrence and sensitivity to induction of experimental atherosclerosis.

Hyperlipidemia, which leads to the development of atherosclerosis, is readily produced in rabbits, pigeons, chickens, turkeys, Japanese quail, pigs, and some nonhuman primates by feeding diets high in cholesterol and saturated fats. Dogs and rats have generally been considered to be resistant to both naturally occurring and experimentally induced atherosclerosis, although, even in these species, advanced atherosclerotic lesions have been produced by adding to the diet cholesterol and coconut oil (dogs) and cholesterol and cholic acid (rats). Of all the animal models, many breeds of pigs and several species of nonhuman primates tend to resemble humans most closely in lipoprotein patterns and the pathologic components of the lesion (Jokinen, Clarkson, and Prichard 1985).

For example, studies in miniature pigs fed hog chow supplemented with cholesterol and either lard or beef fat showed elevations in plasma cholesterol. Myocardial infarctions were observed, and the diet-induced atherosclerosis was very similar to the proliferative lesions of human atherosclerosis. As in humans, individual variability in response to diet was observed (Mahley 1979).

Nonhuman primates have several characteristics that make them valuable as animal models: They are phylogenetically close to human beings; they develop arterial lesions similar to those seen in humans; and dietary manipulation can produce hyperlipidemia that, in some species, resembles that of humans. Some nonhuman primates develop atherosclerosis in their natural habitat, but their lesions are minimal compared with monkeys that consume diets like humans consume in Western societies. Both human and nonhuman primates are variable in their response to dietary cholesterol and subsequent amount of atherosclerosis that develops. Atherogenic diets—high in saturated fatty acids and dietary cholesterol—have reportedly been associated with myocardial infarction in rhesus monkeys and cynomolgus monkeys (Jokinen, Clarkson, and Prichard 1985). Baboons are apparently relatively resistant to diet-induced hyperlipidemia in comparison with other nonhuman primates and rabbits (McGill, McMahn, Kruski, Kelley, et al. 1981), but they develop experimental atherosclerosis, which is positively associated with LDL cholesterol concentrations and inversely associated with HDL cholesterol concentrations (McGill, McMahn, Kruski, and Mott 1981).

Although much of the diet-induced atherosclerosis in animals has been achieved with extreme diets and is thus not directly applicable to humans, some studies illustrate the effects of more moderate diets. Rhesus monkeys fed diets resembling the typical American diet compared with those fed a "prudent" ration reduced in calories, cholesterol, fat, and saturated fat had much higher cholesterol levels and more frequent and more severe atherosclerotic lesions. The lesions seen in the animals fed the average American regimen resembled those seen in autopsy examination of the coronary arteries and aorta of young adult Americans (Wissler et al. 1983). Cholesterol feeding of rhesus monkeys—at levels that do not elevate plasma cholesterol above those achieved on a cholesterol-free diet—may also stimulate atherosclerosis (Armstrong, Megan, and Warner 1974).

Regression of diet-induced atherosclerosis by the reduction of serum cholesterol to normal levels has been demonstrated in pigs, dogs, fowl, and nonhuman primates (Vesselinovitch and Wissler 1978). Extensive investigation of lesion regression has been conducted in rhesus monkeys. Over a dozen studies in at least five centers found that lesions undergo substantial regression on cholesterol lowering regimens (Wissler and Vesselinovitch 1984; Malinow et al. 1983). Rhesus monkeys fed rations containing 25 percent peanut oil and 2 percent cholesterol or 25 percent coconut oil-butter fat and 2 percent cholesterol for 12 to 14 months developed severe

hyperlipidemia and aortic and coronary artery atherosclerosis typical of advanced atherosclerosis in humans (Vesselinovitch and Wissler 1978). A subsequent change to a 12- to 14-month diet in which calories, cholesterol, and fat were reduced to resemble levels recommended by the American Heart Association resulted in a prompt and sustained low serum cholesterol level and a substantial arrest and reversal of advanced aortic and coronary atherosclerosis. Similar evidence of regression was seen when cholestyramine was added either to the low-fat, low-cholesterol diet or to the atherogenic diet.

Regression of atherosclerosis has also been demonstrated in swine. Advanced atherosclerosis was produced by a combination of mechanical injury and a 4-month high-cholesterol, high-fat diet. Fourteen months after the animals were returned to their normal mash diet, significant regression had occurred (Fritz et al. 1976).

A new animal model for endogenous hypercholesterolemia has become available through the discovery of a strain of rabbits designated Watanabe heritable hyperlipidemic (WHHL). In these animals, severe hypercholesterolemia results from a single genetic defect, and fulminant atherosclerosis occurs despite the ingestion of a cholesterol-free diet. The WHHL rabbit has the same defect in the LDL receptor gene that occurs in persons with familial hypercholesterolemia (Goldstein, Kita, and Brown 1983).

Effects of Fatty Acids on Thrombosis

Because atherosclerosis is a multifactorial disease, diet may have effects on CHD that are not mediated through plasma cholesterol and lipoprotein levels. Arterial thrombosis is induced by vascular injury and the response of blood platelets. Dietary studies have shown that platelet reactivity is associated with the fatty acid composition of the diet.

Epidemiologic studies in France and Great Britain (Renaud 1987) have shown that clotting activity of platelets and their response to thrombin-induced aggregation were more closely related to the intake of saturated fatty acids than to serum cholesterol levels. Intervention studies also show that replacement of dietary saturated fat with polyunsaturated vegetable oils is associated with decreased platelet aggregation and clotting activity (Hornstra 1980; Renaud 1987). In animal studies, most saturated fatty acids were found to induce platelet aggregation and arterial thrombosis and to increase plasma cholesterol levels, whereas unsaturated fatty acids tended to reduce platelet aggregation and also tended to lower plasma cholesterol levels (Goodnight et al. 1982).

While long-chain saturated fatty acids tend to induce thrombosis in animal studies, long-chain unsaturated dietary fats are either neutral or antithrombotic. In rats, the most thrombogenic fatty acid is stearic acid (Renaud 1969) despite its apparent neutral effect on serum cholesterol (Keys 1967; Bonanome and Grundy 1988). One study in rats showed that palm oil (containing about 50 percent saturated fat) was similar to polyunsaturated vegetable oils in thrombotic tendency. The reasons for this anomaly are not clear but might be related to some other constituents in palm oil that counteract the thrombogenic properties of the saturated fatty acids (Hornstra and Lussenberg 1975). Oleic acid, the major dietary monounsaturated fatty acid, seems to have little or no effect on thrombosis (Goodnight et al. 1982). The mechanisms by which dietary fatty acids may affect thrombosis are poorly understood but may be related to prostaglandin metabolism (Goodnight et al. 1982).

Linoleic acid, the most common dietary polyunsaturated fatty acid, is the precursor of arachidonic acid and prostaglandins that regulate platelet aggregation and, accordingly, thrombogenesis. Prostacyclin (PGI_2), for example, has been shown to be the most potent *in vivo* vasodilator and antiaggregatory agent in animals and in humans, and to inhibit white cell adherence to vessel walls, nylon fibers, and endothelial monolayers *in vitro* (Moncada 1982). Its effects are counterbalanced by another prostaglandin, thromboxane A_2, a powerful vasoconstrictor and platelet aggregator. It is theorized that arterial thrombosis may depend partly on the ratio between these two prostaglandins.

Linoleic acid is also incorporated directly into membrane phospholipids, thereby altering the structure and the function of the platelet membrane. This process affects the fluidity and, therefore, the permeability of the cells and influences processes including thrombus formation. Contrary to expectation, increasing the dietary intake of linoleic acid does not increase the synthesis of arachidonic acid in platelet membranes, perhaps because of competitive inhibition of certain enzymes. Increased dietary intake of linoleic acid, however, has been associated in humans with significant reduction in platelet aggregability (Hornstra et al. 1973; Jakubowski and Ardlie 1978).

Fish Oils. The consumption of fish and other marine animals may confer special benefits in reducing CHD mortality (Kromhout, Bosschieter, and Coulander 1985). The fatty acids in these species are rich in long-chain polyunsaturated fatty acids of the omega-3 series, particularly eicosapentaenoic acid and docosahexaenoic acid. Most polyunsaturated fatty acids commonly found in vegetables belong to the omega-6 series. The differ-

ences in chemical structure between omega-3 and omega-6 fatty acids affect several metabolic processes related to blood platelet function, thrombosis, and lipid metabolism that may relate to CHD.

Early observations in Greenland suggested that Eskimos who habitually consumed large quantities of fish and other marine animals had a low incidence of CHD despite a high fat and cholesterol intake (Kromann and Green 1980; Dyerberg and Jorgensen 1982). Similar observations have been made in other maritime communities (Kagawa et al. 1982; Yotakis 1981). Subsequent examinations of Greenland Eskimos showed that they have lower serum triglycerides and cholesterol levels and higher HDL levels than Danes consuming a Western-type diet. The blood of Eskimos also takes longer to clot. It has been hypothesized that the low incidence of atherosclerosis and thrombosis in Greenland Eskimos is partly attributable to the high proportion of omega-3 fatty acids in traditional Eskimo diets (Dyerberg and Jorgensen 1982).

A recent prospective study of Dutch men showed that 20-year mortality from CHD was reduced by 50 percent in men who consumed at least 1 oz of fish per day (Kromhout, Bosschieter, and Coulander 1985). Whether the benefit shown in this study can be attributed to omega-3 fatty acid intake or to some other factor associated with fish consumption is uncertain. Men who consumed low-fat fish derived the same benefit as those consuming higher fat varieties. The effect of fish consumption on CHD mortality has been examined in other large prospective studies. One found no relationship (Vollset, Heuch, and Bjelke 1985). In another, fish consumption at entry into the study was inversely associated with 25-year risk of CHD (Shekelle et al. 1985), and in the third study, CHD death rate was higher in the group that consumed no fish compared with the group that consumed fish (Curb and Reed 1985).

Early clinical experiments in which different sources of fat were given showed that fish oils were at least as effective as polyunsaturated vegetable oils in reducing serum cholesterol levels. More recently, fish oils have been studied in relation to their effects on lipoprotein metabolism and other CHD parameters. Clinical studies in normal volunteers and patients with hypertriglyceridemia who were fed diets enriched in omega-3 fatty acids generally showed variable reductions in total cholesterol and LDL cholesterol. In some cases, LDL increased; HDL levels were either unchanged or increased (Phillipson et al. 1985; von Lossonczy et al. 1978). The most consistent and striking effect of fish oil on lipoprotein metabolism has been a reduction in triglyceride and VLDL levels, an effect not observed with vegetable oils (von Lossonczy et al. 1978; Saynor, Verol, and Gillott 1984; Harris and Connor 1980; Nestel et al. 1984).

Most experimental studies have used rather large amounts of fish (200 to 300 g/day) or fish oil (more than 20 g/day). One study sought to determine the effects of more moderate fatty fish consumption. One hundred male volunteers each consumed 3 oz or more of fatty fish at least twice a week for 3 months and little or no fatty fish for another 3 months. Mean plasma triglyceride concentration decreased significantly, by nearly 7 percent, on the fish diet. There were no significant changes in plasma total cholesterol, HDL, or LDL (Fehily et al. 1983).

Another line of investigation involves studies on the effects of fish oils on the vessel wall. A 6-week study in seven healthy men indicated that diets supplemented with 18 g of fish oil per day may have anti-inflammatory properties that could diminish infiltration of lipids in the vessel wall in response to tissue injury (Lee et al. 1985).

In another study, the effect of cod liver oil on the development and progression of atherosclerosis in a hyperlipidemic swine model was assessed. All animals were fed an atherogenic diet, 7 were given a cod liver oil supplement, and 11 controls did not receive the supplement. Significantly less disease was seen in coronary arteries from the animals fed cod liver oil despite severe hyperlipidemia. Differences in the extent of coronary atherosclerosis were not related to differences in plasma lipid levels. Prostaglandin synthesis from arachidonic acid was markedly reduced in the oil-fed group (Weiner et al. 1986).

Role of Other Dietary Factors in CHD

Obesity

Obesity is associated with many important CHD risk factors such as hypertension, low levels of HDL, elevated plasma glucose levels, high blood cholesterol, and hypertriglyceridemia (see chapter on obesity) and hence increases the risk for CHD. Data from the Framingham Heart Study, in which 5,209 men and women were observed for 26 years for the development of CHD, showed that relative weight was a significant independent long-term predictor of CHD incidence, especially in women (Hubert et al. 1983). The association of weight with CHD incidence was most pronounced in those under age 50. Weight gain in adulthood conveyed an added risk. Total calorie consumption has been associated with CHD prevalence in international comparisons. However, studies within populations have shown that a greater caloric intake is associated with a reduced risk for CHD, but increased body weight is associated with increased CHD risk. This suggests that increased energy expenditure, which would tend to increase caloric requirements, may be related to reduced risk for CHD

(Gordon et al. 1981). Current evidence suggests that leanness and avoidance of weight gain before middle age are advisable goals in the prevention of CHD for most men and women (Hubert et al. 1983; Bray 1983). In addition, weight loss often improves the status of other risk factors such as diabetes and high blood pressure (see respective chapters).

Alcohol

The relationship between alcohol consumption and CHD is complex (Hulley and Dzvonik 1984). High alcohol intake has been associated with CHD deaths, as well as deaths from other causes (see chapter on alcohol), but some epidemiologic studies have shown an association between light to moderate alcohol intake and a decreased incidence of CHD (LaPorte, Cresanta, and Kuller 1980). In these studies, light intake is generally considered to be more than one drink per month but fewer than one per day and moderate intake is 1 to 3 oz per day. Numerous cross-sectional studies have shown positive correlations of alcohol intake with HDL cholesterol levels (Castelli et al. 1977), with the response related to doses of alcohol ranging from 0 to 3 oz per day (Ernst et al. 1980; Haskell, Camargo, and Williams 1984). Thus, it has been postulated that the decreased incidence of CHD in those who consume moderate amounts of alcohol might be attributable to an ethanol-induced increase in HDL cholesterol levels. Recent reports suggest, however, that moderate alcohol consumption induces compositional changes in HDL that are inconsistent with current understanding of the anti-atherogenic properties of HDL subfractions, because it increases HDL-3 levels but not those of the antiatherogenic HDL-2 subfractions (Haskell, Camargo, and Williams 1984). The significance of alcohol-induced changes in apoprotein fractions (Camargo et al. 1985) is also uncertain. Since heavy drinking has numerous adverse effects, including several on the cardiovascular system (Burch and Giles 1971), the use of alcohol, even in moderate quantities, for its possible beneficial effects on CHD is not recommended.

Carbohydrate

Major dietary carbohydrates include starch, fiber, and sugars. Customary diets containing 60 to 70 percent of calories from starch, such as those consumed in Asian countries, are associated with low plasma cholesterol levels and a low risk for CHD (Keys 1970). Such diets tend to be relatively high in fiber and very low in fat and thus have been widely advocated for the treatment of hypercholesterolemia. Epidemiologic studies cited previously have shown that intake of starch (Gordon et al. 1981) and intake of fiber (Kushi et al. 1985) were negatively related to CHD. Furthermore, the effect of starch did not appear to be an indirect effect of lowered fat intake. On the

other hand, total carbohydrate was inversely associated with HDL cholesterol—and positively associated with LDL cholesterol—in cross-sectional studies, but these correlations were very weak (U.S.–U.S.S.R. Steering Committee 1984). Some experimental studies have shown that hypertriglyceridemia can be induced with high-starch (70 percent of calories) diets, but the effect is temporary and appears to occur mainly after changing from a high-fat to a high-carbohydrate diet (Little, McGuire, and Derksen 1979; Ahrens 1986).

The water-soluble fiber fractions, as found in oat bran, guar gum, psyllium seeds, certain beans, and pectin, for example, have been shown to have hypocholesterolemic effects in humans (Jenkins et al. 1975; Kirby et al. 1981; Anderson et al. 1984). Addition of fiber to high-carbohydrate diets has been reported to prevent triglyceride elevation on high-carbohydrate diets (Anderson, Chen, and Sieling 1980). A high fiber intake is often associated with low-fat diets, and the net effect may provide additional benefits in cholesterol reduction.

The role of sugars in CHD is unclear. A high sucrose intake has been claimed to play a causal role in CHD (Yudkin and Roddy 1964), but there is little evidence to sustain this view. Although some animal studies have suggested that substitution of sucrose for other sources of calories increases atherogenesis, the major epidemiologic studies of diet and CHD risk have failed to identify an association with sucrose intake (Glinsmann, Irausquin, and Park 1986). Sucrose and fructose have been shown experimentally to promote hypertriglyceridemia in susceptible (carbohydrate-sensitive) individuals. Men appear to be more susceptible than premenopausal women, older persons more than younger persons, and hypertriglyceridemic persons more than normal triglyceridemic persons (Reiser et al. 1981; Coulston et al. 1987). Recommended treatment for patients with elevated plasma triglyceride and VLDL levels includes weight control, alcohol restriction, increased physical activity, and restriction of saturated fat and cholesterol. Substitution of carbohydrate for fat is favored; although increasing dietary carbohydrate may raise triglycerides, the response is usually transient and triglyceride levels (and VLDL) later decline (NIH 1983).

Protein

In animals, high protein levels accelerate the formation of atheromatous lesions. Casein appears to be more atherogenic than soy protein (Kritchevsky 1979). Recent studies on rabbits showed that LDL receptors were suppressed after feeding a cholesterol-free diet composed of carbohydrate and casein (Goldstein, Kita, and Brown 1983). The low levels of plasma

cholesterol observed among strictly vegetarian populations (West and Hayes 1968) may be attributable to the quantity and quality of protein. However, their diets also tend to be lower in saturated fat and cholesterol and higher in complex carbohydrate and fiber than diets of lacto-ovo vegetarian or nonvegetarian groups (Sacks et al. 1985; Sacks et al. 1975; Burslem et al. 1978). Studies involving the substitution of soy protein and other vegetable proteins for animal protein in the diets of hyperlipidemic patients have shown a marked reduction in serum cholesterol levels (Descovich et al. 1980; Sirtori, Gatti, and Mantero 1979) but only a small change in persons with normal plasma cholesterol levels (Forsythe, Green, and Anderson 1986). The mechanism for these effects has not been established.

Coffee

Evidence relating coffee consumption to increases in serum total and LDL cholesterol levels or to CHD has been inconsistent. Recent reports from cross-sectional epidemiologic studies in Norway, Israel, and the United States have shown an independent, positive, linear association with serum cholesterol, nearly all of which can be accounted for by LDL cholesterol (Thelle, Arnesen, and Forde 1983; Kark et al. 1985; Williams et al. 1985). One study associates coffee drinking (five or more cups per day) with increased risk for CHD (LaCroix et al. 1986). The effect of coffee drinking on serum cholesterol has also been examined in controlled experiments. Coffee taken in amounts of six cups or more per day has been reported to increase serum cholesterol levels (Arnesen, Forde, and Thelle 1984). Decaffeinated coffee has also been reported to be associated with such elevations in some studies (Naismith et al. 1970), although not all (Mathias et al. 1985); in most studies, tea did not affect blood cholesterol levels (Prineas et al. 1980; Little et al. 1966; Kark et al. 1985). Such findings would appear to rule out caffeine as a causal factor (Klatsky et al. 1985). Other studies have found no association between coffee and cholesterol (Kovar, Fulwood, and Feinleib 1983) or different effects in men and women (Shirlow and Mathers 1983). Inconsistencies in the results of different studies have been attributed to confounding effects of cigarette smoking and diet as well as to variations in method of preparation. At present, the information regarding the relationship between coffee intake and blood cholesterol levels is insufficient to allow conclusions to be drawn.

Vitamins and Minerals

The relationship of micronutrients (vitamins and minerals) to cardiovascular disease risk has been studied to a much lesser extent than the macronutrients, except in the case of sodium and hypertension (see chapter on high blood pressure). Although dietary patterns that promote high plasma cho-

lesterol levels would be expected to be different in micronutrient content from dietary patterns associated with low plasma cholesterol levels, there is at present no strong evidence linking vitamin and mineral intake to high plasma cholesterol levels or to CHD.

Vitamin E. Vitamin E was once widely advocated for prevention and treatment of CHD (Shute and Taub 1972). Early studies supporting these claims were marred by lack of controls and doubtful diagnosis of CHD, and subsequent studies have failed to confirm them (Hodges 1979).

Vitamin C. Vitamin C (ascorbic acid) deficiency results in scurvy, which is sometimes associated with cardiac abnormalities. Observations that high doses of ascorbic acid reduce serum cholesterol in cholesterol-fed rabbits and guinea pigs have led to the idea that high doses of vitamin C might reduce blood cholesterol levels in patients with elevated levels. To date, uncontrolled clinical trials have yielded conflicting results, and there is no convincing evidence that vitamin C is related to CHD (Hodges 1979; Anonymous 1984).

Thiamin. Thiamin deficiency leads to beriberi, and congestive heart failure is associated with the "wet" form of this disease. Cardiac impairment is generally completely reversible with appropriate administration of thiamin. Thiamin deficiency is uncommon in the United States today, largely because of effective food enrichment programs. Nevertheless, inadequate intakes are sometimes observed among persons with faulty dietary patterns or among hospitalized patients who have been ill for prolonged periods (Hodges 1979).

Niacin. Niacin (nicotinic acid) in pharmacologic (large) doses far in excess of its requirements for vitamin function exerts HDL-raising and lipid-lowering effects, principally in the VLDL fraction (Fredrickson and Levy 1972). The long-term followup of patients treated with niacin in the Coronary Drug Project (as mentioned in the section on Efficacy of Dietary Interventions in CHD) showed significant reduction in coronary and total mortality. In a recent study, nicotinic acid in combination with colestipol and a cholesterol-lowering diet slowed progression of coronary artery lesions in men who had undergone coronary bypass surgery (Blankenhorn et al. 1987). There is no evidence, however, that niacin ingested at physiologic levels exerts any protective effect against factors that elevate blood lipid levels.

Calcium. High serum cholesterol levels have been observed in calcium-deficient rats, and calcium-deficient rabbits and rats fed an atherogenic diet

significantly increased their serum cholesterol and triglyceride levels over control animals fed a stock ration. Supplementation of experimental diets with calcium reduced the plasma lipid levels to near or below the levels of the control group but also was associated with increased incidence of kidney and heart lesions (Mertz 1979). In humans, an uncontrolled study of 10 hyperlipidemic subjects showed that the addition of 800 mg of calcium (as calcium carbonate) daily over 1 year reduced blood cholesterol levels by 25 percent, and another uncontrolled study in older women showed that 750 mg of daily calcium supplementation reduced cholesterol levels 36 mg/dl from a mean 266 mg/dl (Mertz 1979). Such observations remain to be confirmed by controlled clinical trials. The possible role of calcium continues to be a subject of investigation (Renaud 1987).

Magnesium. Magnesium therapy may correct some cardiac arrhythmias, although it is uncertain whether magnesium deficiency causes them (Laban and Chorbon 1986). Magnesium and calcium may interact with dietary fat in the promotion of atherosclerotic lesions. In animals, the increased incidence of kidney and heart lesions associated with very high intake of calcium is reduced or eliminated by high levels of dietary magnesium. This protective effect, however, was evident only at very high dietary calcium levels (0.6 percent by weight) and only in the presence of elevated serum cholesterol (Mertz 1979).

Copper. Copper deficiency has been associated with cardiovascular damage and abnormalities in cholesterol metabolism in animals. In one human study, copper deficiency was shown to produce a rise in plasma cholesterol concentrations, perhaps because copper is a cofactor for enzymes involved in cholesterol synthesis and lipoprotein degradation (Klevay et al. 1984).

Zinc. Because dietary zinc increases the copper requirement (Sandstead et al. 1982), it has been postulated that a high ratio of zinc to copper in the modern American diet could be a risk factor for CHD (Klevay 1975). Long-term zinc supplementation in children, however, has not been associated with any detectable rise in plasma cholesterol levels (Mertz 1979). Although administration of high-dose zinc supplements has been reported to reduce blood levels of HDL cholesterol in human subjects (Hooper et al. 1980), more physiologic doses had no effect on blood lipid values (Crouse et al. 1984).

Selenium. In China, very low levels of dietary selenium have been associated with juvenile cardiomyopathy (Chen et al. 1980). Although a causal role has not been firmly established, epidemiologic studies have also suggested a role for selenium deficiency in CHD. Cardiovascular disease

mortality rates are significantly lower in areas of the United States with high selenium soils. In Sweden, the lowest death rate from cardiovascular diseases was reported in the city of Malmo, which has a higher selenium content of tap water than Stockholm or Gothenburg. Other studies, however, have failed to demonstrate any differences in selenium concentrations in serum and urine of patients with hypertension or in the coronary arteries of persons who died from myocardial infarction and atherosclerosis as compared with control groups (Thomson and Robinson 1980).

Human platelets contain more selenium than other human tissues, suggesting that selenium deficiency may affect thrombosis. Experimental selenium deficiency reduces platelet antioxidant activity, and this activity is restored by selenium supplementation (Levander 1982).

A low serum selenium concentration has been associated with increased clinical manifestations of CHD in a prospective study in Finland (Salonen et al. 1982), yet a subsequent longitudinal case control study in another Finnish population showed that levels of selenium in blood were highly correlated to blood levels of eicosapentaenoic acid. Because fish is a major source of selenium in the Finnish diet, it is difficult to distinguish the antiatherogenic effects of selenium from those of polyunsaturated fatty acids in these studies (Miettinen et al. 1983).

Efficacy of Dietary Intervention in CHD

Clinical studies in free-living populations over long periods of time have been conducted to determine the potential of dietary change to influence blood cholesterol and CHD. In general, large-scale diet studies have achieved 10 to 15 percent blood cholesterol reductions (Rifkind et al. 1983), compared with about 25 percent in controlled metabolic ward studies, probably because of less rigorous adherence to the diet. For example, the *National Diet-Heart Study,* in which the experimental diets contained either 30 percent fat with 15 percent polyunsaturated fatty acids or 40 percent fat with 18 to 20 percent polyunsaturated fatty acids, showed that reductions in serum cholesterol were proportional to the degree of adherence to the diets and that excellent adherence produced an average serum cholesterol reduction of about 13 percent in free-living adults (National Diet-Heart Research Group 1968). The *Oslo Study* achieved 13 to 15 percent reductions (Hjermann et al. 1981).

The *Multiple Risk Factor Intervention Trial* (MRFIT) was a randomized primary prevention trial to test the effect of a multifactor intervention program on CHD mortality in 12,866 men in the upper 10 percent of risk on

account of their levels of cigarette smoking, blood cholesterol, and blood pressure. It resulted in a 5 percent reduction in blood cholesterol in the special care (diet and other intervention) group and 3 percent in the usual care group, suggesting that many people were making changes in their diets even in the absence of direct intervention (MRFIT Research Group 1982). The results of this study were further complicated because of the cholesterol raising effect of diuretics in the hypertensive group and because the men who stopped smoking were less successful in weight control than the men who continued to smoke. Greater reductions in cholesterol were achieved among MRFIT men with elevated cholesterol who were nonhypertensive and nonsmokers over the 6-year intervention trial (Dolecek et al. 1986).

The impact of dietary-induced cholesterol lowering on CHD incidence has also been assessed in several other clinical trials. They have generally reported some reduction in CHD incidence and, taken together, have shown a consistent relationship between degree of cholesterol lowering and CHD risk reduction (Mann and Marr 1981). However, the ability to draw definite conclusions from such trials is made difficult by problems such as small sample size, failure to randomize subjects into treatment and control groups, failure to mask treatment assignment (a pervasive and essentially insoluble problem in all large-scale diet studies), and inadequate followup (Cornfield and Mitchell 1969), as well as the type of problems cited above in the MRFIT.

The Finnish Mental Hospital Study was a trial conducted in two hospitals, one of which replaced whole milk and butter with a skim milk emulsion containing soy oil and a high polyunsaturated margarine while the other retained the usual diet. After 6 years, the diets were reversed, and the study continued an additional 6 years. The study involved the total hospital population in each site and encompassed 29,217 person-years of experience. Results showed that mean serum cholesterol values were reduced 12 to 18 percent and that death rates from all cardiovascular diseases for men and women were 39 percent and 14 percent lower, respectively, on the experimental diet. All-cause mortality for men was 12 percent lower on the experimental diet, but for women it was similar on both diets (Miettinen et al. 1972). The authors attribute the findings in women to an exceptionally low death rate experienced in one hospital during the control period following transfer of chronic cases to another hospital.

The dietary trial conducted in a *Veterans Administration domiciliary facility* in Los Angeles used a double-blind experimental design in which 846 middle-aged and older male participants were randomly assigned to either a control or a cholesterol-lowering diet group. Although the results

suggested that a diet low in saturated fats and cholesterol and high in polyunsaturated fats reduced coronary events, the experimental and control groups did not differ in overall mortality (Dayton et al. 1969). The excessive mortality rate from cancer observed at first in the intervention group has been reinterpreted, and subsequent analysis of the data and those of four similar trials has found no association of cholesterol-lowering diets with any increase in either cancer incidence or mortality rate (Ederer et al. 1971).

The Oslo Study was a primary prevention trial designed to test whether lowering serum lipids by dietary measures and smoking reduction would reduce incidence of new CHD in 1,232 high-risk participants studied over 5 years. The dietary intervention consisted of advice to substitute polyunsaturated fats for saturated fat, to increase intake of whole grain cereals, and to reduce energy intake (in cases of elevated triglyceride levels). At the completion of the trial, mean serum cholesterol levels were reduced 13 percent in the intervention group, and the combined incidence of myocardial infarction and sudden death was significantly reduced in the treated group by 47 percent compared with controls. Statistical analysis identified the predominant effect as the decrease in plasma total cholesterol by diet (Hjermann et al. 1981).

It is widely accepted that diet is a major cause of high blood cholesterol and high LDL levels and that these play a causal role in atherosclerosis. Evidence from animal-experimental studies has shown that reducing diet-induced hypercholesterolemia, whether by diet or other means, reverses the atherosclerotic process. The consistency of these studies supports the conclusion that blood cholesterol lowering *per se* rather than a specific action of the cholesterol-lowering agent produces the benefit. Hence, consideration of evidence from the clinical trials using drugs to lower cholesterol is relevant to assessment of the efficacy of dietary intervention to lower CHD risk.

The Coronary Drug Project assessed the long-term efficacy of five lipid-influencing drugs in 8,341 middle-aged men. Treatment with niacin significantly decreased nonfatal recurrent myocardial infarction but not coronary mortality during the treatment phase of the study (Canner et al. 1986). However, followup at 9 years beyond the study demonstrated that total mortality was reduced in the niacin-treated group.

The *Lipid Research Clinics Coronary Primary Prevention Trial* (LRC-CPPT) was a double-blind placebo-controlled clinical trial in high-risk middle-aged men to test the efficacy of lowering cholesterol levels for the

primary prevention of CHD. The LRC recruited 3,806 men with primary hypercholesterolemia, free of symptomatic CHD at entry, but at high risk for CHD due to elevated LDL cholesterol levels. The study participants were randomly assigned to two groups that were similar in baseline characteristics. The treatment group received the bile acid sequestrant cholestyramine, and the control group received a matched placebo. Although the LRC-CPPT was not designed as a dietary intervention trial, both groups followed a diet plan calculated to achieve a 3 to 5 percent reduction in plasma cholesterol. A net reduction in plasma cholesterol of 9 percent in the treatment group resulted in a 19 percent reduction in fatal and nonfatal myocardial infarctions. Corresponding reductions in angina pectoris, electrocardiographic abnormalities, and bypass surgery were also found in the treatment group (Lipid Research Clinics Program 1984a, 1984b).

The *Helsinki Heart Study* reported substantial benefit in reducing the incidence of CHD by drugs (Frick et al. 1987). The study was a randomized double-blind placebo-controlled primary prevention trial involving 4,081 middle-aged men in a 5-year followup. To qualify, participants had to have LDL plus VLDL cholesterol concentrations equal to or greater than 200 mg/dl. Treatment with gemfibrozil resulted in several changes in plasma lipids: modest (8 percent) reductions in total and LDL cholesterol, a more pronounced (35 percent) decrease in triglycerides, and a moderate (greater than 10 percent) increase in HDL cholesterol. At the end of 5 years, nonfatal myocardial infarction alone was reduced by 37 percent and CHD mortality alone by 26 percent. These results were obtained despite an incidence of CHD in the placebo group that was considerably lower than expected. Total mortality, however, was not significantly affected.

Another approach to assessing benefit of cholesterol lowering is to measure changes in atherosclerotic lesions. Early studies in nonhuman primates demonstrated regression of atherosclerotic lesions with cholesterol-lowering diets or with drugs (Armstrong, Warner, and Connor 1970; Wissler and Vesselinovitch 1984). The effect of cholesterol lowering on coronary arteries can now be assessed with serial angiograms in humans.

In the *Leiden Study*, 39 men with stable angina pectoris and advanced arteriosclerosis, as assessed by coronary angiography, were prescribed a vegetarian diet containing a polyunsaturated-to-saturated-fatty-acid ratio of 2, and dietary cholesterol of less than 100 mg/day. Mean serum cholesterol decreased 10 percent from a baseline value of 267 mg/dl. Since there was no control group, the effect of dietary intervention could not be assessed directly. However, angiographic examination performed after 24 months showed no progression of disease in the group that had maintained lower

values for the ratio of total cholesterol to HDL cholesterol throughout the trial or who significantly lowered their ratio of total cholesterol to HDL cholesterol (Arntzenius et al. 1985).

Another double-blind placebo-controlled trial, the *NHLBI Type II Coronary Intervention Study,* evaluated the efficacy of reduction in cholesterol levels induced by cholestyramine on progression of coronary artery disease. The rate of progression, defined angiographically, was compared in patients treated with cholestyramine plus diet with that of patients treated with placebo plus diet. When the relationship between coronary artery disease progression and lipid changes was examined independent of a specific treatment group, a significant inverse relationship was found between progression at 5 years and the combination of an increase in HDL and a decrease in LDL. These trends were observed in both the placebo-treated and the cholestyramine-treated group (Levy et al. 1984).

The *Cholesterol-Lowering Atherosclerosis Study* (CLAS) was a randomized placebo-controlled angiographic investigation of the ability of drugs (colestipol and niacin) and diet to reduce blood cholesterol levels and to cause regression of atherosclerosis in the coronary arteries. Participants were 162 men who had undergone coronary bypass surgery. The study reported 26 and 43 percent reductions in total blood cholesterol and LDL, respectively, in the treatment plus diet group compared with 4 and 5 percent reductions, respectively, in the placebo plus diet group. There was also a considerable increase in HDL and considerable decrease in triglycerides in the drug plus diet group. These changes were associated with significantly less progression of overall coronary disease in both the grafts and the native coronary arteries with some suggestive evidence of regression (Blankenhorn et al. 1987).

Despite some deficiencies in definition of lesions, control groups, and small numbers of patients, these coronary angiographic studies support the benefit of intervening with blood cholesterol reduction in the presence of established disease.

Aggregate Analysis of Clinical Trials of Blood Cholesterol Lowering

Many of the clinical trials of blood cholesterol lowering to prevent CHD have been hampered by small numbers and modest cholesterol lowering (Mann and Marr 1981; Oliver 1985). However, additional information has been obtained by evaluating them in aggregate.

Joint analysis of dietary trials has shown a linear relationship of cholesterol lowering to risk reduction, with a 1 to 1.5 percent reduction in relative risk

found for each 1 percent reduction in blood cholesterol (Hulley et al. 1981; Mann and Marr 1981). When the various drug studies are analyzed, the results are almost comparable, with a 2 percent reduction in risk resulting from a 1 percent reduction in cholesterol (Lipid Research Clinics Program 1984b). This relationship is close to that predicted from the results of prospective epidemiologic studies such as the Framingham study.

In the Helsinki Heart Study, a greater effect was observed: An 8 percent reduction in total cholesterol resulted in a 34 percent reduction in CHD incidence. This suggests that the moderate increase in HDL cholesterol and marked fall in triglycerides might also have contributed to the benefit (Frick et al. 1987).

Taken together, these clinical trials provide compelling evidence that lowering plasma cholesterol reduces CHD morbidity and mortality. However, the total mortality has generally not been reduced in these studies. A small increase in noncardiovascular deaths was observed in the Los Angeles Veterans Administration Trial, the Helsinki Mental Hospital Study, the WHO Clofibrate Trial, the LRC-CPPT (Oliver 1981; Lipid Research Clinics Program 1984a), and the Helsinki Heart Study (Frick et al. 1987). There is a lack of consistency in the various noncardiovascular causes of death in these studies; in some studies, more cancers have occurred, while in others, more accidental or violent deaths. In the drug trials, some of the observed mortality from various noncoronary causes may have been specific to the drug itself. One study has reported a significant reduction in total mortality. In the Coronary Drug Project, total mortality in the niacin-treated group was 11 percent lower than in the placebo group, a benefit that became evident during a 9-year followup after termination of the trial (Canner et al. 1986). This raises the possibility that the effect of cholesterol lowering on mortality takes longer to emerge than its impact on nonfatal heart attacks. The difficulties in showing an effect on total mortality may reflect the problem that no clinical trial to date has had a sample size sufficiently large to address this issue with adequate statistical power.

Implications for Public Health Policy

Dietary Guidance

General Public

High blood cholesterol is one of the three major modifiable risk factors for CHD. The principal nutritional factors identified with high blood cholesterol and the development of CHD are dietary fat, particularly saturated fatty

acids and cholesterol, and energy imbalance leading to obesity. Other dietary constituents, such as fiber or alcohol, may interact with these factors in ways that are not clearly understood.

The relationship of dietary fat and cholesterol to CHD is supported by extensive and consistent clinical, epidemiologic, metabolic, and animal evidence. These studies strongly indicate that the formation of atherosclerotic lesions in coronary arteries—contributing to the risk for CHD—is increased in proportion to levels of total and LDL cholesterol in blood, which, in turn, are increased by diets high in total and saturated fat but decreased by diets containing polyunsaturated and/or monounsaturated fat. International epidemiologic comparisons and migration studies have revealed strong associations of fat, especially saturated fat, intake to development of elevated blood cholesterol levels, atherosclerosis, and CHD. Evidence from studies within a given population has been less consistent but points in a similar direction. Dietary intervention trials in men with elevated blood cholesterol levels have demonstrated small but significant proportionate improvements such that each 1 percent reduction in total blood cholesterol is accompanied by about a 1.5 percent reduction in heart disease risk. Intervention to lower elevated blood cholesterol levels has been shown in both human and animal studies to reduce CHD risk and to slow lesion progression. Animal studies have shown lesion regression, and there is suggestive evidence from some clinical studies that this also occurs in humans.

Taken together, these studies provide strong support for recommendations for an overall considerable decrease in dietary fat intake by the general public from the present level of 37 percent of total caloric intake and decrease in saturated fat from the present level of about 13 percent of total caloric intake.

Although the effect of dietary cholesterol on blood cholesterol is somewhat weaker and more variable among individuals than that for dietary saturated fatty acids, a reduction in the amount of cholesterol consumed by the general public from present average levels of approximately 305 mg/day for women and 440 mg/day for men seems appropriate.

Obesity is associated with such CHD risk factors as elevated LDL and total blood cholesterol, lower HDL cholesterol, high blood pressure, and diabetes mellitus. It is also a significant independent predictor of CHD, especially in women and in persons under age 50. Thus, current evidence suggests that an overall decrease in the prevalence and severity of overweight in the population, through both a decrease in caloric intake and an

increase in caloric expenditure, is advisable on the basis of the relationship of obesity to heart disease risk.

Studies of animal protein, coffee, and sugar have shown variable associations with increased blood lipid levels, but present evidence of their relationship to CHD, if any, is too weak and insufficient to draw implications for changes in the consumption of these substances. Likewise, evidence from some studies that certain components of dietary fiber and omega-3 fatty acids from fish oils reduce blood cholesterol levels and heart disease risk is too preliminary to recommend changes in average intake of these substances. In addition, advice concerning vitamin and mineral supplements on the basis of their relationship to CHD is unwarranted.

Special Populations

There is a need to identify those individuals with high cholesterol levels, who are therefore at greatest risk. For individuals whose high total and LDL cholesterol levels warrant treatment, the first line of intervention is diet therapy. The recently released National Cholesterol Education Program guidelines on the treatment of high blood cholesterol in adults recommend that intensive dietary treatment should generally be carried out for at least 6 months. As indicated in this Report, only after that period of time, and if the cholesterol level remains significantly high, should the addition of drugs to the dietary regimen be considered. Even then, continuation of diet therapy can reduce the need for drugs and thus their risk of side effects and cost. Furthermore, studies in persons with CHD suggest that diets low in fat, saturated fat, and cholesterol can retard the progression of the disease, including recurrent heart attacks, and perhaps induce regression of atherosclerotic lesions. Persons with such high blood cholesterol levels should receive dietary guidance by qualified health professionals.

Adults with total cholesterol levels of 240 mg/dl or above (whose LDL cholesterol levels are also significantly elevated), and those with total cholesterol levels of 200 to 239 mg/dl with CHD or two or more CHD risk factors should begin a program of supervised dietary treatment. The NCEP guidelines recommend starting dietary therapy with a step-one diet, in which the intake of total fat is less than 30 percent of calories, saturated fat is less than 10 percent of calories, and cholesterol is less than 300 mg/day. If after 3 months on this diet cholesterol lowering is insufficient, the person should progress to a step-two diet, in which saturated fat is further reduced to less than 7 percent of total calories and cholesterol intake is further reduced to less than 200 mg/day.

Although in epidemiologic studies light to moderate alcohol consumption is associated with reduced heart disease risk, a cause-and-effect relationship has not been proved. Since heavy drinking has numerous adverse health consequences (see chapters on maternal and child nutrition and on alcohol), including several on the cardiovascular system, the use, even in moderate quantities, of alcohol for its possible beneficial effects on CHD is not recommended.

Nutrition Programs and Services

Food Labels

Evidence related to the role of dietary factors in CHD supports the need for manufacturers to increase the number of food labels with their total fat, fatty acids, and cholesterol content.

Food Services

Evidence related to the role of dietary factors in CHD suggests that the public would benefit from increased availability of foods low in fat, saturated fat, and cholesterol in food service programs. The need is critical for the one in four persons with cholesterol levels that put them at appreciably high risk for CHD.

Food Products

Evidence related to the role of dietary factors in CHD suggests that food manufacturers should increase availability of foods and food products that are low in fat, saturated fat, and cholesterol.

Special Populations

Persons with high blood cholesterol and their food preparers should be given access to counseling by qualified health professionals and assistance in the development of diets low in fat, saturated fat, and cholesterol as well as in the appropriate balance of caloric intake and expenditure. Education and training opportunities for health professionals should be expanded to meet this need.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in CHD should include investigations into:

- The identification and management of individuals with high blood cholesterol in the general population.
- The most effective educational and dietary intervention strategies to reduce blood lipid levels and heart disease risk.
- Improved methods for assessing American dietary patterns in relation to CHD risk.
- Refinement of current dietary recommendations, including evaluation of other potentially efficacious dietary regimens, evaluation of dietary fiber, and optimal intakes of omega-3 and omega-6 fatty acids to prevent CHD.
- The mechanisms by which alterations in dietary fatty acids affect atherogenesis and the risk for CHD, including degree of saturation, chain length, and fatty acid series.
- Clarification of the role of dietary cholesterol in atherogenesis, including variability in response, effects on cholesterol metabolism in both fasting and postprandial states, and interactions of postprandial lipoproteins and lipoprotein remnants with cells of the arterial wall.

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Chapter 3

High Blood Pressure

Hence if too much salt is used in food,
the pulse hardens.
Huang Ti (the Yellow Emperor, 2697–2597 B.C.)
The Yellow Emperor's Classic of
Internal Medicine

Introduction

Hypertension, the medical name for high blood pressure, is a common chronic medical problem in the United States responsible for a major portion of cardiovascular disease. In recent years, public health efforts have increased public awareness and knowledge of the risks and appropriate treatment of this condition. As a result, almost the entire adult U.S. population has had at least one blood pressure measurement and 73 percent of Americans have had their blood pressure checked within the previous 6 months. By 1985, 77 percent of the public identified high blood pressure as the factor that most increases a person's chances of having a stroke, and 91 percent indicated that high blood pressure increases a persons chances of getting heart disease (Lenfant 1987). The proportion of hypertensive persons who have their high blood pressure under control more than doubled from the early 1970's to 1980 (Subcommittee 1985). The significant decrease in cardiovascular disease deaths and disability that has occurred since the 1970's is believed by many experts to be due to the increased detection and treatment of high blood pressure.

This success in the control of hypertension is generally credited to a combination of improved detection and the use of antihypertensive medication. However, the implications of long-term drug therapy for millions of Americans are unknown. There are documented side effects of the antihypertensive drugs. Thiazide diuretics, for example, can induce short-term increases in serum cholesterol, low density lipoproteins (LDL), and triglyceride levels in some persons. Some studies suggest that these effects

decrease or disappear with long-term therapy, although some clinical trials have shown persistence of the adverse effects (JNC IV 1988). Beta-blockers tend to lower high density lipoprotein (HDL) levels. These and other risks of drug therapy call attention to the potential benefits of nonpharmaceutical treatment of high blood pressure (Kaplan 1985).

Currently, three nondrug methods—weight control, alcohol restriction, and sodium restriction—are recommended as part of the treatment for established hypertension (JNC IV 1988). These measures have also gained support as likely to aid in the prevention of high blood pressure, particularly for those at high risk.

Historical Perspective

The first successful dietary treatment of human hypertension has been attributed to Kempner's rice-fruit diet that provided 20 g of protein, less than 5 g of fat, 150 mg of sodium, 200 mg of chloride, and 3,000 mg of potassium per day (Kempner 1944). Other studies confirmed that a very low sodium intake, for example, 200 mg/day, was effective in lowering blood pressure, although the effect on blood pressure of a moderate sodium intake, for example, 2,000 mg/day, was inconsistent (Watkin et al. 1950). Such studies laid the groundwork for subsequent investigations into the role of sodium in the development of hypertension.

The positive association between body weight and blood pressure was documented more than 60 years ago (Faber 1924). Clinical treatment of hypertension with weight reduction was reported over 60 years ago by Rose, who documented lower blood pressure and relief of edema in obese patients who lost weight (Rose 1922). The historical evidence for dietary associations with high blood pressure has been reviewed extensively (McCarron and Kotchen 1983; McCarron, Filer, and Van Itallie 1982; Horan et al. 1985).

A review of the development of U.S. public health policy on nutrition and hypertension indicates that in a rather brief time period, the focus shifted from acceptance of the association between sodium intake and blood pressure—an emphasis of the 1969 White House Conference on Food, Nutrition, and Health—to congressional attention on the topic of sodium labeling and FDA action to promote sodium labeling to the 1980 issuance of the DHHS/USDA recommendation in the *Dietary Guidelines for Ameri-*

ans to avoid excessive sodium intake. The relatively fast pace of this nutrition policy development can be appreciated by contrasting it with the history of recommendations for dietary change for high blood cholesterol levels (see chapter on coronary heart disease). A few milestones in the development of nutrition-hypertension policy are noted here.

The role of dietary salt in hypertension was a major issue at the White House Conference on Food, Nutrition, and Health and at the Senate Select Committee hearings in 1969 (Mayer 1969). Subsequently, a committee of the National Academy of Sciences recommended that no more than 0.25 percent salt be added to the commercial preparation of infant food (Subcommittee 1970). In 1970, the infant food industry initiated restriction of added salt.

In 1974, the American Academy of Pediatrics Committee on Nutrition recommended dietary modification of sodium intake for the pediatric population at risk for hypertension. The committee also favored the development of guidelines for reducing the use of salt by food processors and recommended that information about the amount of salt added to processed food be made available to consumers (AAP Committee on Nutrition 1974).

The Food and Drug Administration (FDA) sponsored a review of the health implications of added salt as part of an evaluation of substances designated "Generally Recognized As Safe" for use in foods. This evaluation, completed in 1979 by a committee of the Federation of American Societies for Experimental Biology, concluded that consumption of sodium chloride in the United States should be reduced, guidelines should be developed for restricting salt in processed foods, and the sodium content of processed foods should be labeled (Select Committee on GRAS Substances 1979). Subsequently, the FDA proposed that more information on the sodium content of foods be provided as part of nutrition labeling (U.S. Congress 1981; FDA 1982).

Sodium labeling is part of the FDA's five-point sodium program that involves collaboration between the food industry and Government. The effort intends to achieve changes in food labeling and to encourage the food industry to reduce the amount of sodium added to processed foods and to market a greater variety of foods with lowered sodium. The FDA will encourage consumer education about the relationship between sodium and

hypertension. It is intended to monitor changes in the marketplace to see whether efforts to reduce sodium in the food supply and to increase sodium labeling are successful. Legislation to mandate sodium labeling might be considered if voluntary efforts fail (Forbes and Stephenson 1985).

Appropriate caloric intake to maintain desirable weight and avoidance of excessive sodium intake are goals included in the *Surgeon General's Report on Health Promotion and Disease Prevention* (DHEW 1979) and the nutrition component of the 1990 *Objectives for the Nation* (DHHS 1980). These goals are also recommended by the Food and Nutrition Board of the National Academy of Sciences (NRC 1980) and are consistent with the *Dietary Guidelines for Americans*, published by the Departments of Agriculture and Health and Human Services (USDA/DHHS 1980, 1985).

In recognition of the clear social need to reduce illness, disability, and death from uncontrolled hypertension, the National High Blood Pressure Education Program (NHBPEP) was initiated in 1972, led and coordinated by the National Heart, Lung, and Blood Institute. This program includes an extensive network of Federal agencies and major national health organizations. During the time the NHBPEP has been in operation, age-adjusted death rates for stroke and coronary heart disease have substantially declined. The activities of the NHBPEP on improving hypertension control are believed to have contributed to this decline (Lenfant and Roccella 1984).

Significance for Public Health

In the United States, hypertension is a public health problem of enormous magnitude. Estimates of the prevalence of hypertension vary, however, depending upon differences in interpretation and extrapolation of the data. Current definitions of hypertension are listed in Table 3-1. A change in the blood pressure threshold from 160/95 mm Hg (systolic/diastolic measurements in millimeters of mercury) to 140/90 mm Hg was recommended in 1984 (JNC III 1984) and is maintained in the most recent report (JNC IV 1988). According to this definition, almost 58 million individuals have been found to have elevated blood pressure or have reported taking antihypertensive drugs prescribed by a physician (Table 3-2). About 39 million of these people are under the age of 65; less than 3 percent are children. Prevalence of hypertension increases with age in the U.S. population and is higher for black Americans (38 percent) than for white Americans (29 percent) (Subcommittee 1985).

Table 3-1
Classification of Blood Pressure[a] in Adults 18 Years or Older

Range, mm Hg	Category[b]
Diastolic	
< 85	Normal blood pressure
85–89	High normal blood pressure
90–104	Mild hypertension
105–114	Moderate hypertension
> 115	Severe hypertension
Systolic, when diastolic blood pressure is < 90	
< 140	Normal blood pressure
140–159	Borderline isolated systolic hypertension
> 160	Isolated systolic hypertension

[a]Based on the average of two or more readings on two or more occasions.
[b]A classification of borderline isolated systolic hypertension (SBP 140 to 159 mm Hg) or isolated systolic hypertension (SBP > 160 mm Hg) takes precedence over high normal blood pressure (diastolic blood pressure 85 to 89 mm Hg) when both occur in the same person. High normal blood pressure (DBP 85 to 89 mm Hg) takes precedence over a classification of normal blood pressure (SBP < 140 mm Hg) when both occur in the same person.

Source: 1988 Joint National Committee.

Table 3-2
Estimated Prevalence of Cardiovascular Disease in the United States

Hypertension (> 140/90 or on Rx)	57,700,000
Rheumatic fever with or without heart disease	1,500,000
Coronary heart disease	6,700,000
Cardiac arrhythmias	1,400,000
Cerebrovascular disease	2,700,000

Sources: Subcommittee on Definition and Prevalence of the 1984 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure 1985; National Center for Health Statistics 1986.

Hypertension is a major risk factor both for heart disease, which is the leading category of causes of death in the United States, and for stroke,

which is the third most frequent cause of death. All of the cardiovascular diseases are highly prevalent in this country (Table 3-2). A high proportion of end-stage renal failure is due to hypertension. The magnitude of the high blood pressure problem is demonstrated by the fact that in 1980 and 1981, the estimated annual number of visits to physicians' offices by patients with cardiovascular disease was over 56 million. The largest subgroup was for hypertension, a total of 29 million visits (Ezzati and McLemore 1980; NCHS 1984).

Scientific Background

Regulation of Blood Pressure

Blood pressure is regulated by a complex process involving the interactions of multiple factors that are not completely understood. Ultimately, the regulation of blood pressure reflects the interaction of cardiac output (the amount of blood the heart pumps per unit of time) and total peripheral resistance (the resistance to flow that blood encounters in the arteries and arterioles). Therefore, hypertension is an imbalance of the mechanisms that affect either output or resistance, or both. Some of the many mechanisms that affect these functions and, therefore, blood pressure are listed in Table 3-3. These include alterations in hemodynamic factors (plasma volume, cardiac output, and arterial pressure); central nervous system mechanisms that influence the hemodynamic mechanisms; interactions of the renin-angiotensin and adrenergic system that elevate arterial pressure; adrenal hormone secretion and maintenance of water, sodium, and other electrolyte balance; and various other hormonal influences.

In over 95 percent of individuals with high blood pressure, the specific cause cannot be determined, and the condition is referred to as primary or essential hypertension. Primary hypertension may sometimes represent nonspecific disturbances in blood pressure regulation, and the specific mechanism is not always identifiable.

Methodological Issues

Each approach to investigating the effects of diet on blood pressure has limitations. Animal experimentation provides optimal control over intake of specific nutrients, and hypotheses generated from animal models have been useful in the study of human primary hypertension. Different mechanisms, however, may be important in humans. Epidemiologic studies that compare customary diets and average blood pressure levels among populations or among smaller groups within populations can lead to inferences about the relative importance of various nutritional factors, particularly if

Table 3-3
Control Mechanisms for Arterial Pressure

Mechanical (posture, etc.)
Hemodynamic
Autonomic nervous system
Central nervous system
Gastrointestinal system (absorption of fluids and electrolytes)
Renal parenchymal function
Maintenance of sodium and fluid balance
Regulation of excretion of other electrolytes
Renin-angiotensin-aldosterone system
Other hormonal factors
Adrenal cortical hormones
Vasopressin
Growth hormone
Parathormone
Thyroid hormone
Kallikrein-kinin system
Prostaglandin system
Histaminergic mechanisms

Source: Adapted from Frohlich 1983.

data are collected longitudinally. Cross-sectional studies have two key drawbacks: (1) only a few observations may be used to characterize factors that often have large individual fluctuations (e.g., diet, blood pressure), and (2) they do not consider whether the observed dietary intake is typical of long-term habits, reflects an aberration in usual intake, or reflects a dietary pattern that has been recently modified in response to health concerns.

Observational studies cannot distinguish between the effects of highly correlated dietary constituents. For example, in an observational study, both a low intake of potassium and a high intake of sodium may be associated with high blood pressure. A well-designed human intervention study can yield information on the independence or interaction of the nutrients. Such studies require reliable dietary assessment and use of objective measures whenever feasible as well as standardized blinded blood pressure measurements, adequate length of followup, and control of potentially confounding variables such as other nutrients or weight change.

Nutritional Correlates

Research on diet and hypertension is complicated by the need to assess the relative importance of about 50 essential nutrients, dietary fiber, and nutrition-related factors such as obesity in the face of serious methodological problems inherent in studies of the role of diet in chronic disease (Reed et al. 1985). Although certain individual nutrients are implicated in hypertension, future nutrition research may need to focus more on the interrelationships among dietary factors than to consider each separately (Hegsted 1985).

Several symposia have reviewed the role of nutrition in blood pressure regulation as well as the mechanisms by which dietary factors are known or thought to influence blood pressure regulation (McCarron, Filer, and Van Itallie 1982; Horan et al. 1985). The major dietary factors thought to influence blood pressure and the mechanisms by which they may do so are summarized in Table 3-4. The complexity of these interactions explains why ". . . even where there is general agreement about the importance of a specific nutrient's effect on blood pressure, there is not necessarily consensus on the mechanisms involved" (McCarron, Filer, and Van Itallie 1982).

Key Scientific Issues

- Role of Obesity in Hypertension
- Role of Sodium in Hypertension
- Role of Alcohol in Hypertension
- Role of Other Minerals in Hypertension
- Role of Macronutrients in Hypertension
- Role of Caffeine in Hypertension

Of the many dietary factors listed in Table 3-4 that affect blood pressure, three—obesity, sodium, and alcohol—have a role that is well supported by scientific evidence (JNC IV 1988). At present, research on the effects of other dietary factors is suggestive but not conclusive.

Role of Obesity in Hypertension

As was noted in a special supplement on nutrition and blood pressure control (Dustan 1983; Havlik et al. 1983), early studies on the association between body weight and blood pressure have been confirmed in epidemiologic studies of primitive as well as developed populations. In many

Table 3-4
Major Nutrients and Possible Mechanisms for Influencing Blood Pressure

Calories and Macronutrients	Possible Mechanisms
Total calories	Obesity Energy generation
Carbohydrates (and alcohol)	Energy metabolism Membrane synthesis Insulin regulation—sodium excretion Catecholamine regulation—vascular tone
Proteins	Protein/peptide synthesis Control of cellular function Membrane transport systems
Lipids	Energy source Cell membrane components Prostaglandin synthesis
Electrolytes and Minerals	
Sodium	Intravascular volume Hormone regulation Membrane potential
Potassium	Vascular tone Hormone regulation Cation transport
Calcium	Receptor-ligand binding Hormone synthesis/release Vascular tone Contractile protein interactions
Magnesium	Regulation of calcium channels ATP production Contractile protein interaction
Phosphorus	Membrane structure ATP-energy metabolism cAMP component
Trace elements	Copper-vascular integrity Manganese-energy metabolism Chromium-lipid metabolism Vanadium-sodium/potassium ATPase

Source: Adapted from McCarron, Henry, and Morris 1982.

populations where body weight does not increase with age, neither does blood pressure. Further connection between hypertension and obesity has been demonstrated in the Hypertension Detection and Follow-Up Program, which reported that 60 percent of the participants with hypertension were more than 20 percent overweight (Hypertension Detection and Follow-Up Program Cooperative Group 1977).

Evidence for the effect of weight reduction on blood pressure began to accumulate in the early part of this century. This association has now been investigated in many epidemiologic studies and several clinical trials (as reviewed by MacMahon et al. 1987). Although a few studies have reported that treatment of hypertension with weight loss did not result in lower blood pressure, many investigators have reported significant reduction of elevated blood pressure by weight loss (Table 3-5).

Complicating the relationship of obesity to blood pressure is the role of sodium. An early hypothesis was that obese individuals with hypertension are sensitive to the blood pressure-raising effects of a high sodium intake associated with long-term calorie excess (Dahl, Silver, and Christie 1958). However, other investigators have dissociated the two factors and demonstrated that weight loss is effective in lowering blood pressure even in the absence of sodium restriction (Reisen et al. 1981; Maxwell et al. 1984).

In conclusion, increased body weight is related to increased blood pressure. Furthermore, a fall in blood pressure can be expected with weight reduction. Further studies may help to define other factors such as the distribution of body fat (Kalkhoff et al. 1983; Krotkiewski et al. 1983; Berchtold 1985) or specific mechanisms by which obesity might be involved in the development of hypertension.

Weight loss is recommended for all overweight persons, particularly for those with hypertension. It has been suggested that control of obesity would eliminate hypertension in 48 percent of whites and 28 percent of blacks (Tyroler, Heyden, and Hames 1975). Even when weight loss does not reduce blood pressure to normal, health risks may be reduced, and smaller doses of antihypertensive medication may be needed as a result.

Role of Sodium in Hypertension

Definitions

In most human studies, sodium intake is estimated from reported dietary intake of salt (sodium chloride) among the study participants. A more

Table 3-5
Changes in Weight and Blood Pressure (Baseline to Followup) in Treatment (Rx) and Control Groups of Five Randomized Controlled Trials

	N		Followup	Weight Change (kg)		Systolic BP Change		Diastolic BP Change	
	Rx	Control	(months)	Rx	Control	Rx	Control	Rx	Control
Diet trials									
Reisin et al.	57	26	4	−14.9	−1.2	−37.4	−6.9	−23.3	−2.5
Heyden et al.	63	64	12	−8.1	−1.9	−18.0	−12.0	−13.0	−8.0
Ramsay et al.	15	34	12	−5.1	−2.4	−11.9	−8.9	−6.9	−4.4
Haynes et al.	30	30	6	−4.1	−0.8	+4.8	−0.2	+1.4	−0.1
MacMahon et al.	20	18	5	−7.4	+0.5	−13.3	−7.4	−9.8	−3.1
Pooled estimates[a] (Rx vs. control)									
Diet trials	185	172		−9.2		−6.3		−3.1	
(95% confidence limits)				(−8.2, −10.2)		(−3.3, −9.4)		(−1.5, −4.7)	
Pooled estimates[a] (Rx vs. control)									
All trials	336	254		−8.7		−5.3		−3.3	
(95% confidence limits)				(−7.9, −9.5)		(−3.4, −7.3)		(−1.8, −4.7)	

[a]See MacMahon et al. 1987 for methods.

Source: Adapted from MacMahon et al. 1987.

precise measure of sodium intake is 24-hour urinary sodium output, considered to be an accurate reflection of recent dietary sodium intake in persons with normal kidney function. An average urinary sodium output can be estimated to be about 150 mEq/24 hours. Dietary sodium intakes are commonly reported in mEq, mM, or g. One mEq or one mM of sodium equals 23 mg, and 1 g of sodium equals 44 mEq or mM and is equivalent to 2.5 g of sodium chloride (table salt). The average daily sodium intake of adults is about 4 to 6 g (175 to 265 mEq).

Research Evidence

Epidemiology. A relationship of sodium to hypertension is supported by several lines of evidence. In non-Western populations with low salt consumption, blood pressure does not rise with age. Populations with low blood pressure generally do not consume much salt. These associations have been reported among numerous populations such as the Bushmen of Kalahari, Indian tribes in Brazil, and other groups in New Guinea, Malaysia, the Polynesian Islands, and Solomon Islands.

Salt intake is positively correlated with average systolic and diastolic blood pressures in samples of men and women from 25 diverse populations, regardless of methods of measurement (Gleibermann 1973; McCarron, Henry, and Morris 1982); significant positive associations have not been observed in other populations (see review, Subcommittee 1986). Associations among individuals within a population have been less consistent, perhaps for methodological reasons (Liu et al. 1979).

Clinical Studies. Many studies have examined the effect of moderate restriction of sodium consumption on blood pressure in adults. One nonrandomized crossover study, for example, found that a diet considered to be moderate in sodium restriction—that is, "avoiding all foods which had sodium added during preparation"—reduced sodium excretion from 191 to 93 mEq and was accompanied by reductions in systolic and diastolic blood pressure that averaged 7.7 and 4.4 mm Hg, respectively (Parijs et al. 1973).

A randomized study of 37 hypertensive patients with initial diastolic blood pressures of 90 to 110 mm Hg reported that dietary restriction to 50 mEq of sodium/day for 15 to 21 months produced reductions in systolic and diastolic blood pressure that were similar to those achieved by drug treatment (Magnani et al. 1976). Long-term studies have shown that 39 percent of hypertensive patients could control blood pressure with sodium intakes below 50 mEq/day and close supervision by a dietitian and physician, and about one-third of patients with mild hypertension could control blood pressure with a sodium intake of 75 mEq/day or less (Hunt 1977).

Additional studies suggest that even smaller reductions in sodium intake over an extended period may reduce blood pressure, as discussed below. In a 2-year controlled trial, 31 hypertensive patients were instructed to reduce sodium intake by about 70 to 100 mEq. Although sodium excretion declined only from 191 to 157 mEq, indicating a much smaller reduction in intake, the average diastolic blood pressure fell by 7.3 mm Hg, a result similar to that obtained by drug treatment (Morgan et al. 1978).

Similar results have been obtained in even shorter time periods. In a 12-week randomized trial, one-half of 90 drug-treated hypertensive patients were placed on a no-added-sodium diet (estimated to be equivalent to a maximum intake of about 100 to 150 mEq, or 2,300 to 3,450 mg of sodium). Among the salt-restricted patients, sodium excretion decreased from 150 to 37 mEq and diastolic blood pressure decreased by 6.3 mm Hg (compared with a fall of 2.9 mm Hg in the drug-treated control group), and four of five patients were able to discontinue or reduce medication (Beard et al. 1982).

In a randomized 8-week crossover study of 19 hypertensive patients, dietary restriction was associated with a reduction in sodium excretion from 191 to 83 mEq and a fall in mean blood pressure of 7.6 mm Hg (MacGregor, Markandu, et al. 1982). During a later double-blind phase of the trial, a level of sodium excretion of 76 mEq was associated with a mean blood pressure of 7.1 mm Hg lower than that of the control group (MacGregor, Smith, et al. 1982). Results of a nearly identical trial, however, showed no difference in patients' blood pressures (Watt et al. 1983). The differences between these results may be related to a somewhat lower blood pressure at entry, to a slight difference in average sodium excretion, or to chance variation.

A recent review of 13 randomized clinical trials concluded that moderate (37 to 153 mEq/day) sodium restriction does reduce blood pressure, at least to some small extent, and that this practice is most effective for systolic pressures, for older hypertensive patients, and for patients with higher initial blood pressures (Grobbee and Hofman 1986a).

Prevention

The important question of whether reduction in sodium intake might prevent the rise in blood pressure with age has been addressed in a few short-term studies of adults, children, and infants with normal blood pressures (normotensives). Blood pressure response to moderate sodium restriction (to 60 mEq) for 3 months in 16 healthy normotensive husbands and wives was associated with a decrease in sodium excretion from 152.7 to 59.5 mEq/day and significant decreases in systolic and diastolic blood

pressure of 4 and 3 mm Hg, respectively (Miller et al. 1983). In a randomized double-blind trial, 231 infants fed a diet reduced in sodium content by two-thirds during the first 6 months of life had a mean systolic blood pressure that was significantly lower (2.1 mm Hg) than that of 245 infants fed a customary diet (Hofman, Hazebrock, and Valkenburg 1985). These two studies indicate that apparently normal blood pressures can be reduced by dietary sodium restriction, and they suggest that this practice might prevent age-related increases in blood pressure. To date, however, no reported studies have tested this hypothesis directly.

Variability in Response

The disparate blood pressure responses to sodium intake in animals attributed to genetic influence (Dahl, Heine, and Tassinari 1962) have led to the proposal that dietary sodium and blood pressure relationships are controlled by similar genetic factors in humans (Dahl 1972). Support for the concept of individual variability in human blood pressure response has been provided by a study of 20 hypertensive patients in hospital metabolic units who were fed daily sodium intakes of 9 mEq, 109 mEq, and 249 mEq. Investigators were able to distinguish a salt-sensitive group, whose blood pressures fell in response to sodium restriction, and a salt-resistant group, whose blood pressures tended not to be influenced by changes in salt intake (Kawasaki et al. 1978). It has not yet been possible, however, to identify a way to consistently distinguish salt-sensitive from salt-resistant persons other than by measuring the blood pressure response itself.

While acknowledging that there are some hypertensive individuals whose blood pressures do not respond to sodium restriction, some investigators believe that patients who continue to consume low-salt diets have a more benign course than those who revert to a high salt intake (Dahl 1977).

Two dietary intervention studies suggest that weight loss or sodium restriction or both can retard the return of high blood pressure in patients who have achieved normal blood pressure levels through drug treatment. The Dietary Intervention Study in Hypertension assessed whether hypertensive patients whose hypertension was controlled with drugs could discontinue these medications with or without dietary therapy. The 415 patients who discontinued medications were randomized, stratified by body weight, either to control, weight loss (mean loss of 10 lb), or sodium restriction (mean decrease of 40 mEq/day). The patients in the dietary intervention groups were more than twice as successful as those in the control group in maintaining normal blood pressure. At the end of 56 weeks, 50 percent of these patients remained normotensive without medication. This success rate was higher for patients with pretreatment mild

hypertension than for those with pretreatment severe hypertension. In the former group, 71.5 percent in the weight loss group and 78 percent in the nonobese sodium restriction group remained normotensive (Langford et al. 1985).

Similar results were noted in a 4-year trial, the Hypertension Control Program. Among patients with pretreatment mild hypertension who discontinued antihypertensive medications but who restricted calories and sodium and alcohol intake, 39 percent maintained normal blood pressure after 4 years. In contrast, only 4 percent of those patients who did not receive nutritional intervention remained normotensive (Stamler et al. 1987).

It should be noted that in the two studies previously described, the patients had relatively mild hypertension that had been controlled successfully with drugs for the preceding 5 years. Although the long-term effectiveness of dietary intervention in persons with more severe elevations in blood pressure remains to be established, these studies have important implications for the millions of Americans who are being treated for high blood pressure or who have elevated diastolic blood pressure. Many persons who adhere to a dietary regimen to control blood pressure can reduce or stop drug therapy, with potential economic and health advantages.

Role of Alcohol in Hypertension

Epidemiologic studies have shown that individuals who regularly consume large amounts of alcohol have higher blood pressure than people who abstain from alcohol or who drink only moderate amounts. The epidemiologic literature for the existence and nature of an association between blood pressure and alcohol consumption has been reviewed (MacMahon 1987). In the 12 cross-sectional North American studies reviewed (Table 3-6), with the exception of the Canada Health Study, all reports showed a significant positive association that was independent of age, relative body weight, exercise, and smoking status. In most U.S. studies, a J-shaped or U-shaped association is observed between blood pressure and alcohol consumption, with blood pressure greater in nondrinkers than in those consuming one to two drinks per day. It is not clear whether this might be partially explained by other factors, such as obesity. A more consistent finding was elevation of blood pressure at levels of three drinks or more per day. The prospective, observational studies of the association of blood pressure with alcohol consumption (Table 3-7) have also been reviewed (MacMahon 1987). In this group of investigators, only the Honolulu Heart Study failed to show a positive association with either systolic or

Table 3-6
Studies of the Cross-Sectional Association of Blood Pressure With Alcohol Consumption

Year	Study[a]	No. of Subjects	Male Subjects (%)	Age (years)
	North American			
1967	Los Angeles Heart	865	100	21+
1977	Chicago W. Electric	1,899	100	40–55
1977	Kaiser-Permanente I	83,947	45	15–79
1980	Tecumseh	3,390	47	18+
1981	Lipid Research Clinics	4,783	52	20+
1981	Honolulu Heart	8,006	100	46–68
1983	Stanford Five City	1,842	48	20–74
1983	Framingham	5,209	42	29–62
1985	Canada Health	1,418	51	20+
1985	NHANES	9,553	45	18–74
1986	Kaiser-Permanente II	66,510	44	—
1986	Albany	1,910	100	38–55
	European			
1974	Copenhagen	5,249	100	40–59
1980	Yugoslavia	11,121	100	35–62
1982	Lyon	1,134	100	20–59
1983	North Karelia/Kuopio	8,479	50	30–64
1984	Munich Blood Pressure	3,198	33	30–69
1985	Wurttemberg	3,351	88	20–65
1985	Zutphen	794	100	40–59
	Australian and New Zealand			
1980	Tasmania	85	100	36[b]
1981	CSIRO	350	100	23[b]
1982	Sydney Hospital	20,920	65	18–70
1982	Perth	491	100	20–45
1984	Medicheck	11,000	75	43[b]
1984	Australian RFPS	5,550	50	19+
1985	Milton	901	56	19+
1985	Auckland	1,429	66	35–64
	Japanese			
1984	Osaka/Akita	887	100	40–69
1984	Minamikawachi	3,083	37	53[b]

[a]CSIRO = Commonwealth Scientific and Industrial Research Organization; NHANES = National Health and Nutrition Examination Survey; RFPS = Risk Factor Prevalence Study.
[b]Mean age.

Source: Adapted from MacMahon 1987.

Table 3-7
Prospective Observational Studies of the Association of Blood Pressure With Alcohol Consumption

Year	Study	No. of Subjects	Male Subjects (%)	Age (years)	Followup (years)
1977	Chicago People's Gas	1,340	100	40–59	4
1981	Chicago W. Electric	871	100	40–55	4
1982	Honolulu Heart	6,858	100	46–68	6
1983	Framingham	5,209	42	29–62	4
1985	Zutphen	794	100	40–59	10
1986	Albany	1,910	100	38–55	18

Source: Adapted from MacMahon 1987.

diastolic blood pressure at followup with alcohol intake either at baseline or followup. This evidence, in summary, indicates the potential importance of alcohol restriction in blood pressure control.

Role of Other Minerals in Hypertension

Potassium

One of the earliest observations of the association of dietary potassium with reduced blood pressure concluded that "potassium salt regularly produced a decline in blood pressure, while sodium salt just as regularly produced a rise" (Addison 1928). It was later observed that potassium lowered blood pressure in individuals with hypertension even when dietary salt intake remained high (McQuarrie, Thompson, and Anderson 1936). This protective effect has also been observed in rats (Meneely, Ball, and Youmans 1957). These inverse associations have been reviewed extensively (Meneely and Battarbee 1976; Tannen 1983; Prineas and Blackburn 1985).

Population studies have shown both a positive relationship between sodium intake and blood pressure and an inverse relationship between potassium intake and blood pressure (Maddocks 1967; Sinnett and Whyte 1973; Bulpitt et al. 1986). Although the Framingham study showed no relationship between urinary potassium levels and blood pressure (Dawber et al. 1967), potassium intake was more strongly correlated than any other dietary factor to blood pressure in a Hawaii study (Reed et al. 1985). In disease prevalence studies in Evans County, Georgia, hypertension was more strongly associated with lower potassium intake in black adults than in white adults with similar sodium intakes (Grim et al. 1980). In a Southern California cohort of 859 men and women ages 50 to 79 years, an inverse relationship was observed between dietary potassium, estimated by 24-

hour dietary recall at the baseline examination, and death from stroke, identified by examination of death certificates, in the 12-year followup (Khaw and Barrett-Connor 1987).

Intervention trials have attempted to lower blood pressure in hypertensive patients with the use of potassium supplements. The effect of 60 mEq of potassium supplementation was compared with that of placebo and was documented in a double-blind 4-week crossover trial in 23 patients with hypertension. A small but significant lowering of both systolic and diastolic blood pressure occurred in the supplementation period compared with the placebo period (MacGregor, Smith, et al. 1982). In another double-blind crossover trial, 20 normotensive subjects taking a 64 mEq of potassium supplement reduced diastolic blood pressure significantly (by 2.4 mm Hg) in 2 weeks compared with subjects taking a placebo (Khaw and Thom 1982). A double-blind clinical trial that enrolled 116 adults with mild hypertension for 8 weeks found a 3.4 mm Hg greater decrease in systolic blood pressure and a 1.8 mm Hg greater decrease in diastolic blood pressure in the group taking potassium supplements of 120 mEq/day than in the group taking placebo. A much greater decrease was observed in the five black patients taking potassium compared with placebo (Svetkey et al. 1987). In a 15-week clinical trial that randomized 37 mildly hypertensive patients, there was a mean difference (lower) of 14 mm Hg in systolic blood pressure and 10.5 mm Hg in diastolic blood pressure in the patients taking 48 mEq/day of potassium compared with placebo (Siani et al. 1987). These beneficial effects of potassium on blood pressure in hypertensive patients have been confirmed in another randomized blinded crossover study of 19 hypertensive patients with diuretic-induced potassium depletion. Potassium supplements of 60 mEq/day reduced mean blood pressures by 5.5 mm Hg (Kaplan, Carnegie, and Raskin 1985). In contrast to these findings, an unblinded crossover study of 12 mildly hypertensive subjects showed no influence of potassium supplementation on blood pressure (Richards et al. 1984). One extensive review of the literature concluded that a high potassium intake has no effect on blood pressure in normotensive animals or humans, although a potassium intake of 120 to 175 mEq/day appears to reduce blood pressure in hypertensive patients by 3 to 10 percent (Tannen 1983).

If potassium does have an effect, it is likely influenced by sodium. In a randomized 12-week crossover study of increased sodium intake and added potassium in hypertensive and normotensive adults, blood pressure rose in both hypertensive and normotensive subjects who consumed increased sodium, but among hypertensives who consumed supplemental potassium, blood pressure fell (Parfrey et al. 1981).

The relationship between sodium, potassium, and blood pressure in normotensive adults has been found to be dependent on family history of hypertension (Pietinen, Wong, and Altschul 1979). The response to dietary potassium and sodium has been assessed in male medical students with and without a family history of hypertension. In just the group with a positive family history, diastolic blood pressure was reduced by about 11 mm Hg when sodium intake was lowered in the presence of high potassium intake compared with 7 mm Hg with reduced sodium intake alone (Parfrey et al. 1981). A reanalysis of these data confirmed this effect of potassium (Holly et al. 1981). Also consistent with these data that show a lack of potassium influence in those with a negative family history of hypertension are two trials that failed to find a blood pressure-lowering effect of potassium in those persons who achieved substantial reduction of sodium intake (Morgan et al. 1983; Smith et al. 1985). Because the duration of the majority of these studies has been only weeks or months, longer term intervention studies have been recommended to evaluate the effects on blood pressure of both increased potassium and reduced sodium (Prineas and Blackburn 1985).

Calcium

A possible role for dietary calcium in the regulation of blood pressure is suggested by experimental studies in animals, epidemiologic studies, and clinical studies, including clinical trials (Kaplan and Meese 1986).

Experimental studies in spontaneously hypertensive rats have suggested that supplemental dietary calcium may prevent the development of hypertension (Ayachi 1979; McCarron, Henry, and Morris 1982; Schleiffer et al. 1984). One study, however, reported no such effect (Stern et al. 1984).

An association between calcium and blood pressure was suggested by reports that "hard" drinking water (containing calcium) was associated with reduced prevalence of cardiovascular disease (Schroeder 1960). This association between calcium and blood pressure is supported by observations from the Puerto Rico Heart Health Program that individuals who drank no milk (which is high in calcium) had twice the prevalence of hypertension as those who consumed a quart of milk or more per day (Garcia-Palmieri et al. 1984). An analysis of data for 5,050 adults in Southern California surveyed for heart disease risk factors as part of a Lipid Research Clinics population study indicated that hypertensive men, but not hypertensive women, had a significantly lower intake of calcium from milk than normotensive individuals; in men, diastolic blood pressure decreased significantly with reported increasing milk consumption (Ackley, Barrett-Connor, and Juarez 1983). In a case-control study, dietary calcium

intake assessed by 24-hour dietary recall in 46 hypertensive patients and normotensive controls showed that calcium intake was 22 percent less in the hypertensive group (McCarron, Morris, and Cole 1982).

An analysis of the National Health and Nutrition Examination Survey I (NHANES I) data found an inverse, although inconsistent, association between dietary calcium and blood pressure; the lower blood pressures were correlated with higher levels of serum calcium (Harlan et al. 1984). Although a subsequent examination of a subset of NHANES I data also suggested an inverse relationship between dietary calcium intake and blood pressure (McCarron et al. 1984), the analysis was hindered by methodological shortcomings: the salt added in food preparation and at the table were excluded from dietary intake data; the results were examined using only systolic blood pressure measures; and the analyses did not control consistently for age, race, sex, and body mass index (Feinleib, Lenfant, and Miller 1984). Subsequent analyses of both NHANES I and II data have failed to identify a relationship between dietary calcium and blood pressure except among black males in NHANES I (Sempos et al. 1986).

In a randomized placebo-controlled clinical trial, normotensive adults taking 1,000 mg of calcium per day for 8 weeks had blood pressures that were 6 to 9 percent lower than those receiving placebos (Belizan et al. 1983). In an uncontrolled clinical study, 2,000 mg of oral calcium carbonate taken for 5 days lowered blood pressure in people with low plasma renin activity (Resnick, Nicholson, and Laragh 1984). A blood pressure-lowering effect of calcium has been noted after 5 months in an uncontrolled study of individuals with mild-to-moderate hypertension (Resnick, Nicholson, and Laragh 1984).

Another randomized placebo-controlled crossover trial provided 1,000 mg/day of oral calcium for 8 weeks to 48 hypertensive and 32 normotensive individuals. In the hypertensive group, standing systolic and diastolic pressures were significantly reduced (by 6 and 2 mm Hg, respectively), as was supine systolic (by 3 mm Hg)—but not diastolic—pressure. Among normotensive persons, only supine diastolic blood pressure was significantly lowered with calcium (McCarron and Morris 1985). Supplements of 1,500 mg of calcium per day produced modest (2 to 3 mm Hg) reductions of systolic and diastolic pressures in both white and black normotensive men in a recent study (Lyle et al. 1987). An oral calcium supplement of 10 or 20 mM/day was given for 2 months in a double-blind randomized crossover study involving 51 hypertensive and 51 normotensive patients. There was an apparent trend for lower systolic blood pressure. The diastolic blood

pressure did not change significantly. In the normotensive group, there were no significant changes in blood pressure (Nowson and Morgan 1986). The effect of 1 g of calcium lactate gluconate or calcium carbonate in 23 patients with mild-to-moderate hypertension was observed for 8 weeks in another double-blind crossover study. These investigators reported no evidence that oral calcium supplements lowered blood pressure in these patients (Zoccali et al. 1986).

Analyzed collectively, the preceding evidence suggests that a disturbance in cellular calcium metabolism may contribute to the development of hypertension, although the physiologic mechanism for this effect is as yet unknown (Pak 1985). The possibility that calcium supplements may lower blood pressure only in patients with mildly elevated levels of parathyroid hormone that have occurred as a result of abnormally high kidney excretion of calcium (and consequent lowering of blood calcium levels) has been proposed on the basis of a study of 90 hypertensive patients (Grobbee and Hofman 1986b). At present, the role of calcium in blood pressure regulation must be considered uncertain and the clinical evidence considered inconclusive (Kaplan and Meese 1986).

Chloride

In early studies, the blood pressure-raising effect of sodium chloride was attributed to its chloride portion. Since the mid-1950's, however, the sodium component of sodium chloride typically has been considered more important (Dahl and Love 1954).

The effect of dietary chloride on the pathogenesis of sodium-dependent hypertension has been examined in experimental animals. Steroid-treated rats with one kidney removed developed hypertension when fed sodium chloride but not when they were fed sodium bicarbonate. These different responses could not be explained by differences in caloric intake, weight gain, or the balance of sodium, water, or potassium (Kurtz and Morris 1983).

The observation that salt-sensitive hypertension depends on the presence of both chloride and sodium has induced some investigators to suggest that chloride—rather than sodium—induces hypertension. In one study of salt-sensitive rats, for example, blood pressures were shown to be significantly higher after 5 weeks of loading with sodium chloride, but they remained normal when sodium bicarbonate was substituted for sodium chloride in the diet (Kotchen, Luke, and Ott 1983). The effect of a nonchloride sodium salt on blood pressure was recently tested in five hypertensive men. At 10 mEq/day of sodium chloride, blood pressure was normal. A 230 mEq of

sodium chloride supplement induced a significant increase in blood pressure, which was reversed with a supplement of an equimolar amount of sodium as sodium citrate (Kurtz, Al-Bander, and Morris 1987). This study again raises the possibility that the chloride ion may independently contribute to the sodium chloride-induced increases in blood pressure. The need for further investigation is reinforced by the report that chloride concentrations and activity are decreased in erythrocytes of humans with essential hypertension (Kurtz and Morris 1985).

Magnesium

An early study showed that clinical administration of magnesium salts lowered blood pressure (Blackfan and Hamilton 1925), and recent epidemiologic data have rekindled an interest in this effect (Joffres, Reed, and Yano 1987). Because magnesium, along with calcium, is present in "hard" drinking water, an association between dietary magnesium and blood pressure is also suggested by the finding of lower rates of cardiovascular disease in hard-water areas. The possible association between magnesium and blood pressure is supported to some extent by an observation that magnesium-deficient rats had both higher blood pressure levels and reduced diameter of tiny blood vessels than control animals (Altura et al. 1984).

Among elderly people in Denmark, low serum magnesium concentration has been associated with increased blood pressure (Petersen et al. 1977), and magnesium intakes have been found to be reduced among hypertensive patients (McCarron 1982). One randomized study of 18 patients taking diuretic medications for hypertension or congestive heart failure showed that magnesium supplementation was followed by a significant fall in both systolic (by 12 mm Hg) and diastolic (by 8 mm Hg) blood pressure (Dyckner and Webster 1983). As stated in the chapter on drug-nutrient interactions, thiazide diuretics have been associated with magnesium depletion, and this may be a factor in the blood pressure changes seen during magnesium supplementation. However, in another study in which patients with mild to moderate hypertension not on diuretics were given either magnesium supplements or a placebo, blood pressures did not fall in either group, despite a significant increase in plasma magnesium concentration and in urinary magnesium in the group taking the supplement (Cappuccio, Markandu, and Beynor 1985). The inconsistency of data regarding magnesium and blood pressure levels indicates that there are many unanswered questions regarding the role of magnesium in hypertension.

Trace Elements

Little is known about the role of trace elements in the regulation of blood pressure. Because trace elements such as zinc, copper, and iron participate in enzyme reactions related to blood pressure regulation, they could be factors in the development of hypertension, although they are unlikely to be its primary cause (Saltman 1983). In a comprehensive review of this topic, cadmium was the only trace element that appeared to be related to blood pressure (Mertz 1985), and experimental data from animals and the results of some human studies are consistent with a potential causative role for this element. This role, however, lacks confirmation and is complicated by the many interactions of cadmium with selenium, copper, zinc, and lead. Epidemiologic and animal data also suggest a direct relationship between lead levels and blood pressure (Pirkle et al. 1985), but existing data do not support a major role for this or any other trace element in the pathogenesis of hypertension.

Role of Macronutrients in Hypertension

Carbohydrates

There is some evidence that carbohydrates may play a role in blood pressure regulation. Studies in rats have indicated that dietary sucrose increases blood pressure, whereas starch decreases it (Ahrens et al. 1980). Normotensive humans who supplemented their diets with 200 g/day of sucrose had diastolic blood pressures 5 mm Hg higher than those who consumed no added sucrose (Ahrens 1974). Both a high sucrose and a high glucose solution—but not galactose or lactose—consumed after an overnight fast produce transient increases in blood pressure in normotensive men. These observations suggest that carbohydrates might influence blood pressure-regulating hormones in rats, but investigations conducted to date have failed to find a similar effect in humans (Hodges and Rebello 1985).

Fiber

There is some indication that plant fiber may reduce blood pressure levels (Anderson 1983; Anderson and Tietyen-Clark 1986), but it is uncertain whether dietary fiber plays a role in blood pressure regulation that is independent of other concomitant dietary changes, such as replacement of fat or facilitation of lower sodium intake (Mendeloff 1985).

Fat

The effect of dietary fats on blood pressure has been recently reviewed (Sacks et al. 1987). Neither the effect of total fat content nor responses to major changes in fatty acid intake have been sufficiently studied with desirable methodology, controlling potentially confounding variables for an adequate time period.

Polyunsaturated Fatty Acids. Considerable interest has focused on observational studies indicating that an increased intake of polyunsaturated fatty acids is associated with lower blood pressure (Iacono, Puska, and Dougherty 1983; Puska et al. 1985). Although it is uncertain whether the lower blood pressures were attributable to the change in the type of dietary fat, an action of the fatty acids on blood pressure might be mediated through changes in prostaglandin metabolism caused by increased intake of the polyunsaturated fatty acid, linoleic acid. Some prostaglandin metabolites influence salt and water excretion and can cause contraction or dilation of small blood vessels, thereby affecting blood pressure (Iacono et al. 1981). A single-blind randomized control experiment among hypertensive and normotensive men and women in North Karelia, Finland, found that a low-fat diet with a P/S ratio of 1.0 was associated with reductions in systolic and diastolic blood pressure of 8.9 and 7.6 mm Hg, respectively, reductions greater than those observed in parallel control groups receiving sodium restriction or no dietary change (Puska et al. 1983). Another team of investigators has shown that compared with the baseline diet, decreasing saturated fats and increasing polyunsaturated fats are associated with lower blood pressure (Iacono et al. 1975; Iacono et al. 1981; Iacono, Dougherty, and Puska 1982).

No significant change in blood pressure was observed after feeding either a low-fat diet (22 percent of calories from fat) or a diet high in polyunsaturated fatty acids (19 percent of calories from polyunsaturated fatty acids—compared with the U.S. average of about 7 percent) to 15 to 18 normotensive young adults (Brussaard et al. 1981). A double-blind randomized control trial of 6 weeks studying 21 mildly hypertensive patients found that increasing the polyunsaturated fatty acid linoleate from 4.6 to 13 percent of calories and reducing saturated fatty acids from 16 to 10 percent failed to produce any significant changes in blood pressure (Sacks et al. 1987).

Monounsaturated Fatty Acids. An association between increased consumption of the monounsaturate oleic acid and reductions in both systolic and diastolic blood pressures has been observed recently in a cross-sectional survey that examined 3-day food records and resting blood

pressure in 76 normotensive men. Although no physiologic explanation for this association is evident, it is consistent with the lower prevalence of hypertension among Mediterranean populations who consume diets rich in oleic acid-containing olive oil; Mediterranean populations also have a high carbohydrate intake and low saturated fatty acid intake compared with the U.S. population (Williams et al. 1987).

Omega-3 Fatty Acids. The role of omega-3 fatty acids in blood pressure lowering has also received attention. Investigators have reported that the ingestion of enough fish to provide 5 g of omega-3 fatty acids per day for 2 weeks caused a significant fall in blood pressure, and the lower blood pressure could be maintained subsequently by the weekly consumption of 20 oz of fish that provided 1.2 g/day of omega-3 fatty acids (Singer et al. 1986).

In summary, these results indicating that the type of fat intake may influence blood pressure level require further investigation to resolve inconsistencies, confirm the observations, and establish their clinical significance (Iacono, Dougherty, and Puska 1982).

Protein

The possibility of an effect of protein level on blood pressure regulation and whether specific amino acids might have an antihypertensive role has received little scientific study. In a study of spontaneously hypertensive rats, those rats fed American rat chow containing 25.3 percent protein, compared with rats fed Japanese rat chow containing 19.7 percent protein, developed a lower incidence of stroke (30 percent versus 80 percent). When the rats previously fed American rat chow were fed the Japanese diet, an accelerated rate of cerebral lesions and stroke occurred. This observation led to a search for specific amino acids in proteins that might affect blood pressure; tryptophan and tyrosine, as well as total protein intake, were cited as leading possibilities. Taurine has been demonstrated as having an antihypertensive effect in patients with hypertension (Kohashi et al. 1983) as well as in rats (Abe et al. 1987). One hypothesis is that amino acids or protein may affect blood pressure either at the vascular level or through changes in neuronal control of the cardiovascular system (Yamori et al. 1984), but this idea has yet to be confirmed.

Role of Caffeine in Hypertension

The consumption of 150 mg of caffeine (two to three cups of brewed coffee) may promote an increase in blood pressure by 5 to 15 mm Hg within 15

minutes that is maintained for as long as 2 hours. These short-term effects are primarily mediated by an increase in cardiac output, with systolic pressure usually rising more than diastolic; they are demonstrable both in individuals who do not habitually consume caffeine and in those who do habitually ingest caffeine if they abstain for 12 hours or more. The cause of these effects is uncertain; short-term effects are not directly attributable to rises in plasma catecholamines, vassopressin, or renin activity (Izzo et al. 1983).

Chronic caffeine consumption, however, neither maintains high blood pressure nor is it associated with increased rates of hypertension (Robertson et al. 1984). Prolonged administration of caffeine—as much as 504 mg/day for 4 weeks—has not been associated with significant rises in blood pressure either in normotensive (Ammon et al. 1983) or hypertensive individuals (Robertson et al. 1984). Thus, there appears to be adaptation or tolerance to the hemodynamic effects of caffeine.

Implications for Public Health Policy

Dietary Guidance

General Public

Dietary factors that clearly contribute to high blood pressure include obesity and excessive intake of sodium and alcohol. The average daily sodium consumption of 4 to 6 g by adult Americans is substantially above the National Research Council's recommended range of 1.1 to 3.3 g for safe and adequate intake and is 5 to 10 times higher than the amount required. Many individuals are able to maintain normal blood pressure levels over a large range of sodium intake; the lack of known harm from moderate sodium restriction, however, and the potential benefit to people whose blood pressures rise with increased sodium intake suggest that those who ingest excess sodium—most Americans—should consider reducing their dietary sodium intake.

The strong association between obesity and hypertension and the demonstrated reduction in blood pressure that occurs with weight loss suggest that maintenance of desirable body weight should be a goal for the population.

Similarly, there is a direct association between blood pressure and alcohol consumption beyond about two standard-sized drinks daily. (One standard-sized drink is defined as 12 oz of regular beer, 5 oz of wine, or 1½ oz of distilled spirits.)

Some evidence indicates that a reduction in blood pressure is associated with increased dietary intake of potassium, calcium, magnesium, and fiber. This evidence is, as yet, too preliminary to recommend increased intake of these factors for the general population for the purpose of hypertension control. Likewise, although increased intake of certain lipids (e.g., omega-6 or omega-3 polyunsaturated fatty acids) may decrease blood pressure, additional research is needed before any recommendations can be made.

Special Populations

Achieving and maintaining desirable body weight and moderating sodium and alcohol intake can lower blood pressure in patients with mild and moderate hypertension and reduce the need for antihypertensive medications. Such patients should be informed of the likely benefit of these dietary practices, along with the importance of adequate caloric expenditure through exercise, and the moderation of fat intake, especially saturated fatty acids, to reduce high blood cholesterol levels and the risk for heart attack.

Nutrition Programs and Services

Food Labels

Evidence related to the role of dietary factors in hypertension supports the need for nutrition labeling on a wide selection of foods so that the consumer has the option of choosing foods with known amounts of calories and sodium.

Food Services

Evidence related to the role of dietary factors in hypertension suggests that food service programs should provide adequate choices of foods that provide essential nutrients and energy to maintain desirable body weight and should include foods that are low in sodium.

Food Products

Evidence related to the role of dietary factors in hypertension suggests that food manufacturers should continue to reduce sodium in products and continue the research and development of products low in calories and sodium.

Special Populations

Counseling and assistance in the selection and preparation of foods low in sodium and calories and assistance with the development of dietary pat-

terns that control energy, sodium, and alcohol should be available to individuals whose blood pressure places them in the mild-to-moderate as well as high range of hypertension.

Research and Surveillance

Special priority is attached to the following research and surveillance tasks related to the role of diet in hypertension:

- Development of practical methods for the rapid and reliable identification of individuals at high risk for hypertension because they are salt sensitive.
- Investigation of the interactions of sodium with other nutrients—such as potassium, calcium, chloride, magnesium, fatty acids, and fiber—in influencing blood pressure.
- Investigation of the role of specific dietary factors, including potassium, calcium, fatty acids, fiber, amino acids, trace elements, and alcohol, in the cause and potential prevention of hypertension and the mechanisms for these effects.
- Investigation of the mechanism of obesity-associated hypertension and determination of the ratio of fat to lean body mass that might prevent development of hypertension.

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Chapter 4

Cancer

One should eat and drink in moderation (not in excess, not at a rapid rate, foods not too hot and not overly hard), maintain an even temperament, eat a good diet and Ye Ge (esophageal cancer) will not develop.
Ancient Chinese aphorism of Yan,
quoted in O'Connor and Campbell (1986)

Introduction

Cancer, the second leading cause of death in the United States, is a group of conditions of uncontrolled growth of cells originating from almost any tissue of the body. The fundamental basis of cancer has been explained as follows: "Every minute 10 million cells divide in the human body. Usually, they divide in the right way and at the right time, governed by a complex set of controls that have yet to be fully elucidated. When those controls fail, cancer may arise. The carefully ordered pattern of cell growth, division, and differentiation is lost" (Bishop 1984). This chapter reviews the scientific evidence for the role of dietary factors in these processes.

Historical Perspective

Although diet has been suspected as a cause of cancer since the disease was recognized in the 1st century (Armstrong and Mann 1985), empirical evidence was not reported until the early 20th century (Van Alstyne and Beebe 1913). The current era of research grows out of studies that were reported more than 50 years ago. In one of the earliest investigations, dietary information obtained from 462 cancer patients suggested protective effects of whole meal bread, cruciferous vegetables, and fresh milk (Stocks and Kay 1933). Records from insurance companies suggested that overweight people were at higher risk for cancer than normal or underweight people (Tannenbaum 1940b).

This finding stimulated a series of animal experiments that demonstrated a lower incidence of skin tumors, mammary tumors, sarcomas, hepatomas, lung adenomas, and pituitary adenomas in severely underfed animals

(Tannenbaum 1940a; Tannenbaum and Silverstone 1957). Early rodent studies showed that high-fat diets favored development of mammary tumors (Silverstone and Tannenbaum 1950) and that vitamin A deficiency was associated with gastric papillomas (Fujimaki 1926). These and other early studies of diet and cancer causation have been reviewed (Armstrong and Mann 1985; Carroll and Khor 1975).

Although research on the effects of dietary modification on induction of cancer in rodents continued, there was little attempt to relate the results of this research to humans. Interest in the role of nutrition in human carcinogenesis renewed in the 1960's when a report from the World Health Organization examined lifestyle and environmental factors associated with cancer risk and concluded "that the majority of human cancer is potentially preventable" (WHO 1964). Since then, epidemiologic and experimental research on the relationship between diet, nutrition, and cancer has expanded rapidly. In 1980, the National Cancer Institute commissioned the National Academy of Sciences (NAS) to review available information, develop dietary recommendations for public distribution, and develop recommendations for further research on diet, nutrition, and cancer (NRC 1982). This chapter reviews the evidence available at the time the recommendations of the NAS report were developed as well as findings since that time.

Significance for Public Health

Cancer accounted for 22 percent of all deaths in the United States in 1984. It has been estimated that 965,000 new cases of cancer were diagnosed and 483,000 people died of cancer in the United States in 1987 (Silverberg and Lubera 1987). An American born in 1985 has an approximately 30 percent chance of eventually dying of cancer (Seidman et al. 1985). Although the annual number of cancer cases has been steadily increasing as the population grows, the age-adjusted total cancer incidence and mortality rates for sites other than respiratory tract (cancers that are primarily due to cigarette smoking) have as a whole remained stable during the past 30 to 40 years (NRC 1982).

Incidence and mortality rates for cancer are significantly higher in black than in white Americans or members of other minority groups. This difference is especially pronounced in males. Blacks also have the lowest survival rates for cancers at most sites. These differences in cancer experience are more readily explained by social and environmental factors than by biologic differences. Although their cancer rates vary greatly according to

disease site and specific tribal group, Native Americans have the lowest overall cancer rates among the U.S. population (DHHS 1985).

The costs of this illness can be divided into those that are economic (direct and indirect) and psychosocial (Hodgson and Meiners 1982). The direct costs of cancer treatment in the United States were estimated to be $22 billion and the indirect costs $50 billion in 1985 (Sondik et al. 1987). Thus, successful strategies to prevent cancer could have an enormous public health impact on the saving of both lives and dollars.

Cancer may arise in any organ in the body, but tumors of the lung, colon and rectum, breast, skin, and prostate occur most frequently. Cancers of 10 sites—lung, colon-rectum, breast, prostate, pancreas, leukemias, stomach, ovary, bladder, and liver-biliary cancers—account for more than 73 percent of all cancer deaths in the United States (Silverberg and Lubera 1987) and are variably associated with dietary factors. Although the exact proportion is unknown, several researchers have attempted to provide quantitative estimates of the percentage of cancer in the United States attributable at least in part to diet. One group estimated the proportion of cancer deaths attributed to diet to be 40 percent in men and 60 percent in women (Wynder and Gori 1977), and another estimated it to be 35 percent overall, with a range of 10 to 70 percent (Doll and Peto 1981) (Table 4-1).

Scientific Background

Lifestyle Factors and Cancer Risk

In searching for the causes of cancer, considerable effort has been devoted to studying both environmental and genetic factors on the incidence of cancer. In the course of this research, it has become clear that many cancers have external causes and, in principle, should therefore be preventable. These conclusions are supported by several lines of evidence.

Comparisons of Incidence Rates Between Populations. Incidence rates of specific cancers differ as much as 100-fold among populations. These variations are illustrated in Figure 4-1 for several types of cancer. Because the incidence of cancer increases with age, rates are age adjusted for comparison of populations with different age structures. Different groups within the same country may also have distinctly different cancer incidence rates. For example, a comparison of Mormons versus non-Mormons in Utah in 1967–1975 demonstrated overall cancer rates that were 28 percent greater in the non-Mormons even after all smoking-associated cancers were eliminated (Lyon, Gardner, and West 1980). Environmental and social factors, including diet and nutrition, have been implicated as partial causes of this variation.

Table 4-1
Proportions of Cancer Deaths Attributed to Various Factors[a]

Factor or Class of Factors	Percent of All Cancer Deaths: Best Estimate	Percent of All Cancer Deaths: Range of Acceptable Estimates
Tobacco	30	25–40
Alcohol	3	2–4
Diet	35	10–70
Food additives	1	(−5[b])–2
Reproductive and sexual behavior	7	1–13
Occupation	4	2–8
Pollution	2	1–5
Industrial products	1	1–2
Medicines and medical procedures	1	0.5–3
Geophysical factors	3	2–4
Infection	10?	1–?
Unknown	?	?

[a]It should be understood that these figures are speculative, and there is considerable uncertainty associated with them.
[b]Some factors (e.g., food fortification) may be protective.

Source: Doll and Peto 1981.

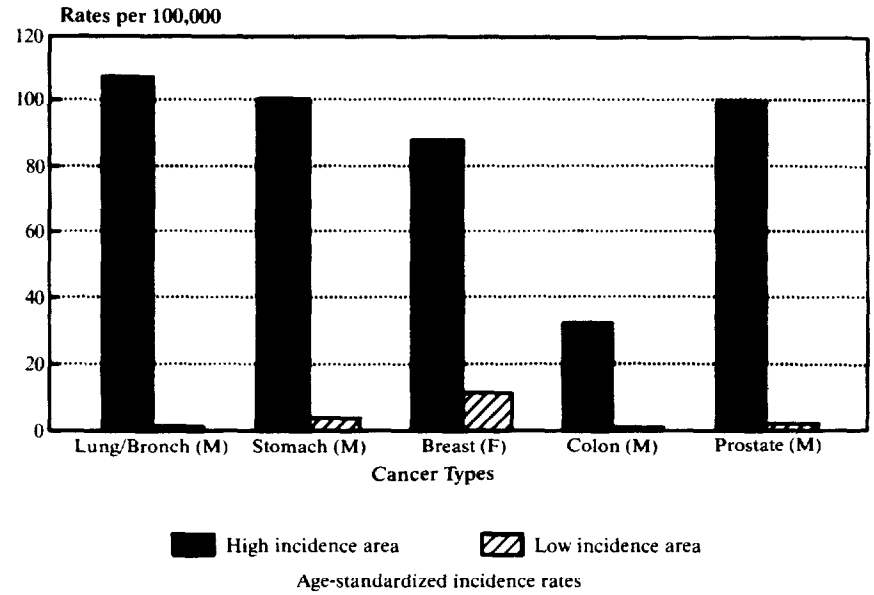

Figure 4-1. Range of incidence rates (international comparisons).

Source: Adapted from Howe 1986.

Variation in Rates Within a Population Over Time. Changes in cancer rates in a stable population must be due to environmental rather than genetic causes, but it is not always easy to distinguish between actual changes in rates and those due to improvements in screening, diagnosing, and treating as well as identifying cancer as a cause of death. Table 4-2 demonstrates rate changes over time for stomach and lung cancer mortality, two cancers for which death records are fairly reliable and survival is relatively short. These data indicate that the rate of stomach cancer mortality in the United States declined by 61 percent from 1950–51 to 1975—the reasons for this decline have not been established (Silverberg and Lubera 1987)—while the rate of lung cancer increased 148 percent. The increase in rate of lung cancer mortality is due primarily to increases in cigarette smoking.

Migrant Studies. Studies of migrants offer clear support for the roles of life style and environment in cancer etiology because such populations have "unwittingly performed etiological experiments on a large scale by migration from one environment to another" (Steiner 1954). Table 4-3 compares cancer incidence rates among Filipinos in the Philippines (Manila), migrants to Hawaii, and Hawaiian Caucasians and indicates a migration-related decrease in cancers of the stomach, liver, and cervix, as well as an

Table 4-2
International Changes Since 1950 in Death Certification Rates for Cancers of Stomach and Lung

Country	Period	Stomach	Lung
Australia	1950-51 to 1975	−53	+146
Austria	1952-53 to 1976	−53	−8
Chile	1950-51 to 1975	−56	+38
Denmark	1952-53 to 1976	−62	+87
England and Wales	1950-51 to 1975	−49	+33
West Germany	1952-53 to 1975	−50	+36
Ireland	1950-51 to 1975	−54	+177
Israel	1950-51 to 1975	−49	+58
Japan	1950-51 to 1976	−37	+408
The Netherlands	1950-51 to 1976	−60	+89
New Zealand	1950-51 to 1975	−54	+137
Norway	1952-53 to 1975	−59	+118
Scotland	1950-51 to 1975	−46	+44
Switzerland	1952-53 to 1976	−64	+72
United States	1950-51 to 1975	−61	+148

Average of male and female rates at ages 35 to 64, standardized for age.

Source: Doll and Peto 1981.

Table 4-3
Cancer Incidence Rates in the Philippines and Among Filipinos and Caucasians in Hawaii

Cancer Site	Philippines	Hawaii		
	Manila 1977	Filipinos 1962–65	Filipinos 1978–81	Caucasians 1978–81
Males				
Stomach	10	7.1	6.6	14.8
Colon	5	14.3	18.8	33.6
Rectum	6	12.4	16.2	17.5
Liver	20	7.5	4.1	5.6
Lung	29	15.9	27.3	75.3
Thyroid	2	5.0	5.6	1.0[a]
Prostate	8	14.0	33.4	69.0
Females				
Colon	4	6.4	11.6	26.7
Lung	9	17.3	16.3	36.4
Thyroid	5	22.4	17.4	6.3
Breast	31	18.2	36.2	92.9
Cervix	16	16.6	7.5	10.2

Average annual incidence per 100,000 population, age-adjusted to the World Population Standard.

[a]Rate is based on fewer than 10 cases.

Source: Adapted from Kolonel, Hankin, and Nomura 1986.

increase in cancers of the colon, thyroid, prostate, and breast. Similar trends have been noted for Japanese migrants (Doll and Peto 1981). Although migrant studies suffer from variations in the source and quality of data, these studies do imply that environmental conditions, rather than genetics, are responsible for the changing incidence patterns (Modan 1980; Haenszel 1982).

Carcinogenic Agents. Identification of carcinogenic agents through animal assays may suggest sources of exposure through contamination of food or water supplies. However, because of continuous monitoring of the food supply and regulatory requirements that prevent the addition of or minimize the concentration of food contaminants that have carcinogenic potential, this possible source of cancer risk has a nondetectable impact on cancer incidence in the United States.

Concepts of Carcinogenesis

The complex process of cancer development can work through multiple paths. Figure 4-2 illustrates a current view of the steps that lead to cancer.

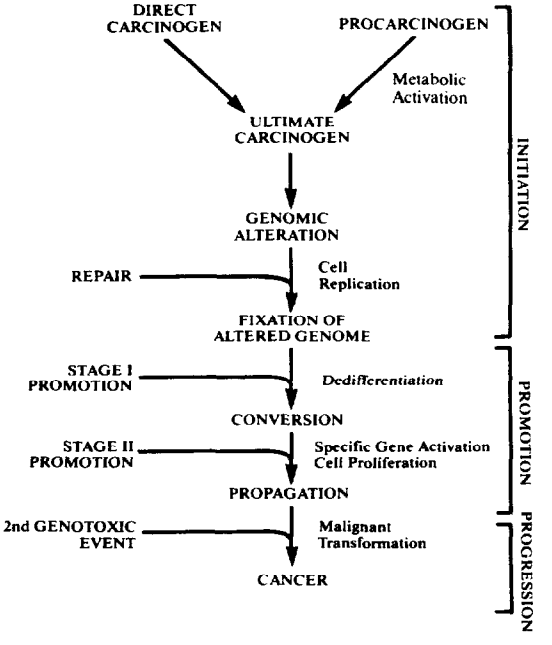

Figure 4-2. Carcinogenesis.

Initiation of carcinogenesis alters the genetic information (i.e., DNA) of the cell. Promotion then leads to expression of genetic changes as malignancy, which involves loss of control over cellular proliferation. According to this model, both events are required for malignant transformation, and they must occur in this order. Many factors, including dietary factors, may enhance or inhibit this process at certain stages. Recent advances in molecular biology have revealed the presence of cancer-inducing genes (oncogenes) within cells that can be activated under specific environmental conditions (Bishop 1987). Current knowledge of initiation, promotion, and regulation of oncogene expression is consistent with suggestions that most cancers have external causes and therefore are likely preventable.

Carcinogenesis is complete when cells become neoplastic and are independent of normal biologic controls. These tumor cells grow in number during a silent interval, which may last 5 years or more, sometimes much more, before a tumor can be detected clinically. This long latent period makes it difficult to establish the time of onset of carcinogenesis and requires that studies of dietary effects on cancer estimate dietary intake for times up to 20 or more years before diagnosis.

Diet and Carcinogenesis

Several mechanisms have been proposed to account for observed associations between diet, digestive processes, and cancer. These include:

- Carcinogens in food that are present naturally, that are inadvertent contaminants, or that form as products of cooking or preservation.
- Diet-induced metabolic activation or deactivation of carcinogens (Miller and Miller 1976). For example, formation of oxygen radicals and lipid peroxidation products can be retarded or blocked by normal enzymatic processes or by the selenium or beta-carotene present in food (Ames 1983).
- Biologic formation of carcinogens *in vivo*, as with conversion of bile acids to tumor-promoting chemicals by normal colonic bacteria (Hill et al. 1971). The bacteria that accomplish this conversion may be affected by diet.
- Enhancement (e.g., by fats) or inhibition (e.g., by vitamin A) of promotion (Doll and Peto 1981).
- Nutrient imbalance may impair immunity (Beisel 1984) and thus may influence early rejection of malignant cells or the ability of cells to repair damaged DNA (Wood and Watson 1984). This topic has been reviewed extensively (Good 1981; Gershwin, Beach, and Hurley 1985; Watson 1984).

Nutritional Support With Cancer Treatment

Severe losses of weight, digestive and absorptive ability, and cellular immune competence are frequent consequences of cancer, and cancer patients may exhibit classic signs of extreme malnutrition. This cachexia of cancer has been attributed to reduced food intake due to anorexia, which may be compounded by disorders of taste and smell; to gastrointestinal malfunction caused by radiation, chemotherapy, or surgical therapy (Brennan and Copeland 1981); and to metabolic abnormalities induced by the tumor itself (Anonymous 1984).

The observation that some cancer patients show marked weight loss has led to the idea that correction of malnutrition by diet or by tube or intravenous feeding might improve the tolerance of patients to therapy as well as improve the quality and length of life. Despite some inconsistencies in results, numerous studies have demonstrated the ability of nutritional support to restore body weight and other indices of nutritional status, functional ability, and feelings of well-being in cachectic cancer patients (Brennan 1981). On the other hand, although some studies have demon-

strated improved ability of well-nourished patients to withstand therapy with radiation (McArdle, Laplante, and Freeman 1986), many others have not (Donaldson 1984). Most prospective clinical trials to determine the effects of nutritional support on the survival of cancer patients have also failed to demonstrate an improvement (Koretz 1984).

Suggestions that macrobiotic diets, high doses of vitamins, minerals, and other nutritional supplements or other unorthodox nutritional methods might cure cancer or delay its course have not been supported by controlled scientific investigations (ACS 1984; Herbert 1986). The use of high-dose (10 g/day) vitamin C, for example, has been used in attempts to prolong the quality of life and the lifespan of terminally ill cancer patients (Cameron and Pauling 1978), but controlled studies have found no difference in outcome among patients taking vitamin C or placebos (Creagan et al. 1979; Moertel et al. 1985).

Methodological Issues

Different types of studies provide different types of information, and no studies are without limitations. An important consideration in reaching conclusions is consistency of data. The conclusions reached must be based on the relevance, quality, and the degree of concordance between the epidemiologic data and laboratory evidence, as applicable.

Interpretation of the associations between diet and cancer depends upon a critical evaluation of the study design and methods of analysis used to reach conclusions. The following types of investigations have yielded important information about diet-cancer relationships.

Epidemiologic Studies. Much of the evidence on diet and cancer risk derives from epidemiology, "the study of the distribution and determinants of health-related states and events in populations, and the application of this study to control of health problems" (Last 1983). Epidemiology is a relatively young science that has contributed to the expansion of knowledge and improvement of public health (Feinstein 1987). Epidemiologic studies are generally classified as correlation (ecologic), case-control (retrospective), and cohort (retrospective or prospective) studies (for reviews see NRC 1982; Byers and Funch 1984). Case-control and cohort studies tend to be stronger scientifically than ecologic studies because they use data from individuals, rather than population averages, to reach their conclusions. However, they sometimes are limited by narrow ranges of variation in exposure (e.g., to food groups or nutrients), which reduces the opportunity to see a potentially true biologic association. The ability to

detect a meaningful level of association is determined by the range of exposure as well as the size of the sample studied (Self et al. 1988).

Ecologic Studies. These studies permit analysis of a variety of diets, especially in international comparisons, that might not be observable in case-control or cohort studies. They can also assess changes over long periods of time. In such studies, cancer rates among various populations can be correlated with data on food disappearance, dietary surveys, or blood chemistries. This type of study is most useful for generating hypotheses about dietary factors related to cancer risk. An example is the high correlation between dietary fat intake and death rate from breast cancer illustrated in Figure 4-3. Ecologic studies can also relate metabolic or biochemical changes in circulating hormones or fecal bile acids, for example, to dietary intake and cancer incidence (Reddy et al. 1980). Such comparisons usually rely on average population data rather than on individual measures, and they tend to focus on cancer mortality rather than on incidence. Their most serious weakness is the potential for an "ecologic fallacy," which means that populations may differ with respect to two associated variables (e.g., dietary fat, colon cancer) but that the individuals who get the disease (i.e., colon cancer) may not necessarily be the ones who had the exposure (e.g., high fat); variables other than the one of interest, such as obesity, or caloric intake, may account for the observed difference in disease incidence or mortality (Last 1983). Despite such limitations, ecologic studies allow multiple comparisons and correlations that permit relatively inexpensive rapid generation and examination of hypotheses regarding the causes of disease (DHHS 1982).

Case-Control Studies. Case-control studies begin with selection of individuals who have the disease of interest (the cases) and compare their present or past exposure to potential risk factors to that of persons without the disease (the controls). The greater the proportion of cases exposed to a factor, the stronger is the hypothesis that the factor increases disease risk. Increased risk is often expressed as a relative odds, or odds ratio, which for uncommon diseases like cancer expresses the risk of disease in persons exposed to the factor as a ratio or multiple of the risk in persons not exposed. An important component of the study design is that cases and controls should be drawn from the same population so that the potential contribution of confounding variables can be minimized. Case-control studies are advantageous for studying rare cancers with long latent periods because they require relatively few subjects and can be used to assess multiple hypotheses for causation. However, they can be affected by uncertainties regarding the representativeness of both cases and controls and the validity of dietary measures. Statistical significance of such rela

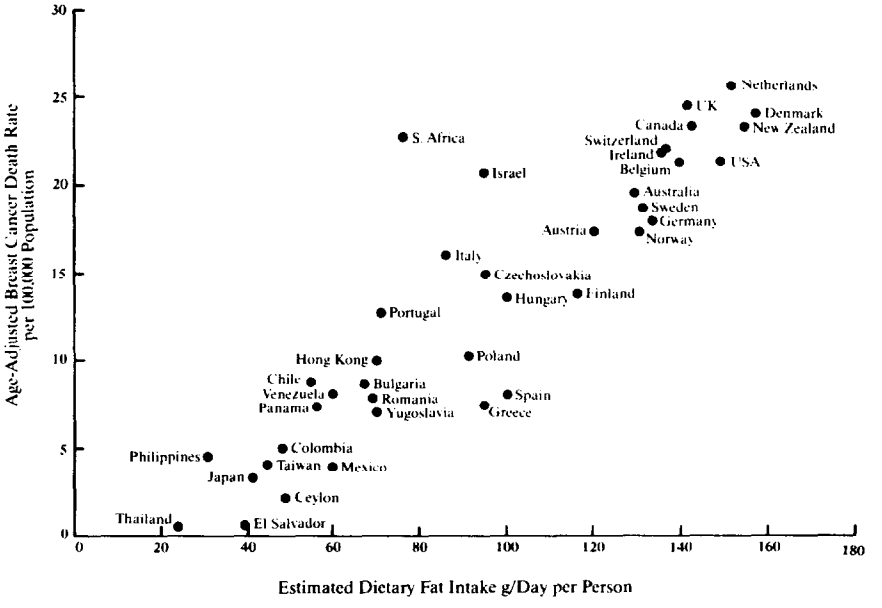

Figure 4-3. Dietary fat intake in relation to breast cancer-related death rate.

Source: Carroll, K.K., and Khor, H.T. 1975. Dietary fat in relation to tumorigenesis. *Progress in Biochemical Pharmacology* 10:308-53. Reprinted with permission from S. Karger AG, Basel.

tionships, however, does not guarantee a causal association, nor does lack of statistical significance necessarily indicate a noncausal association (Schlesselman 1982). Case-control studies may fail to confirm strong associations observed in correlation studies of diet and disease. Whether this is caused by the better control of confounding variables, by the inability of studies on individuals to make sufficiently valid measurements of diets, by insufficient variation of diets within a single population, or by a combination of these or other factors needs to be evaluated.

Several potential constraints must be addressed for a case-control study to identify a relationship between a dietary pattern and a disease outcome. If, for example, a population is homogeneous in intake of a food or nutrient, or if amounts ingested by most members of the population are insufficient to observe an effect, one may find little difference in exposure between cases and controls, even for dietary factors that show associations in other studies. Case-control studies also depend on the sensitivity of the dietary questionnaire or other instrument of measure. Cancer itself, or another

preexisting condition, may lead to dietary changes and result in spurious associations because the measured exposure at the time of disease onset may be quite different from the exposure at the time the case is found.

Cohort Studies. Cohort studies solve some of these problems by comparing groups that have and do not have the dietary patterns of interest. The main difference in concept between cohort and case-control studies is that in cohort studies, subjects were selected on the basis of exposure versus nonexposure, while subjects are selected for case-control studies on the basis of disease versus nondisease. Because prospective cohort studies assess the risk of disease after a given exposure, they require more time and resources than case-control studies. In such studies, there is no need to attempt retrospective measures of diet and, therefore, less concern about the possibility of biased recall. When the relationship of dietary exposure to subsequent cancer risk is to be studied, a very large group must be followed for many years because of the long latency period for a sufficient number of incident cases to be collected. In such studies, a sufficient exposure difference must also exist between the two groups for a potential effect to be noticed, and diligent surveillance is required to ensure that no cases of cancer are missed. The advantages of cohort studies are that exposure is known at a given point in time, greater control over measurement techniques is afforded, and exposure is known to occur before the onset of disease. While good cohort studies can provide stronger scientific information than case-control studies, they still suffer from the potential limited range of dietary exposure and require many years for completion.

Clinical Intervention Trials. Clinical trials provide the strongest research design to test whether an intervention will have the hypothesized effect. A specificity not possible in epidemiologic studies derives from the prospective nature and use of random assignment to a treatment (such as a diet) in clinical trials. These trials may show whether animal studies are applicable to people and whether people will adhere to the intervention for the duration of the trial (Greenwald, Sondik, and Lynch 1986). In clinical trials, a prospective cohort is randomly assigned to an intervention or to a control group—for example, assigning women at increased risk for breast cancer to either a customary diet or a long-term intervention program to lower dietary fat to less than 20 percent of daily calories. To achieve the statistical power necessary to reach solid conclusions in the face of diseases of multiple etiologies and widespread risk factor exposure may require trials involving many thousands of participants and many millions of dollars. On the other hand, the expense and effort are warranted if the results can be expected to benefit a large share of the population.

To facilitate the conduct of these clinical trials, methodological improvements are needed. Present methods to determine the relationship between diet and cancer risk require long waiting periods to identify end points. The lack of sensitive and specific markers of carcinogenesis makes nutrient and chemoprevention trials difficult, although advances in molecular biology may improve this situation (Perera 1987). Finally, ethical issues may be important in such trials—for example, withholding an intervention that might benefit a group on one or several dimensions—and have been reviewed recently (Freedman 1987).

Animal Studies. Animal studies offer the advantage of confined populations and closer control of experimental variables, and they provide invaluable opportunities to study the mechanisms that underlie the relationship of diet and cancer. The use of very high levels of a specific nutrient or food type (e.g., vitamin C or wheat bran) to maximize efficiency and minimize costs in these studies complicates extrapolation of results to humans. An important weakness is that virtually all animal studies test single, genetically uniform (inbred) strains of one or two nonhuman species under highly uniform conditions of diet, temperature, stress, exposure to infectious diseases, etc., so that there are often serious constraints in generalization of results to a highly variable human population. However, animal studies may complement human studies, and these two basic approaches should be used in conjunction when possible (NRC 1982).

Association and Causation. When an epidemiologic study shows an association between a dietary factor and the risk of a specific cancer, other studies may not necessarily show the same degree of association because of variations in research design, length of observation, relevant nondietary exposures, variation in human response, or chance associations. To demonstrate a true association, it is necessary to rule out spurious correlations due to artifacts or biases (problems of validity) that stem from systematic errors in design or analysis (Lilienfeld and Lilienfeld 1980; Sackett 1979). Even statistical associations between diet and disease do not guarantee that a specific factor causes the disease; noncausal (confounding) associations may exist (Miettinen and Cook 1981). Statistical methods to identify problems of bias and confounding can strengthen the interpretation of study results (Kleinbaum, Kupper, and Morgenstern 1982) but cannot solve all of the problems encountered in interpreting results and in isolating "true" effects.

Dietary Interactions. Complex interrelationships and interactions among nutrients are often not appropriately considered. For example, dietary fats supply more than twice the calories per gram as protein or carbohydrates.

Although fat consumption would be expected to correlate with caloric intake, few studies of the role of fat in colorectal cancer have taken this into account. Distinctions between tightly linked nutrients may not always be possible. Methods to control highly correlated variables, however, can result in difficulty in interpreting results because control for the effect of the confounding variable may also remove variance due to the "true" effect. Thus, the statistical instability of highly correlated variables often makes use and interpretation of multivariance analysis difficult if not impossible (Pilch 1987).

Another type of interaction of nutrients and food components can result in a synergistic effect, an effect greater than that expected from the sum of the individual effects. The synergy between asbestos exposure and smoking in causing lung cancer is a well-known example of a synergistic effect. It is also possible to have factors that counterbalance each other. Nutrient synergies in cancer etiology are not as well established, but a recent study correlating cancer with low serum levels of selenium and alpha-tocopherol (vitamin E) is illustrative. While the relative risk for cancer was 5.8 for low selenium level and 1.6 for low alpha-tocopherol level, the interactive risk was 11.4 for both occurring together (Salonen et al. 1985).

Detailed food diaries, the usual instruments for assessing diet (Sorenson 1982), are generally recorded only for days or weeks, whereas dietary histories over several years may be most pertinent (Byers and Graham 1984). More recent dietary survey instruments may improve the validity and efficiency of dietary assessment (Byers and Graham 1984; Willett and MacMahon 1984a, 1984b).

These methodological problems, the limited understanding of cancer at the molecular level, the variety of foods, and the complexity of the composition of foods in the diet have hindered our understanding of the relationship among diet, nutrition, and cancer. Despite uncertainties, evidence supports a role for several dietary components in prevention or causation of specific cancers. The most important of these reported associations are summarized in Table 4-4 and discussed further below.

Dietary Guidelines for Cancer Prevention

Dietary changes beyond the minimum intakes required for preventing nutritional deficiencies may decrease an individual's risk for cancer (EOC-CPS 1986). Translation of research results into dietary guidelines has always been controversial, but in 1979 the Director of the National Cancer Institute proposed a series of recommendations (Upton 1979). Also in

Table 4-4
Reported Relationship Between Selected Dietary Components and Cancer

Selected cancer sites in descending order of incidence (Age-adjusted incidence, SEER, 1984)		Fat	Body Weight and Calories	Fiber	Fruits and Vegetables	Alcohol	Smoked, Salted, and Pickled Foods
Lung	(55)[a]				−	+[b]	
Breast	(51)	+	+		−	+	
Colon	(36)	+	+	−	−		
Prostate	(34)	+	+		−		
Bladder	(16)				−		
Rectum	(15)	+				+	
Endometrium	(13)	+	+				
Oral Cavity	(11)				−	+	
Stomach	(8)				−		+
Kidney	(8)		+				
Cervix	(5)		+		−		
Thyroid	(4)		+				
Esophagus	(4)					+	+

Key: + = Positive association; increased intake with increased cancer.
− = Negative association; increased intake with decreased cancer.

[a]Rate per 100,000 population, age-adjusted incidence from United States, 1984, Sondik et al. 1987.
[b]Synergistic with smoking.

1980, the National Cancer Institute commissioned the NAS to conduct a comprehensive review of research findings on diet, nutrition, and cancer to use as a basis for development of dietary guidelines and recommendations for future investigation (NRC 1982). The most recent dietary guidelines from the National Cancer Institute (Butrum, Clifford, and Lanza 1988) are listed in Table 4-5.

As shown in Table 4-6 and discussed in the introductory chapter, dietary guidelines have been issued by the National Cancer Institute, the American Cancer Society, the Federal Government (USDA and DHHS), and the American Heart Association. They tend to be similar in making general recommendations about maintenance of desirable weight, the importance of a variety of wholesome foods, reduction of fat, adequate levels of fiber, and, at most, moderate levels of alcohol intake. They vary, however, in the development of quantitative guidelines and in the rationale used to indicate a link between dietary intake and the risk for various diseases.

Key Scientific Issues

- Role of Dietary Fats in Cancer
- Role of Calories and Body Weight in Cancer
- Role of Dietary Fiber in Cancer
- Role of Vitamin A and Carotenoids in Cancer
- Role of Alcohol in Cancer
- Role of Other Dietary Constituents in Cancer

Table 4-5
National Cancer Institute
Dietary Guidelines

1. Reduce fat intake to 30 percent or less of calories.
2. Increase fiber intake to 20 to 30 grams daily, with an upper limit of 35 grams.
3. Include a variety of vegetables and fruits in the daily diet.
4. Avoid obesity.
5. Consume alcoholic beverages in moderation, if at all.
6. Minimize consumption of salt-cured, salt-pickled, and smoked foods.

Source: Butrum, Clifford, and Lanza 1988.

Table 4-6
Comparison of Dietary Guidelines for the American Public

	Fat	Fiber	Fruits and Vegetables	Obesity	Alcohol	Salt
NCI Dietary Guidelines Butrum et al. 1988	Reduce fat intake to 30% or less of calories	Increase fiber intake to 20 to 30 g, not to exceed 35 g	Include a variety of fruits and vegetables in the daily diet	Avoid obesity	Consume alcoholic beverages in moderation, if at all	Minimize consumption of salt-cured, salt-pickled, and smoked foods
American Cancer Society 1985	Cut down total fat intake	Eat more high-fiber foods	Include foods rich in vitamins A and C; include cruciferous vegetables	Avoid obesity	Keep alcohol consumption moderate if you do drink	Keep consumption of salt-cured, smoked, and nitrite-cured foods moderate
USDA/DHHS 1985 *Dietary Guidelines for Americans*	Avoid too much fat, saturated fat, and cholesterol	Eat foods with adequate starch and fiber	Eat a variety of foods	Maintain desirable body weight	If you drink alcoholic beverages, do so in moderation	Avoid too much sodium
American Heart Association 1985	Total fat, 30% or less of calories; saturated fat, 10% of calories; cholesterol, 100 mg/1,000 calories—not 300 mg/day	Include breads, cereals, pasta, and starchy vegetables containing natural complex carbohydrates	Include at least 3 servings/day of fruits and 3 servings/day of vegetables	Achieve and maintain desirable weight	If you drink, do so in moderation	Limit salt intake

Source: Butrum, Clifford, and Lanza 1988.

Role of Dietary Fats in Cancer

Despite some inconsistencies in the data relating dietary fat to cancer causation, animal studies show an effect on carcinogenesis and support a cancer-promoting role, and international epidemiologic studies have suggested that differences in dietary fat intake may provide a meaningful key to prevention of cancer. For example, substantial epidemiologic and animal evidence supports a relationship between dietary fat and the incidence of both breast cancer (Kakar and Henderson 1985) and colon cancer (Kolonel and Le Marchand 1986). Indeed, a comparison of populations indicates that death rates for cancers of the breast, colon, and prostate are directly proportional to estimated dietary fat intakes (Wynder et al. 1981; Rose 1986). Other cancers that have been related to fat intake are those of the rectum (Armstrong and Doll 1975), ovaries (Rose, Boyar, and Wynder 1986), and endometrium (Mahboubi, Eyler, and Wynder 1982). Considerable uncertainties remain to be resolved about these relationships. For example, the effects of different types of dietary fat (i.e., saturated vs. unsaturated; animal vs. plant origin) have not been separated in most human studies. But the weights of the studies to date are strongly suggestive of the role for dietary fat in the etiology of some types of cancer.

Human Epidemiologic Studies

The risk for breast cancer is correlated with total fat consumption in comparisons of countries (Armstrong and Doll 1975; Gray, Pike, and Henderson 1979; Rose, Boyar, and Wynder 1986), districts in Japan (Hirayama 1977), and ethnic groups in Hawaii (Kolonel, Hankin, et al. 1981). The risk for cancers of the colon and prostate is also correlated with total fat consumption in international comparisons (Armstrong and Doll 1975; Knox 1977; Liu et al. 1979). A worldwide correlation between breast and colon cancer mortality and total fat consumption has been demonstrated (Carroll and Khor 1975) and is illustrated for breast cancer death rates in Figure 4-3.

Although further epidemiologic study is needed to verify the association between diet and breast cancer and to elucidate its biologic basis, the consistency of the evidence derived from the epidemiologic and animal studies suggests that the association may be causal (Miller 1986). Table 4-7 summarizes certain key (although limited) dimensions of the human epidemiologic studies of diet and breast cancer. Correlation studies show the strongest associations. Migrant studies often show that people who move to a country with a higher incidence of breast cancer than their native country tend to acquire the dietary habits of their new country of residence

and may experience a cancer incidence that changes with the change in dietary fat (Kolonel, Nomura, et al. 1981; Gori 1979). Case-control and cohort studies relate the risk for breast cancer to total fat consumption in some (Miller et al. 1978; Lubin, Wax, and Modan 1986) but not all (Graham et al. 1982; Willett et al. 1987) studies. While methodological problems may have obscured a true risk association in these negative studies (Willett et al. 1987; Hebert and Wynder 1987; Self et al. 1988), they reinforce the need for cautious interpretation and additional study of diet and breast cancer risk.

A Canadian case-control study has related an elevated risk for colon cancer with an increased intake of calories, total fat, and saturated fat (Jain et al. 1980). Fat consumption has been associated with colon cancer in American blacks (Dales et al. 1978) and in Americans of Bohemian ancestry in Nebraska (Pickle et al. 1984). Other studies have demonstrated no excess risk for colon cancer, and a recent review has found the evidence to be inconclusive (Kolonel 1987).

Some studies show associations between breast or colon cancer and meat intake that are similar to those with fat intake (McKeown-Eyssen and Bright-See 1985; Armstrong and Doll 1975; Lubin et al. 1981). At present, these data do not establish meat and other animal protein intake as risk factors independent of fat intake (Kolonel and Le Marchand 1986). In postmenopausal breast cancer, the association of dietary fat may be related to a higher intake of total calories during a high-fat diet, to obesity, or to a lower intake of foods that provide protective micronutrients (Willett 1987). In colon cancer, if various hypotheses hold true, the carcinogenesis-enhancing effects of dietary fat may interact with the possibly protective effects of dietary fiber (Jensen, MacLennan, and Wahrendorf 1982).

The effect of dietary cholesterol on cancer incidence is difficult to determine both because of the strong correlation of cholesterol with animal fat, and therefore with protein intake, and because blood cholesterol levels reflect more than *dietary* cholesterol levels. In one study, the correlation with colon cancer incidence was stronger for dietary cholesterol than for dietary fat (Liu et al. 1979). On the other hand, some studies that have examined blood cholesterol correlations and cancer suggest that very low blood cholesterol levels may be a risk factor for cancer (McMichael et al. 1984). Much more work is needed before firm conclusions can be drawn about the relationship of either dietary or blood cholesterol levels to cancer.

Table 4-7
Summary of Epidemiologic Studies Examining Dietary Fat and Breast Cancer

Author(s)	Total Fat	Animal Fat	Meat	Eggs	Vegetable Fat
International Correlation					
Lea 1966	+(a)				
Carroll et al. 1968	+				
Hems 1970	+				
Drasar & Irving 1973	+	+	+(b)	+	
Armstrong & Doll 1975	+		+(c)		
Carroll & Khor 1975	+				
Hems 1978	+				
Gray et al. 1979	+		+(b)		
Carroll 1980	+	+			0
Rose et al. 1986	+	+	+(d)		0
Within-Country Correlation					
Hirayama 1977	+				
Enig et al. 1978	+	−			+
Nomura et al. 1978			+		+
Gaskill et al. 1979		+(e)		−	
Ingram 1981	+		+		
Kolonel et al. 1981	+	+	+(b)		
Kinlen 1982			0		
Case-Control Studies					
Phillips 1975					+(d)
Miller et al. 1978	+				
Lubin et al. 1981			+(g)		
Graham et al. 1982	0				
Talamini et al. 1984		+(h)	0		
Nomura et al. 1985	0				
Le et al. 1986		+/−(i)			
Hislop et al. 1986		+/−(j)	+(b)		
Katsouyanni et al. 1986	0(a)				
Lubin et al. 1986	+		+(b)		
Hirohata et al. 1987	0		0(b)		

Table 4-7 (continued)

Author(s)	Total Fat	Animal Fat	Meat	Eggs	Vegetable Fat
Cohort Studies					
Hirayama 1978			+		
Phillips & Snowden 1983			0		
Willett et al. 1987	0				
Jones et al. 1987	0				

Key: (a) = Fats and oils.
(b) = Animal protein.
(c) = Meat and animal protein.
(d) = Meat, milk, and animal protein.
(e) = Milk.
(f) = Fried potatoes.
(g) = Beef and pork.
(h) = Dairy products.
(i) = Positive for cheese and fat in milk. Negative for yogurt. No association for butter.
(j) = Positive for gravy, beef, and pork. Negative for fish.

Animal Studies

Animals fed a high-fat diet often have higher rates of carcinogen-induced cancers of the breast, colon, and pancreas than those fed low-fat diets (Carroll 1986). Animal studies that indicate that dietary fat could influence carcinogenesis date back more than half a century (Watson and Mellanby 1930), with experiments indicating that the incidence of skin tumors on coal-tar-treated mice could be increased by more than 70 percent by feeding them diets higher in saturated fat. Investigators studying mammary tumors in mice found that the later a high-fat diet was begun, the lower the incidence of tumors; that tumors occurred more frequently in obese mice (Tannenbaum and Silverstone 1957); and that fat restriction inhibited mammary tumorigenesis in normal mice (Tannenbaum 1942). Rats fed a low-fat diet (2 percent linoleic acid) were noted to have markedly lower rates of chemically induced (7,12-dimethylbenz[a]anthracene (DMBA)) mammary tumors than those fed high polyunsaturated (20 percent corn oil) or saturated (18 percent coconut oil, 2 percent linoleic acid) fats (McCay et al. 1980).

Various animal studies have also associated intestinal tumors with higher levels of dietary fat. Rats fed 35 percent of total calories as beef fat were

noted to develop both more intestinal tumors and more metastases in response to azoxymethane (AOM) than rats fed normal chow (Nigro et al. 1975). Rats given 1,2-dimethylhydrazine (DMH) for tumor induction were noted to have more large bowel tumors on 30 percent lard diets than on low-fat standard diets (Bansal, Rhoads, and Bansal 1978). The role of fat as a tumor promoter, rather than inducer, is suggested by studies such as one indicating that, relative to a 5 percent beef fat diet, a diet of 30 percent beef fat increased the rate of intestinal tumors only when fed to rats after AOM administration (Bull et al. 1979).

Some studies suggest that polyunsaturated fat has the greatest tumor-enhancing effect for mammary (Cohen 1986), pancreatic (Birt and Roebuck 1986), and colon (Reddy 1986) cancers. High intakes of oleic (monounsaturated) and linoleic (polyunsaturated) acids correlate with increased mammary tumor incidence (Chan, Ferguson, and Dao 1983). In contrast, highly unsaturated omega-3 fatty acids derived from fish oils may protect against cancer (Braden and Carroll 1984), reduce tumor growth rates (Karmali, Marsh, and Fuchs 1984), and minimize the incidence of tumors promoted by high amounts of dietary corn oil (Ip, Ip, and Sylvester 1986). Hypotheses regarding types of fat and cancer risk require additional study.

Biochemical Mechanisms

Although dietary fat generally exerts its maximum effect when fed after carcinogen administration, it appears that sufficient duration of exposure to high dietary fat levels before carcinogen administration might affect tumor initiation as well; such an effect has been demonstrated for rat mammary carcinogenesis (Dao and Chan 1983).

The effect of dietary fat may be direct or indirect (Cohen 1986). Fat directly affects many cellular functions, including cell membrane fluidity, prostaglandin metabolism, and synthesis of potentially mutagenic lipid peroxide radicals (Welsch 1987). Direct effects also include changes in hormone receptors (which might promote hormonally mediated tumor growth), cell growth characteristics, and various intracellular chemicals. Fat-induced changes in bile acid composition in the colon may promote bacterial conversion of bile acids to tumor-promoting substances or may directly damage the colonic mucosa (Kritchevsky 1982; Goldin 1986).

Role of Calories and Body Weight in Cancer

Animal studies and a few epidemiologic investigations support the hypothesis that total caloric intake affects the risk of cancer. Some animal studies compared normal controls with animals on diets severely restricted in calories; others have compared normal and obese animals (Stunkard 1983). Because accurate measures of caloric intake over long periods of time are difficult, human studies usually focus on indirect measures such as body weight, relative body weight, or body weight indices that are presumed to correlate with increased caloric intake. Complicating these studies is the question of energy expenditure in maintaining caloric balance. The relationship between caloric intake, body weight, and cancer was the subject of a recent review (Albanes 1987) and a symposium (Pariza and Simopoulos 1987). This symposium also contains several studies on the association of exercise to cancer prevention.

Human Epidemiologic Studies

In international studies, a correlation between total per capita calories and cancers of the breast, colon, rectum, uterus, and kidney has been reported (Armstrong and Doll 1975). Case-control studies have found positive associations between energy intake and breast cancer (Miller et al. 1978) and energy intake and colorectal cancer (Jain et al. 1980; Lyon et al. 1987).

A positive association between increased body weight or body mass index and an increased risk for cancer has been observed for several cancers, including breast (de Waard and Baanders-van Halewijn 1974; Hirayama 1978; Mirra, Cole, and MacMahon 1971), kidney (Goodman, Morgenstern, and Wynder 1986), endometrium (La Vecchia et al. 1984), and prostate (Snowdon, Phillips, and Choi 1984). Other studies report no effect of body weight on increased risk for cancers of the breast (Adami et al. 1977; Soini 1977), colon (Wynder et al. 1969), and prostate (Greenwald et al. 1974). Table 4-8 summarizes some of these and other retrospective human studies of cancer and body weight.

In a large cohort study conducted by the American Cancer Society, the lowest overall cancer mortality was observed in men whose body weights ranged from 10 percent below to 20 percent above the average for their age and height. The lowest risk overall for women was seen in those whose weights ranged from 20 percent below to 10 percent above the average for their age and height. Nonsmoking males (who usually weigh more than

Table 4-8
Retrospective Human Studies Relating Body Weight and Cancer

First Author/ Year	Location	Comments
Breast		
de Waard 1964	The Netherlands	No statistical tests presented; 30% increased risk for obesity, and 60% increased risk for obesity plus hypertension; opposite trend in premenstrual women.
Valaoras 1969	Greece	Positive association with height, BW, and BMI.
Mirra 1971	Brazil	Associations observed among women 50 years old only; positive association with height, BW, and BMI.
Lin 1971	Taiwan	Increased effect among women 50 years old; no effect for height; positive effect for weight.
Adami 1977	Sweden	Nonsignificant case-control differences in mean BW and BMI in postmenopausal women. Opposite trend in premenopausal women also not significant; no effect for height; used measured BW for cases, self-reported BW for controls.
Soini 1977	Finland	Nonsignificant case-control differences for BW or BMI. Nonsignificant positive association with height; limited age range (41–60 years), and no analysis by menopausal status.
Hirayama 1978	Japan	Increased risk for postmenopausal women greater than for premenopausal. Independent positive associations for both BW and height.
Choi 1978	Canada	Increased BW in postmenopausal cases. Decreased BW in premenopausal cases. Postmenopausal cases also taller.
Paffenbarger 1980	U.S.	Increased risk with BMI in postmenopausal women. Decreased risk in premenopausal women. Increased height in premenopausal cases.

Table 4-8 (continued)

First Author/ Year	Location	Comments
Breast (continued)		
Kelsey 1981	U.S.	Increased risk with BW in postmenopausal women. Decreased risk in premenopausal women.
Brisson 1984	U.S.	Increased risk with BW in pre- and postmenopausal women; inverse association with height.
Kidney		
Wynder 1974	U.S.	Greater proportion cases with RBW > 125% in females only.
McLaughlin 1984	U.S.	Increased risk with BMI in females. Positive association for weight gain since age 20 in females.
Maclure 1985 (abstr)	U.S.	Increased risk with BMI in men and women.
Goodman 1986	U.S.	Increased risk with BMI in men and women.
Asal 1985 (abstr)	U.S.	Increased risk with BMI in men and women.
Yu 1986	U.S.	Increased risk with BMI in men and women independent of tobacco and other risk factors.
Endometrium		
Kelsey 1982	U.S.	Increased risk with BW and similar trend for BMI (not presented by authors).
Henderson 1983	U.S.	Increased risk with BW and similar trends for BMI and BW at age 20.
La Vecchia 1984	Italy	Increased risk with BMI greater for premenopausal than for postmenopausal women.

Table 4-8 (continued)

First Author/ Year	Location	Comments
Prostate		
Wynder 1971	U.S.	No significant difference in RBW between cases and controls with no significant difference in height.
Colorectal		
Wynder 1969	Japan	No significant difference in RBW between cases and controls.
Thyroid		
McTiernan 1985 (abstr)	U.S.	Increased risk with BW in > = 60 vs. < = 52 kg. Only women studied.
Meningioma		
Bellur 1983	U.S.	Increased risk for "obese" women. No significant difference among men.

Key: BW = body weight.
BMI = body mass index.
RBW = relative body weight.
P values for test for trend, unless otherwise indicated.

Source: Adapted from Albanes 1987.

smokers but have a lower cancer risk) showed a relationship between relative body weight and cancer death that was nearly linear (Lew and Garfinkel 1979). In the United States, individuals greater than 40 percent overweight have mortality ratios (observed cancer deaths divided by expected cancer deaths) higher than average-weight individuals by 33 percent for men and 55 percent for women (Garfinkel 1985). In men, this relationship was statistically significant for cancer of the colon, rectum, and prostate, and in women, for cancer of the breast, uterus (cervix and endometrium), ovary, and gallbladder.

Animal Studies

Restriction of caloric intake reduces the incidence of many different cancers and increases the lifespan of laboratory animals (Tannenbaum 1940a; Kritchevsky and Klurfeld 1987). Some of these suggest that the greatest reduction in cancer incidence is associated with lifelong restriction of

calories, but caloric restriction begun in adulthood may also have a protective effect (Weindruch and Walford 1982).

Total caloric intake as well as calories derived from fat affect cancer risk, but their relative importance may vary for different tumor types (Kritchevsky, Weber, and Klurfeld 1984). One study that has attempted to separate the effects of calories from those of fat suggested that tumor incidence in rats depends on energy intake, energy retention, and body size rather than on percent of fat calories in the diet (Boissonneault, Elson, and Pariza 1986).

Biochemical Mechanisms

While no unifying principle to explain the relationship has emerged, current investigations in animals support the idea that overnutrition increases cancer risk (Pariza and Boutwell 1987). One hypothesis is that chemical carcinogens may be stored in body fat for mobilization and transport to target tissues. A second hypothesis is that the supply of available energy is one factor that controls cell growth (Pardee et al. 1978; Scott, Wille, and Wier 1984), and an excess of available energy may increase cell multiplication and affect the promotion phase of carcinogenesis. Excess energy could also shorten the latent period. A third hypothesis involves the influences of female hormones on breast, ovarian, and uterine cancers, with metabolism of hormones in adipose tissue possibly playing a role in tumor formation and growth. Androstenedione from the adrenal gland can be converted to estrogen in adipose tissue and may stimulate cell division in the target organs of obese individuals (Siiteri 1987). Thus, although animal studies suggest that caloric restriction might reduce cancer incidence, the results of human studies are not wholly consistent (see Table 4-8). To resolve these inconsistencies, additional studies are needed to separate the individual effects of calories, fat, and obesity (Willett 1987).

Role of Dietary Fiber in Cancer

Dietary fiber includes components of plant materials that, when eaten, resist the action of human digestive enzymes. Dietary fiber has diverse chemical constituents, including carbohydrate and carbohydrate-like cellulose, hemicelluloses, lignin, gums, and pectins. Major food sources of fiber are fruits, vegetables, and whole grain cereals.

In some studies, particularly correlation studies, consumption of high-fiber foods has been correlated with lower risk of colon cancer. An important

issue in human studies is the lack of information about the specific components of dietary fiber and how they may affect cancer risk. Although rodent studies have provided conflicting results, they do suggest that the type of fiber is important. In those studies that showed a protective effect, wheat bran, a source of water-insoluble fiber, was more consistently associated with lower risk of colon cancer than other fiber sources (Pilch 1987).

Human Epidemiologic Studies

The results from 44 epidemiologic studies conducted between 1973 and 1987 are summarized in Table 4-9. Numerous correlation studies have suggested a protective effect of dietary fiber against colon cancer (Burkitt 1980; Reddy 1982; Greenwald, Lanza, and Eddy 1987). Of the 24 correlation studies, 21 identified an inverse association of dietary fiber, fiber-rich diets, or other measures of fiber consumption with occurrence of colon cancer; 3 showed no association; and none reported a positive association. One international study that found an inverse association with total dietary fiber also found a protective effect of cereal fiber, even after adjustment for intake of fat or meat (McKeown-Eyssen and Bright-See 1985).

In some studies, correlations with other nutrients were also observed. Thus, while patterns of eating foods high in fiber show good correlation with low colon cancer rates, other dietary components might also be influencing this association. It must also be noted that international correlation studies (seven studies) tend to derive their food data from similar sources.

Several epidemiologic studies that include biochemical markers have correlated cancer rates to measures of stool weights, fecal bile acids, enzymes from colonic bacteria, and fecal mutagens. Comparison of rural Finns (who have low rates of colon cancer) to their urban counterparts shows that intake of calories and fat is similar for both groups, but the rural Finns have a higher intake of dietary fiber, a greater stool weight, and a lower level of fecal bile acids than urban Finns (Englyst et al. 1982; Cummings and Branch 1982; Jensen, MacLennan, and Wahrendorf 1982; Bingham et al. 1982).

The importance of these observations derives in part from the fact that secondary bile acids, formed by bacterial degradation of primary bile acids in the intestine, have been shown to promote tumors in animals (Wynder and Reddy 1983), may be mutagenic (Wilpart et al. 1983), and are directly correlated with population incidence of colon cancer (Hill 1983). Fecal mutagens are also correlated with the incidence of colon cancer in popula-

Table 4-9
Summary of Epidemiologic Studies Examining Dietary Fiber and Colon Cancer

Authors	Year	Fiber	Cereals	Vege-tables	High Fiber/ Low Fat
International Correlation Studies					
Drasar & Irving	1973	0			
Irving & Drasar	1973		−(a)		
Armstrong & Doll	1975		−(a)		
Howell	1975		−	−	
Knox	1977		−	−	
Liu et al.	1979	−(a)			
McKeown-Eyssen & Bright-See	1985	−			
Within-Country Correlation Studies					
Malhotra	1977	−(b)			
Lyon & Sorenson	1978	0			
Enstrom	1980			−(b)	
Rozen et al.	1981	−			
Maisto & Bremner	1981	−(b)			
Jensen	1983	−(b)		−	
Bingham et al.	1985	−			
Metabolic Correlation Studies					
MacLennan et al.	1978	−	−		
Reddy et al.	1978		−		
Reddy et al.	1980	−			
Jensen et al.	1982	−	−		
Reddy et al.	1983	−			
Nair et al.	1984	−			
Walker et al.	1986	0			
Time Trend Correlation Studies					
McMichael et al.	1979	−(b)			
Helms et al.	1982	−			
Powles & Williams	1984	−	−(a)		

Table 4-9 (continued)

Authors	Year	Fiber	Cereals	Vege-tables	High Fiber/ Low Fat
Case-Control Studies					
Haenszel et al.	1973			+	
Bjelke	1974a			−	
Bjelke	1974b			−	
Phillips	1975			−(b)	
Modan et al.	1975	−			
Graham et al.	1978			−	
Dales et al.	1978				−
Moskowitz et al.	1979	0			
Haenszel et al.	1980			−	
Hunter et al.	1980	−(b)			
Jain et al.	1980	0			
Martinez et al.	1981	+	+		
Manousos et al.	1983			−	
Pickle et al.	1984	0			
Potter & McMichael	1986	+(a)	+(a)		
Tuyns	1986			−	
Macquart-Moulin	1986	−(a)		−	
Lyon et al.	1987	−(b)			
Kune et al.	1987	−		−	
Cohort Studies					
Hirayama	1981			−	

Key: 0 = No association.
− = Inverse association (decreased risk).
+ = Direct association (increased risk).
(a) = Adjustment for other food components removes the association.
(b) = No test for significance or not statistically significant.

tions (Wilkins and Van Tassell 1983), although no such correlations have been observed for individuals (Correa 1981). Recently, fecal mutagens have been shown to be modulated by dietary fiber (Reddy et al. 1987). In addition, fermentation of fiber in the colon by intestinal bacteria results in the release of short-chain fatty acids, which may directly influence colonic mucosal cells (Reddy 1982). Further research is needed to elucidate the role of fecal mutagens in colon cancer and the influence of various dietary fibers (Pilch 1987).

Additional support for generating the fiber/cancer hypothesis comes from time-trend correlation studies. Long-term trends in colon cancer for several population groups also offer insights into the role of dietary fiber. In

Denmark, the decrease in dietary fiber consumption from 1927 to 1977 has been correlated to the rise in prevalence of colon cancer (Helms et al. 1982). In seven other countries, changes in flour milling practices during World War II led to increased consumption of total fiber, which correlated with a reduced mortality of colon cancer in those countries 15 years later (Powles and Williams 1984). Other wartime lifestyle changes, such as decreased fat or meat consumption, however, could have also influenced mortality.

To date, 19 case-control studies have assessed the role of fiber-containing foods in colon cancer: 3 of these studies found no effect (Moskowitz et al. 1979; Jain et al. 1980; Pickle et al. 1984), 3 found an increased risk (Haenszel et al. 1973; Martinez et al. 1981; Potter and McMichael 1986), and 13 observed a protective effect of fiber-containing foods, especially vegetables. Protective effects have been found in two case-control studies that examined the relative risk for a high-fat, low-fiber diet (Dales et al. 1978; Manousos et al. 1983). Overall, case-control studies present mixed results. Some show fiber and fiber-containing foods to be protective; others do not.

Animal Studies

Animal studies of dietary fiber and colon cancer have provided inconsistent results due to a number of factors, including differences in the nature of the carcinogen used, variations in composition of the diet, qualitative and quantitative differences in the fibers fed, animal strain, or duration of the experiment (Reddy 1986; Pilch 1987). In the past decade, a number of studies have been conducted on laboratory rats fed diets of various fiber sources and levels and exposed to certain known colonic carcinogens: DMH, AOM, DMAB, and methylnitrosurea (MNU). When wheat bran was used as the source of dietary fiber, a protective effect was seen in the majority (Reddy 1982; Barbolt and Abraham 1978) but not all studies (Bauer et al. 1979; Jacobs 1983). A protective effect against colon cancer was found in studies of chemical carcinogens requiring microsomal activation (DMH, AOM, DMAB) but not in one study with MNU, a direct-acting carcinogen. Other studies reported were less suggestive of protection. Although two-thirds of studies showed that dietary cellulose was protective for rats exposed to DMH and AOM, no effect was observed for the rest. Studies of the effect of corn bran, rice bran, oat bran, pectin, and guar gum must be considered indeterminant, with some showing a protective effect, more showing an enhancing effect, and others showing no effect (Pilch 1987). The relevance of these animal models to human cancer needs to be determined.

Biochemical Mechanisms

The means by which fiber may exert its protective action are not understood. Several possibilities have been advanced: Fiber may act to reduce transit time in the bowel and therefore decrease the time for exposure to potential carcinogens; through its hydrophilic nature, it can dilute the concentration of carcinogens in the colon; it can affect the production of bile acids and other potential carcinogens in the stool; it can alter the nature of fecal bile acids by virtue of its influence on the composition and metabolic activity of fecal flora; and it can reduce colonic pH by increasing fermentation and short-chain fatty acid production (NRC 1982; Eastwood, McKay, and Brydon 1986).

Limited information is available on the types of dietary fiber that might protect against cancer. Research will have to define the importance of various fiber compounds relative to the risk for specific cancers. The term fiber embraces a broad range of food components whose primary commonality is their relative indigestibility. Different types of fiber have very different qualities. Some are classified as soluble, others insoluble. Some, but not all, appear to affect gastric emptying. Some affect absorption of certain nutrients, others do not. Animal studies suggest that different types of fiber work differently with respect to the occurrence of colon cancer. As noted earlier, wheat bran, which decreases gastrointestinal transit time and increases stool weight, appears to more consistently reduce the frequency of colon tumors in animals than other types of fiber (Pilch 1987). However, until better methods for analyzing the fiber content of foods are developed, the influence of fiber components such as pentosan fractions (Bingham et al. 1979), uronic acids (pectins), or cellulose (Bingham, Williams, and Cummings 1985) must be considered uncertain.

In humans, a sudden change from a low-fiber to a high-fiber diet may provoke symptoms of gastrointestinal distress, although effects are not generally seen with gradual increases. The most frequently suggested adverse effect of high fiber intake is mineral imbalance. While the evidence is mixed, a recent review suggested that consumption of diets containing about 20 to 25 g of insoluble fiber from foods per day does not appear to pose a problem relative to mineral availability (Pilch 1987). This amount translates to approximately 30 to 35 g of total dietary fiber from a mixed adult diet and is consistent with current recommendations of the National Cancer Institute (20 to 30 g daily from a variety of food sources, including vegetables, fruits, and whole grain cereals).

Role of Vitamin A and Carotenoids in Cancer

A large body of evidence suggests that foods high in vitamin A and carotenoids are protective against a variety of epithelial cancers (Mettlin 1984; Kummet, Moon, and Meyskens 1983; Bertram, Kolonel, and Meyskens 1987; Palgi 1984).

Vitamin A in foods occurs in two forms: (1) preformed vitamin A (retinol and retinol esters) from animal foods and (2) provitamin A (carotenoids that the body can convert to vitamin A) from plant foods. Hundreds of other carotenoid compounds in fruits and vegetables seem to have no vitamin A activity. Beta-carotene-containing foods have been extensively studied in cancer epidemiology (Peto et al. 1981). Although beta-carotene is most efficiently converted (Linder 1985), it still has only one-sixth the biologic activity of retinol. Many reports on the effects of vitamin A do not specify whether they are studying preformed vitamin A, carotenoids in general, retinoid analogs of vitamin A, or beta-carotene alone (NRC 1982). This chapter uses the term vitamin A to include all of the above unless otherwise specified.

Epidemiologic studies have used food intake records to analyze the intake of beta-carotene, carotenoids, and retinol, or a "vitamin A index" that combines these. A methodological difficulty is that foods such as green and orange-yellow vegetables may contain protective factors in addition to carotenoids (Mettlin 1984). Other complications are presented because inverse correlations between blood levels of beta-carotene and retinol and risk for cancer have been identified in some but not all studies (Willett and MacMahon 1984a). Future studies that better distinguish the individual effects of beta-carotene, carotenoids, retinol, and other food components will require improved dietary assessment methods (Russell-Briefel, Caggiula, and Kuller 1985).

Human Epidemiologic Studies

Low levels of vitamin A (or retinol) in blood have been associated with an increased risk for cancer in some (Wald, Idle, and Boreham 1980; Kark et al. 1981) but not all (Wald et al. 1984; Willett et al. 1984; Nomura et al. 1985; Salonen et al. 1985) studies. Low levels of beta-carotene in stored blood also have been associated with an increased risk for cancer in some (Nomura et al. 1985; Stahelin et al. 1984) but not all (Willett et al. 1984; Menkes and Comstock 1984) studies. There are problems, however, in relating blood levels to cancer risk. Blood retinol remains unchanged across a wide range of dietary intakes because of homeostatic mechanisms.

Thus, increased vitamin A is unlikely to result in increased serum retinol, except during vitamin A depletion. Consequently, the association between serum retinol and cancer may be due to factors that regulate serum retinol rather than to dietary vitamin A itself. In contrast, serum carotenoids may better reflect dietary carotenoids, and the relationship between dietary carotenoids (or the foods that contain them) and cancer may be more direct than that between serum retinol and cancer. A major weakness of these studies is that blood levels of vitamin A or carotenoids observed at the time of diagnosis may be different from those present when the disease began.

One prospective cohort study on the older population in Massachusetts has shown that the risk for all cancers decreases with increasing intake of carotenoid-containing vegetables (Colditz et al. 1985). Foods containing vitamin A may be protective against cancer of the oropharynx (Ibrahim, Jafarey, and Zuberi 1977), larynx (Graham et al. 1981), breast (Graham et al. 1982), stomach (Stehr et al. 1985), cervix (La Vecchia et al. 1984), colon (Modan, Cuckle, and Lubin 1981), and bladder (Mettlin, Graham, and Swanson 1979). Results for cancer of the prostate have been mixed, however, with one study showing a protective effect (Schuman et al. 1982), two studies showing the opposite (Graham et al. 1983; Heshmat et al. 1985), and one showing no effect (Whelan, Walker, and Kelleher 1983).

Lung Cancer. The strongest evidence for the role of vitamin A in prevention of human cancer comes from epidemiologic studies that correlate consumption of carotenoid-containing vegetables or foods with a high vitamin A index to protection against cancer of the lung (Shekelle et al. 1981; Kvale, Bjelke, and Gart 1983). These studies are summarized in Table 4-10. The Western Electric Study of 1,984 middle-aged men, for example, found a protective effect with provitamin A (beta-carotene) but not preformed vitamin A (Shekelle et al. 1981). A case-control study of lung cancer in white males in New Jersey showed a 30 percent greater risk of cancer for men in the lowest quartile of carotenoid intake but no increased risk for a low consumption of retinol or total vitamin A intake (Ziegler et al. 1986). The Western New York Diet Study showed a protective effect for both total vitamin A and vitamin A from fruits and vegetables in men but not in women (Byers et al. 1987).

An important question in each of these studies is whether the protective effects attributed to vitamin A activity, as discussed above, are truly attributable to vitamin A or whether they are due to some other factor that may be present in the foods. For example, epidemiologic studies have shown an inverse association between the consumption of cruciferous vegetables such as cabbage, broccoli, Brussels sprouts, or cauliflower and

Table 4-10
Dietary Vitamin A and Lung Cancer Risk: A Summary of Previous Studies

Reference (location)	No. of Cases: Controls or Cohort Size	Sex	No. of Foods	Nutrient	Nutrient Level	Findings (Approximate % of Study Group)	Relative Risk
Case-Control Studies							
MacLennan et al. 1978 (Singapore)	233:300	Males and females	100	Green, leafy vegetables	Low High	(NP)[a] (NP)	2.2 1.0
Mettlin et al. 1979 (New York)	292:801	Males	33	Vitamin A	Low Medium High	(49) (27) (24)	1.7 1.5 1.0
Gregor et al. 1980 (England)	78:110	Males	10	Vitamin A	Low Medium High	(32) (46) (22)	2.5 2.8 1.0
Hinds et al. 1984 (Hawaii)	364:627	Males and females	85	Carotene	Lowest 1 2 3 Highest 4	(25) (25) (25) (25)	1.6 1.2 1.1 1.0
Ziegler et al. 1986 (New Jersey)	763:900	Males	44	Carotene	Low Medium High	(25) (50) (25)	1.3 1.3 1.0
Samet et al. 1985 (New Mexico)	342:546 (Anglos only)	Males and females	55	Carotene	Low Medium High	(33) (33) (33)	1.5 1.5 1.0

Table 4-10 (continued)

Wu et al. 1985 (Los Angeles)							
Adenocarcinoma	149:149	Females	21	Carotene	Lowest 1	(25)	2.5
					2	(25)	1.3
					3	(25)	0.8
					Highest 4	(25)	1.0
Squamous cell	71:71	Females	21	Carotene	Low	(50)	1.5
					High	(50)	1.0
Byers et al. 1987 (New York)	450:902	Males and females	129	Fat, vits. A, C, E, fiber, protein	Lowest 1	(25)	1.8
					2	(25)	1.8
					3	(25)	1.0
					Highest 4	(25)	1.0 (fruits/vegs.)
Prospective Studies							
Bjelke 1975 (Norway)	8,278	Males	50	Vitamin A	Low	(32)	2.6
					High	(68)	1.0
Hirayama 1979 (Japan)	265,118	Males and females	1	Green-yellow vegetables	Low[b]	(NP)	1.8
					High[b]	(NP)	1.0
Shekelle et al. 1981 (Chicago)	3,102	Males	26	Carotene	Lowest 1	(25)	7.2
					2	(25)	5.5
					3	(25)	3.0
					Highest 4	(25)	1.0
Kvale et al. 1983 (Norway)	16,713	Males and females	50	Vitamin A	Low	(35)	1.4
					Medium	(29)	1.2
					High	(36)	1.0

[a]NP = Not presented.
[b]For Hirayama, low = not daily; high = daily.

Source: Byers, T.E.; Graham, S.; Haughey, B.P.; Marshall, J.R.; and Swanson, M.K. 1987. Diet and lung cancer risk: findings from the Western New York Diet Study. *American Journal of Epidemiology* 125:351–63. Reprinted with permission.

cancers of the alimentary tract (Hirayama 1977; Haenszel et al. 1976) and large bowel (Graham et al. 1978). A study of lung cancer among New Jersey white males showed a protective effect for fruits and vegetables that was greatest for dark yellow-orange and green vegetables, but no statistically significant effect for retinol, carotenoids, or vitamin A activity (Zeigler et al. 1986). The protective effect could have been due to unmeasured carotenoids, vitamin C, indoles, or other unknown components present in these foods (Wattenberg and Loub 1978; NRC 1982). The lack of association for vitamin A or carotenoids might also be due to problems in calculating vitamin A and carotenoid intake from food composition tables based on dietary records (Beecher and Khachik 1984).

Animal Studies

Vitamin A and synthetic retinoids protect against epithelial cancers of the skin, lung, bladder, and breast in animals (Sporn 1980). High doses suppress induction of cancers of the cervix, vagina, colon, skin, forestomach, tracheobronchi, pancreas, and liver (Welsch, Zile, and Cullum 1986). Retinoids have also been shown to reverse the effects of carcinogens in mouse prostate organ cultures (Lasnitzki and Goodman 1974). Although beta-carotene is protective against skin cancer in animals, it has not received as much attention as vitamin A or retinoids because beta-carotene is poorly absorbed in animals. Synthetic analogs may have greater effects, greater site specificity, and less toxicity than natural vitamin A (Sporn and Roberts 1984).

Biochemical Mechanisms

Because retinoids are required for normal cell differentiation, their deficiency leads to improper differentiation of stem cells in epithelial tissue. In animals, retinoids may inhibit initiation and promotion stages of carcinogenesis (Welsch, Zile, and Cullum 1986). Retinoids may also have a role in reversing cancerous changes, as has been demonstrated in mouse prostate organ cultures (Sporn 1980).

Antioxidant chemicals are thought to protect against certain promoters of carcinogenesis (Ames 1983). Foods containing vitamin A have been shown to protect against the formation of oxygen radicals and lipid peroxidation (Welsch, Zile, and Cullum 1986), and beta-carotene is a very efficient neutralizer of oxygen radicals (Foote 1976). Vitamin A, along with vitamin C, vitamin E, and selenium, may neutralize peroxidation effects and minimize carcinogenesis (Ames 1983), although these hypotheses remain to be confirmed.

Clinical Trials

Recurrence of urinary bladder cancer has been shown to decrease by about half with synthetic retinoid treatment in two clinical trials (Studer et al. 1984; Alftlan et al. 1983). Micronucleus formation, a marker for cellular genetic damage, has been reversed by beta-carotene treatment of people who chew betel nuts and tobacco (Stich et al. 1984). Synthetic retinoid treatment causes regression of bronchial dysplasia (Gouveia et al. 1982). Clinical trials are now in progress to determine the efficacy of retinoids in the prevention and treatment of cervical cancer, malignant melanoma, and other cancers (Meyskens 1982). The National Cancer Institute is funding a number of trials (Table 4-11) to determine the effects of beta-carotene and other antioxidant nutrients on several cancer types. These will produce results in the early 1990's.

Large amounts of retinoids in the blood or tissues, however, can be toxic and may cause birth defects (Kamm 1982) and adverse effects on skin, liver, and neurologic tissue (Olson 1983). Excessive intake of preformed vitamin A or retinoid supplements should be avoided, especially by pregnant women. However, increased intake of carotenoids from foods alone is unlikely to have any adverse effects, other than skin discoloration at very large intakes.

Role of Alcohol in Cancer

Reviews of experimental and epidemiologic data suggest an association between alcohol consumption and human cancer that is strongest for certain head and neck cancers (Tuyns 1982; NRC 1982). Alcohol intake and smoking act synergistically to increase the risk for cancer of the mouth, larynx, and esophagus (Broitman, Vitale, and Gottlieb 1983). Although alcohol has an effect independent of smoking in increasing cancer risk, it remains uncertain whether the responsible agent is alcohol itself or any of the more than 400 congeners (other chemicals) identified in alcoholic beverages (Darby 1982). Consumption of excess alcohol is often accompanied by poor eating habits, but the effects of alcohol and nutrition can be distinguished (see chapter on alcohol), and poor nutritional intake and alcohol intake appear to have separate and multiplicative effects on the risks of esophageal cancer (Ziegler et al. 1981). Chronic alcoholism, particularly in the marginally nourished individual, can deplete various essential nutrients (Vitale, Broitman, and Gottlieb 1981). As discussed in the chapter on infections and immunity, the nutritional deficiencies produced in alcoholics could be associated with impaired immune function, permitting increased carcinogenesis (Watson 1984).

Table 4-11
NCI-Sponsored Prevention Clinical Trials Related to Vitamin A

Investigator/Cancer Site/Agent	Population Under Study
Hennekens/all sites/beta-carotene, aspirin	U.S. male physicians, 40–84 years old. No evidence of cancer, heart disease, or stroke.
Greenberg/skin/beta-carotene	Males and females less than 85 years of age, basal or squamous cell carcinoma within past year.
Luande/skin/beta-carotene	African albinos with epidermal atrophy, dermal hypertrophy, or stage III solar keratoses.
Bowen/colon/beta-carotene	Males and females with prior adenomatous colonic polyp.
Kuller/lung/beta-carotene	Males, 55–70 years old, moderate to heavy cigarette smokers.
Albanes/lung/beta-carotene, alpha-tocopherol	Finnish males, 50–69 years old, cigarette smokers.
Safai/skin/beta-carotene, vitamins C and E	Males and females, 40–80 years old, 2 or more prior basal cell carcinomas.
Greenberg/colon/beta-carotene, vitamins C and E	Males and females, less than 75 years old, prior neoplastic polyp.
Moon/skin/retinol	Males and females, 21–85 years old, more than 10 prior actinic keratoses.
Tangrea, Peck/skin/13-*cis* retinoic acid	Males and females, 40–75 years old, 2 or more prior basal cell carcinomas.
Meyskens/skin/retinol, 13-*cis* retinoic acid	Males and females, 40–85 years old, 8 or more prior basal cell or squamous cell carcinomas.
Taylor/esophagus/beta-carotene	Males and females, 40–69 years old, severe esophageal dysplasia, Linxian, China.
Taylor/esophagus/beta-carotene, multiple vitamins and/or minerals	Males and females, 40–69 years old, general population, Linxian, China.
Omenn/lung/retinol, beta-carotene	Males and females, minimum age 45 years, at least 20 years since first exposure to asbestos, diagnosis of asbestosis.

Table 4-11 (continued)

Investigator/Cancer Site/Agent	Population Under Study
Goodman/lung/retinol, beta-carotene	Males and females, 50–67 years old, smoking history of 20 pack years or greater, current smokers or those who have quit smoking less than 6 years previously.
McLarty/lung/retinol, beta-carotene	Males and postmenopausal females, former asbestos workers verified by the Tyler Asbestos Workers Program, University of Texas Health Center patients with moderate or severe sputum cytology atypia.
Schatzkin/lung/beta-carotene, retinol, vitamin E, selenium	Tin miners active and retired, more than 40 years of age, at least 10 years of underground experience.
Surwit/cervix/*trans*-retinoic acid, retinyl acetate	18–45 years old, moderate or severe cervical dysplasia.

An international comparison shows a correlation between intake of beer and the incidence of colorectal cancer (Vitale, Broitman, and Gottlieb 1981). A strong association between beer intake and rectal cancer and a weak association between wine or whiskey and lung cancer have been found in a prospective cohort study of Japanese men in Hawaii (Pollack et al. 1984). These associations were seen only at high intakes, and no increased risk was observed at moderate intakes. Case-control studies have failed to show a consistent relationship between alcohol and colon or rectal cancers, possibly due to confounding variables, including contaminants in alcoholic beverages. An increased incidence of liver cancer among alcoholic patients appears to be due to increased exposure to hepatitis B virus rather than to alcohol itself (Brechot et al. 1982).

Although it is difficult to determine true levels of alcohol consumption, women with breast cancer are reported to consume more alcohol than controls (Williams and Horm 1977). A slightly greater risk for breast cancer in women has been associated with intake of as few as three alcoholic drinks per week (Schatzkin et al. 1987). Another recent study found increased risk associated with an average of one drink per day in a cohort of 89,538 U.S. women (Willett et al. 1987). Results of other analytical studies are inconsistent.

Although the associations observed between alcohol and oral, esophageal, and laryngeal cancers may be due in part to smoking, appropriate study designs and analyses have demonstrated independent effects of alcohol (Misslbeck and Campbell 1986). If the consumption of alcoholic beverages is reduced, a sizeable decrease in the incidence of cancers of the buccal cavity, pharynx, larynx, and esophagus should be possible (Tuyns 1982).

Role of Other Dietary Constituents in Cancer

Vitamin C

Vitamin C functions as a chemical-reducing agent and antioxidant. It is synthesized in adequate amounts by most animals but not by some primates, fish, guinea pigs, and humans (Linder 1985).

Human studies have shown a protective association between foods that contain vitamin C and cancers of the esophagus (Aoki et al. 1982; Ackerman, Weinstein, and Kaplan 1978), stomach (Graham, Schotz, and Martino 1972; Higginson 1967; Kolonel, Nomura, et al. 1981), and cervix (Wassertheil-Smoller et al. 1981). Small-scale studies have indicated that colonic polyps regress (DeCosse et al. 1975) or decrease in area (Bussey et al. 1982) with vitamin C therapy. Recurrence of colonic polyps after polypectomy was reduced among patients in the treatment group of a study with 200 subjects (McKeown-Eyssen et al. 1987). Supplements of vitamins C and E have been shown to reduce the formation of mutagens in the feces in one study (Dion et al. 1982) but not in another (Wilkins, Lederman, and Van Tassell 1981). While many studies support a role of vitamin C in reducing cancer risk (Block and Menkes 1988), no wholly consistent picture of the role of vitamin C in human cancer has been defined.

Experimental animal studies have found that animals given both precursors of carcinogenic nitrosamines and vitamin C develop fewer tumors than animals given these precursors alone (Mirvish et al. 1976). Vitamin C protects hamster lung cultures from the mutagenic effects of tobacco smoke (Leuchtenberger and Leuchtenberger 1977) and has been shown to reduce bladder tumors induced by one carcinogen (Pipkin et al. 1969) but not by another (Soloway et al. 1975).

Biochemical studies suggest that vitamin C blocks the formation of carcinogenic nitrosamines from nitrates and nitrites within the digestive tract (Weisburger et al. 1980; Mirvish et al. 1975) and prevents oxidation of certain chemicals to active carcinogenic forms (Pipkin et al. 1969).

Because most studies demonstrating a beneficial effect of vitamin C have not quantified its actual intake levels, associations between vitamin C and cancer prevention are subject to the same difficulties as those discussed for vitamin A. Amounts of vitamin C in excess of the Recommended Dietary Allowances (RDA's) may cause rare adverse effects, including gastrointestinal disturbances, iron overload in susceptible individuals, altered metabolism of certain drugs, precipitation of calcium oxalate kidney stones, altered absorption (both positive and negative) of several minerals, and interference with several laboratory tests (Sestili 1983). Despite limitations in data, the American Cancer Society guidelines recommend "foods rich in vitamins A and C" (ACS 1984), and the National Cancer Institute suggests eating a variety of fruits and vegetables, thus ensuring an adequate supply of vitamin C (Butrum, Clifford, and Lanza 1988). There is no adequate evidence that larger amounts of vitamin C provide any additional benefits.

Vitamin E

Studies on vitamin E and the development of cancer are complicated by its instability in stored blood serum, its wide prevalence in the food supply, and its multiple chemical forms. Perhaps because of these problems, there are relatively few studies on the role of vitamin E and cancer, but the role of vitamin E as an antioxidant justifies its further consideration as a potential preventive agent in cancer control (Willett and MacMahon 1984a).

In human studies, no relationship has been found between vitamin E levels and the risk for cancer when incidence rates at all sites are combined in either prospective (Willett et al. 1984; Stahelin et al. 1984) or case-control analyses (Salonen et al. 1985; Nomura et al. 1985). In one case-control analysis of prospective data, serum vitamin E had no statistically significant independent association with cancer mortality, but low vitamin E enhanced an independent risk observed for low serum selenium levels (Salonen et al. 1985). A protective effect of serum vitamin E against cancer of the breast has been found in one (Wald et al. 1984) but not a second (Willett et al. 1984) study. In the positive study, an increased risk was associated only with the lowest 20 percent of serum vitamin E levels. Low vitamin E levels have also been correlated with an increased risk for lung cancer (Menkes and Comstock 1984) and intestinal cancer (Gey, Brubacher, and Stahelin 1987), but a recent study found no such association with ovarian cancer (Heinonen, Koskinen, and Tuimala 1985).

Variable results have also been observed in experimental animal studies. Vitamin E was protective in carcinogen-induced tumor systems (Shamberger and Rudolph 1966; Bonmasser, Dallavalle, and Guiliani 1968) or

when administered as a dietary supplement (Haber and Wissler 1962), but other studies have not observed this effect (Cook and McNamara 1980; Epstein et al. 1967). A recent review states that the animal evidence is inconsistent but suggests a protective effect of vitamin E in carcinogen-induced tumor systems (Newberne and Suphakarn 1983).

Biochemical studies indicate that vitamin E functions as a lipid-soluble antioxidant and free radical scavenger. Thus, the protective role tentatively assigned to both carotenoids and vitamin C may also apply to vitamin E and its derivatives. Vitamin E, like vitamin C, blocks the *in vitro* formation of nitrosamines. The fact that vitamin E is lipid soluble permits this action in a lipid environment, as opposed to the water-soluble vitamin C. Knowledge of carcinogenic mechanisms from experimental and animal studies justifies further exploration of the vitamin E and cancer prevention hypothesis. Some concern has been expressed that reduced fat intake would compromise availability of this fat-soluble vitamin, but it has been estimated that a reduction in fat intake to 20 to 25 percent of daily calories should not result in adverse effects from lowered vitamin E or other fat-soluble vitamin intake (Judd, Kelsay, and Mertz 1983).

Selenium

Selenium is present in animal and plant foods as selenate, selenocystine, selenomethionine, and other yet unidentified forms. A suggested daily dietary intake for selenium has been established by extrapolation from animal studies, but the range of 50 to 200 μg per person (NRC 1980) does not imply greater benefit at the upper limit (Diplock 1987). Well over 90 percent of selenium intake is from cereal grains, fish, meat, and poultry (Lo and Sandi 1980).

The average per capita consumption of dietary selenium in 27 countries was inversely correlated with total cancer mortality as well as deaths from leukemia and cancers of the colon, rectum, breast, ovary, and lung (Schrauzer, White, and Schneider 1977). Inverse correlations between local soil and crop levels of selenium and regional cancer incidence in the United States (Shamberger and Willis 1971) and between the average blood selenium concentration of residents in different regions of the United States and the incidence of cancer of the breast, colon, rectum, and lung in these regions (Schrauzer, White, and Schneider 1977) have been reported. These studies must be interpreted cautiously due to the mobility of both food supply and population.

In several case-control studies, persons with cancer had lower blood selenium levels than controls (Shamberger et al. 1973; McConnell et al. 1980). These studies must also be interpreted cautiously because these low levels of blood selenium may be a consequence of illness rather than its cause (Helzlsouer 1983).

Prospective studies can show whether low serum levels precede cancer. One prospective study showed that risk for cancer was increased in a group with low serum levels of selenium and vitamins A and E (Willett et al. 1983). Two other prospective studies in Finland, where selenium intake is half that of the United States, found an increased risk for cancer at all sites among the population with low serum levels of selenium (Salonen et al. 1984; Salonen et al. 1985). All three of these prospective studies as well as a subsequent case-control study (Kok et al. 1987) support the hypothesis that serum selenium is a risk factor for cancer death in men but not in women. These studies are summarized in Table 4-12.

Selenium inhibits neoplastic transformation in a variety of epithelial organs in animals (Medina 1985). Studies have demonstrated protective effects against cancer of the liver (Daoud and Griffin 1978), breast (Ip 1981), colon (Jacobs, Matney, and Griffin 1977), and skin (Shamberger 1970) from selenite, selenate, or organic selenium. However, the dose giving this protective effect in most experiments is similar to the dose that may be toxic with long-term administration (Helzlsouer 1983).

Selenium is among the most toxic essential elements (Longnecker et al. 1987). Its effects in humans have been mostly limited to occupational hazards (Buell 1973), but toxic effects have been reported among individuals consuming excessive selenium supplements (CDC 1984). Selenium is present in the active site of glutathione peroxidase, an enzyme that helps to prevent perioxidative damage to the cells. Although the molecular basis for the function of selenium as an inhibitor of neoplastic transformation is not understood, its enzymatic role may explain this relationship. The documented toxicity and the narrow range of safe levels of intake of this nutrient suggest that recommendations for increasing dietary intakes are not warranted.

Protein

An association between protein consumption, especially animal protein, and the incidence of certain cancers has been observed in several human epidemiologic studies. However, the association of cancer and protein intake is confounded by a high correlation of protein intake to many other

Findings	Cancer Site	No. of Studies Showing the Association	No. of Studies Not Showing the Association	Specific Nature of the Association
		Correlation Studies		
Inverse relationship between cancer rates and selenium exposure	General	4		Selenium in forage crops
			1	Selenium in forage crops; association a direct one for some sites
		1		Selenium in soil and water
		1		Dietary selenium intake
		2		Blood selenium levels
	Colon-rectum		1	Selenium in water; association a direct one
		Case-Control Studies		
Lower blood selenium levels in cases than in controls	General	1		Gastrointestinal tract cancers and Hodgkin's disease
		2	1	Carcinoma only
	Leukemias & Lymphomas	1		Chronic lymphocytic leukemia only
			3	
	Mouth & Pharynx		1	Plasma selenium increased in cases, but RBC selenium and glutathione peroxidase levels decreased
	Breast	1		
	Skin	1		Both basal and squamous cell types
		Cohort Studies		
Lower prediagnostic serum selenium levels in cases than in noncases	General	3		Association especially evident in males and smokers

Source: Adapted from Bertram, Kolonel, and Meyskens 1987.

nutrients, including fat. Thus, it has not been possible to define an independent effect for protein (Kolonel and Le Marchand 1986; Palmer 1986). In one international correlational study, for example, a positive association was observed between total protein and animal protein and breast, colon, prostate, renal, and endometrial cancers (Armstrong and Doll 1975). Similarly, a migrant study indicated an association between meat consumption and cancer of the breast and colon (Kolonel 1987). In a recent case-control study of breast cancer, the greatest positive association was with a high-protein, high-fat, and low-fiber diet, but when these three dietary components were assessed independently, fat had the strongest association (Lubin, Wax, and Modan 1986). A positive association between protein and colon cancer has been found in another study, but again, the association with fat was stronger (Jain et al. 1980). In an Australian case-control study on large bowel cancer, the highest risk was assigned to a high-protein, high-energy, low-fiber diet (Potter and McMichael 1986). Studies have also found an association between breast cancer and meat intake (Lubin et al. 1981) and an association of meat, especially beef, with large bowel cancer among Japanese (Haenszel et al. 1973), although a subsequent study found a lower risk for all cancers among Japanese who consumed a higher daily intake of meat (Hirayama 1981).

In animal studies, an excessive intake of protein is not consistently associated with an increased incidence of tumors at most sites. When animals were fed *ad libitum* diets with a protein content ranging from 10 to 51 percent of calories, the total incidence of tumors was not affected (Ross and Bras 1973; Tannenbaum and Silverstone 1949), although certain tumors such as bladder papillomas and mammary tumors are enhanced by increased protein intake (NRC 1982). These same studies reported that high-protein diets in early life increased the incidence of tumors (Ross and Bras 1973). Because very low-protein diets have a suboptimal nutritional value, the decreased tumor risk at very low intake is not relevant for guidelines for human diets.

Salt-Pickled, Salt-Cured, and Smoked Foods

Methods of storage and preparation of foods vary widely in different parts of the world, and these differences may contribute to the large international variation in some types of cancer. Smoked and charred foods acquire polycyclic aromatic hydrocarbons (PAH's), some of which are known to be carcinogenic in animals (Chu and Malmgren 1965; Ames 1983). These and other potential carcinogenic agents may be formed within foods during cooking in amounts that may be related to the temperature and duration of cooking at very high temperatures (Lijinsky and Shubik 1964; Lijinsky and Ross 1967; Weisburger, Horn, and Barnes 1983). For example, high temper-

ature grilling and broiling with open flames produces carcinogenic PAH's on the charred surface of foods (Sugimura 1982). Burning amino acids with sugars during cooking results in a variety of mutagenic chemicals, some of which may be carcinogenic (Pourie et al. 1981). Salt-cured and salt-pickled foods contain nitrates and nitrites that can form carcinogenic nitrosamines in the mouth and stomach (Weisburger, Barnes, and Czerniak 1986). Salt-cured and salt-pickled foods have been linked to gastric cancer, possibly because of effects of salt on gastric mucosa (Joossens and Geboers 1985) or conversion of nitrates to carcinogenic nitrosamines (Weisburger, Barnes, and Czerniak 1986). Except for a few instances, however, potential causative agents have not been identified in cured, pickled, or smoked foods (Palmer and Bakshi 1983).

International epidemiologic evidence suggests that populations consuming diets high in salt-cured, salt-pickled, and smoked foods have a higher incidence of stomach and esophageal cancers. Stomach cancer has been linked to pickled vegetables in Japan (Haenszel et al. 1972), salted fish in Norway (Bjelke 1978), and smoked trout and mutton in northwestern Iceland (Dungal 1961). Nitrates, nitrites, and N-nitroso compounds in food and water (Weisburger, Barnes, and Czerniak 1986) and salted foods (Geboers, Joossens, and Kesteloot 1985) have been associated with gastric cancer in several epidemiologic studies. Salt-pickled and salt-cured foods have been associated with an increased risk for cancers of the nasopharynx (Sasco, Hubert, and De The 1985) and esophagus (Tuyns, Riboli, and Doornbos 1985). Esophageal cancer in China has been linked to the consumption of pickled vegetables and nitroso compounds (Yang 1980). Most international epidemiologic studies have linked smoked foods to gastric or esophageal cancers (Bjelke 1978).

Esophageal (Tuyns, Riboli, and Doornbos 1985) and stomach cancers (Geboers, Joossens, and Kesteloot 1985) have been associated with poor nutrition. In fact, almost all diet and stomach cancer studies have found a protective effect of vegetable and fruit intake (Cordle 1986), and even the *in vitro* formation of N-nitroso compounds can be minimized by antioxidants such as vitamins E and C (Weisburger, Barnes, and Czerniak 1986).

Nevertheless, the impact of risks from salt-cured, salt-pickled, and smoked foods in the U.S. diet appear to be small, because rates of stomach and esophageal cancers are low compared with those in other parts of the world and because consumption of smoked, salt-cured, and salt-pickled foods generally is not high.

Food and Color Additives

The FDA approves (or disapproves) all new food and color additives after detailed review of the safety, purpose, and anticipated exposure. The FDA also monitors the food supply for chemical contaminants such as pesticides, environmental contaminants, and heavy metals through the annual Total Diet Study, which has been conducted since the mid-1960's (NRC 1982). Before substances are approved for marketing, they are evaluated for safety on the basis of experimental studies in animals and relevant clinical studies demonstrating their suitability for their intended use. After marketing, if new evidence on the safety of the substance is brought to light, such evidence is reviewed in depth to determine if there should be a change in the regulatory status of the substance. This process should protect the U.S. population against the presence of added substances in the food supply that could involve a risk to health, including cancer.

Implications for Public Health Policy

Dietary Guidance

General Public

The dietary factors evaluated for the possible relationship to cancer risk are fat, calories, fiber, foods high in vitamin A and carotenoids, and alcohol. Roles for vitamin C, vitamin E, selenium, protein, and salt-cured, salt-pickled, and smoked foods have been proposed.

Studies of carcinogen-induced tumorigenesis in experimental animals and international epidemiologic comparisons have provided substantial but not conclusive evidence that dietary fat increases the risk for cancers of the breast, colon, rectum, endometrium, and prostate. The results of epidemiologic investigations within more homogeneous population groups, however, are inconsistent. Because fat contains more than twice the calories per given quantity of protein or carbohydrate, high-fat diets are generally high in calories. Despite such complications, the animal and international epidemiologic data suggest that a decrease in fat consumption by the general public from the current 37 percent of total caloric intake might reduce the risk for certain cancers.

Results from animal and human studies of obesity and cancer are not wholly consistent, perhaps because of the difficulty of separating the effects of calories, fat, and body weight. Furthermore, the level of caloric restriction that seems effective in preventing cancer in most animal studies

is at a food intake level not advisable for most humans. Consistent with other health recommendations, maintenance of desirable weight is recommended and may potentially decrease the risk of breast, colon, prostate, and endometrial cancers.

Correlational epidemiologic studies suggest an association between diets low in fiber and increased risk for colon cancer, while results from case-control studies are mixed. Studies in experimental animals indicate that further research is needed on the effects of different types of fiber. While inconclusive, evidence suggests that an overall increase in intake of foods high in fiber might decrease the risk for colorectal cancer. Despite the need for additional evidence, this recommendation is consistent with guidance for reducing gastrointestinal disease.

Likewise, epidemiologic studies provide suggestive evidence that consumption of foods containing carotenoids, including the beta-carotene precursor of vitamin A, protects against development of epithelial cell cancers such as those of the oral cavity, bladder, or lung. These studies have generally shown lower rates of cancer among individuals consuming the highest overall levels of vitamin A, carotenoids, or fruits and vegetables. These studies have not distinguished the specific form of vitamin A associated with protection, nor have they ruled out the possibility of protection from as yet unidentified components of fruits and vegetables. Until the results of clinical trials examining these relationships become available, an increase in consumption of fruits and vegetables might benefit persons who now consume below-average amounts of these foods. There is no evidence that vitamin A in amounts greater than the RDA is beneficial.

Despite some difficulties in distinguishing the cancer-producing effects of excessive alcohol intake from those of cigarette smoking, evidence suggests that a reduction in alcohol intake among the portion of a population that drinks most heavily would help to reduce the prevalence of cancers of the mouth, esophagus, pharynx, and perhaps other sites.

Excessive selenium intake is toxic. This fact and limitations in information about selenium intake in the general population suggest that selenium intake should not be increased above levels now in the average diet.

Although some epidemiologic studies suggest an association between dietary protein and cancer incidence, these studies are limited and not consistently supported by animal evidence. Thus, the evidence does not justify a recommendation to the general public to decrease protein on the basis of its relationship to cancer.

There is some suggestive but not conclusive evidence that correlates consumption of salt-pickled, salt-cured, and smoked foods with stomach and esophageal cancers, indicating that the public should continue to limit its intake of these foods to the current low levels of consumption.

Special Populations

Persons at high risk for diet-related cancers because of family history, obesity, or excessive alcohol intake should receive counseling from qualified health professionals to design approaches that could reduce their elevated risk for cancer.

Patients with cancer should receive appropriate nutritional support and dietary advice to maintain optimal nutritional status throughout medical, surgical, or radiological therapy. There is no credible evidence that nutritional changes specifically help in the cure of cancer patients.

Children and older persons are not currently targeted by the dietary guidelines relative to cancer risk due to limited data for these groups.

Nutrition Programs and Services

Food Labels

Evidence related to the role of dietary factors in cancer suggests that food manufacturers should include on package labels information about nutritional content of the food, especially for fat and carbohydrate components (and including fiber components to the extent permitted by analytical methods).

Food Services

Evidence related to the possible role of dietary factors in cancer suggests that the public might benefit from increased availability of foods low in fat and high in fiber.

Food Products

Evidence related to the role of dietary factors in cancer suggests that foods low or reduced in calories and fat and high in fiber should be made increasingly available by food manufacturers.

Special Populations

Persons with cancer should be provided with counseling and assistance in the development of diets appropriate to their condition.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in cancer should include investigations into:

- Molecular mechanisms of carcinogenesis and the ways in which initiating or promoting events may be affected by specific components of dietary fat, fiber, protein, alcohol, vitamin A, carotenoids, and other vitamins or minerals.
- Quantitative relationships between food and nutrient intake and cancer incidence through chemoprevention and dietary clinical trials.
- The effect of specific components of dietary fat, fiber, vitamin A, and carotenoids on cancer etiology.
- Interactions between dietary factors such as fat, fiber, calories, protein, and specific vitamins and minerals in cancer prevention and causation.
- Development of biochemical markers of dietary intake to better monitor effects of dietary intervention on cancer risk.
- Patterns of food intake best associated with cancer prevention.
- Development of national population data on food and nutrient consumption patterns and specific cancer rates, including more accurate assessment of intake of specific dietary factors within relatively homogeneous population groups.
- Levels of carcinogenic and mutagenic substances in the food supply.
- Dietary guidance methods that are most effective in helping people improve patterns of food intake.
- The causes of wasting and malnutrition in cancer patients and the effects of nutritional support on response to therapy and survival in these patients.

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Chapter 5

Diabetes

. . . urine wonderfully sweet, as if imbued
with honey or sugar.
Thomas Willis, physician to
Charles II of England, 1670

Introduction

Diabetes mellitus (commonly called diabetes) is the name given to a spectrum of conditions found in 11 million Americans. Diabetes is characterized by metabolic abnormalities (of which the most evident is hyperglycemia, an elevated concentration of glucose in blood) and by long-term complications involving multiple organs, especially the eyes, kidneys, nerves, and blood vessels. These complications result from a deficiency of the hormone insulin, a reduction in the effectiveness of insulin, or other less well understood metabolic disorders. There are two major forms of diabetes mellitus: Type I, or insulin-dependent, and Type II, or noninsulin-dependent. These types are distinguished by the need in Type I diabetes for exogenous replacement of insulin, which is necessary for the metabolism of glucose. The treatment goal for both types of diabetes is to prevent or reduce the risk and severity of complications; generally this goal is best achieved by maintaining normal or near-normal blood glucose and blood lipid levels. In longstanding diabetes, certain other aims of treatment assume great importance, including blood pressure control and reducing protein load on the kidney (see the following section and the chapter on kidney diseases).

Type I diabetes, or insulin-dependent diabetes mellitus (IDDM), formerly known as juvenile-onset diabetes, accounts for about 10 percent of diabetes in the United States. It is characterized by an absolute deficiency of insulin, caused by beta-cell destruction of the islets of Langerhans in the pancreas. Genetic factors, including an autoimmune response (Eisenbarth 1986), affect the risk of beta-cell destruction as well as environmental factors such as viral agents or cytotoxic chemicals (Arky 1983).

Type I diabetes usually appears before age 40 and begins abruptly. Typical symptoms are thirst, excessive urination, increased appetite, rapid weight loss, breath that smells of acetone, and urine that is sweet because of its high sugar concentration. Affected persons are usually of normal body weight. Because their insulin levels are low, persons with Type I diabetes require insulin for survival. Treatment usually includes administration of insulin, diet coordinated with the insulin dosage schedule, and regular physical exercise. At present, no method to prevent development of this form of the disease has been identified (Browner 1986).

Type II diabetes, or noninsulin-dependent diabetes mellitus (NIDDM), also known as adult- or maturity-onset diabetes, accounts for approximately 90 percent of all cases and affects at least 10 million Americans. It usually appears in mid-life, most commonly among people who are overweight or obese. Its onset is gradual, and many persons have a long history of mild symptoms or display no symptoms at all. Often, the condition is first diagnosed among individuals with no overt symptoms who display elevated fasting blood glucose levels during a routine physical examination. Genetic predisposition appears to play an important role in Type II as well as in Type I diabetes.

Persons with Type II diabetes may display normal pancreatic histology, secrete insulin in response to glucose ingestion, and have normal levels of insulin in their blood. But because the body is less able to use this insulin, or perhaps for some other as yet unknown reason (Feldberg, Pyke, and Stubbs 1985), blood sugar levels are inappropriately high, and insulin levels are insufficient. The three principal approaches to diabetes management are diet, exercise, and treatment with oral antidiabetic agents or insulin. Overweight persons able to lose weight can be managed by diet and exercise alone. Some individuals unable to lose weight may respond to treatment with sulfonylurea and other antidiabetic, hypoglycemic drugs (agents that reduce blood sugar levels), but others will need insulin treatment to control their diabetes.

Although it is generally believed that maintenance of normal blood glucose levels will prevent or reduce the complications and premature mortality associated with diabetes, this supposition has yet to be proved.

Historical Perspective

Since ancient times, diet has been recognized as a cornerstone of diabetes management, yet ideas about the most effective dietary treatment have varied widely throughout history (Bierman 1979). The uncertainty has

been whether the sugar lost in the urine of persons with diabetes should be replaced or whether carbohydrate intake should be restricted to prevent further sugar loss. The fluctuations in recommendations for the relative proportions of carbohydrate and fat in the diet of persons with diabetes are outlined in Table 5-1.

In Egypt, the Ebers papyrus of 1550 B.C. described the use of wheat grains, fresh grits, grapes, honey, berries, and sweet beer "to drive away the passing of too much urine" (Wood and Bierman 1972). Around the time of Christ, Aretaeus, a Cappadocian from a Roman province in East Asia Minor, recommended a diet of milk, cereals and starch, fruits, and sweet wines—another high-carbohydrate diet. Willis, in the 17th century, was the first to describe in English medical literature the sweet taste of diabetic urine. He believed that the lost sugar should be replaced and recommended a diet rich in carbohydrates but limited to milk and barley water boiled with bread.

Later, Rollo, a surgeon general of the Royal Artillery in the English Army, deviated from the common diet of the time and recommended complete avoidance of dietary carbohydrates. He advocated "animal food and con-

Table 5-1
History of Dietary Composition (Relative Proportion of Carbohydrate and Fat Calories) Used in Management of Diabetes

Date	Source	Carbohydrate	Fat
1550 B.C. (approx.)	Ebers papyrus (Egypt)	High	
1 A.D. (approx.)	Aretaeus (Asia Minor)	High	
1675	Willis	High	
1797	Rollo	Very low	High
1860–80	Bouchardat	Low	High
1900–20	Naunyn; Allen	Low (+ fasting)	Low
1900–20	von Noorden	High	
1923	Geyelin	High	
1929	Sansum	Normal	Normal
1931	Rabinowitch	Moderate	Low
1935	Himsworth	High	
1940–60	Kempner; Ernest	High	Low
1940–70	ADA[a] (U.S.)	Limited	Moderate
1971 to date	ADA (U.S.)	Increased	Reduced

[a]ADA = American Diabetes Association.

Source: Bierman, E.L. 1979. Nutritional management of adult and juvenile diabetics. In *Nutritional management of genetic disorders*, ed. M. Winick, pp. 107–17. New York: Wiley. Copyright 1979, John Wiley & Sons, Inc., reprinted with permission.

finement, with an entire abstinence from every kind of vegetable matter. . . ." (Wood and Bierman 1972). The noon meal prescribed by Rollo consisted of "plain blood puddings, made of blood and suet, and dinners of game or old meats which have been long kept, and as far as the stomach may bear, fat and rancid old meats, as pork." Pile of the University of Pennsylvania believed in Rollo's approach but found that while it met with some success, ". . . unfortunately for the patient he soon becomes so disgusted with this kind of diet as to refuse it altogether, and returns to his old manner of living, which in no little while neutralizes all the efforts of months of abstinence." In France, Bouchardat introduced green vegetables into the Rollo diet to decrease the monotony. Bouchardat, often referred to as the most brilliant clinician in the history of diabetes, noted that the urinary sugar levels of his patients with diabetes fell during the German blockade of Paris in the Franco-Prussian war of 1870 to 1871, a time of food shortages, and he developed the concept of caloric deprivation for diabetes treatment (Wood and Bierman 1972).

Shortly before the discovery of insulin, the dietary treatment of diabetes was based on the teaching of Naunyn, a German physician who believed in limiting both protein and carbohydrates and, in the most severe cases, total caloric intake. Allen of the Rockefeller Institute modified Naunyn's recommendations, and in 1912 with the "Allen Starvation Treatment," he showed that weight loss due to caloric restriction was beneficial to overweight persons with diabetes. Although low-carbohydrate and low-calorie diets predominated from the time of Rollo to the advent of insulin, the carbohydrate "cures" also had followers. For example, von Noorden of Frankfurt and Vienna found that patients showed marked improvement when placed on oatmeal diets for the treatment of digestive disturbances.

The discovery of insulin in 1921 led to a reappraisal of the diabetic diet. Geyelin of Columbia University was the first to try high-carbohydrate diets in patients treated with insulin beginning in 1923. He expected an increase in the need for insulin with the high-carbohydrate diets but found some cases in which insulin requirements were actually lowered. In 1929, Sansum, Gray, and Bowden recommended in their textbook that persons with and without diabetes should have the same diet because it would be more palatable; thus, people would follow it more consistently, and improved physical and mental activity would result. At about the same time, Rabinowitch of McGill University recommended that patients stay 5 to 10 lb under their average body weight and advocated the use of low-fat diets (less than 50 g/day) for this purpose, noting that "if we could lower the incidence of cardiovascular-renal disease . . . our diabetic death rate would correspond to that of normal populations" (Wood and Bierman 1972). In

1935, Himsworth of the University of London observed that the glucose tolerance of normal subjects improved consistently as the percentage of carbohydrate in the diet increased. Other workers, such as Kempner of Duke University (using a rice diet providing 90 to 95 percent carbohydrate) and Ernest and coworkers at the University of Goteborg (using a 72 percent carbohydrate diet), noted improvements in both serum cholesterol levels and diabetic symptoms. Despite the preponderance of this evidence, low-carbohydrate, high-fat diets continued to be widely used.

Since the early 1970's, this trend has been reversed, based on new studies demonstrating that high-carbohydrate intakes lead to improvement in glucose tolerance and insulin sensitivity (Bierman et al. 1971; Brunzell et al. 1971; Brunzell et al. 1974). The change to a higher carbohydrate diet was intended to reduce total and saturated fat to levels associated with decreased risk of atherosclerotic heart disease (Bierman and Ross 1977). In the present era, the availability of insulin has allowed clinicians to move beyond short-term prevention of hyperglycemia and other metabolic abnormalities toward the prevention, delay, or reduction of long-term complications. Nevertheless, the question of how much carbohydrate should be in the diabetic diet remains controversial (Reavan 1980; Jarrett 1981).

Throughout history, few physicians or researchers have agreed about the best approach to nutritional therapy of diabetes. No specific dietary approach beyond caloric restriction and weight loss in the obese has proved more advantageous than another. Even recent trends toward the use of high-carbohydrate, low-fat, high-fiber diets (described later in this chapter) need further validation. Clinicians must still make therapeutic decisions about diet based on inadequate information, yet they are increasingly able to attain treatment goals through individualized diets, self-monitoring of blood glucose, and more physiologic provision of pharmacotherapy. Future research may better define the optimal "diabetic diet" and quantify its contributions to therapeutic goals.

Significance for Public Health

The substantial impact of diabetes on the health of Americans has been documented extensively (NDDG 1985). Approximately 11 million people in the United States are estimated to have diabetes, but almost half are not yet diagnosed (Harris et al. 1987; Kovar, Harris, and Hadden 1987). In addition to Type I and Type II diabetes, gestational diabetes (impaired glucose tolerance during pregnancy) occurs in 2 to 5 percent of all pregnancies, placing both mother and baby at special risk, but in 98 percent of these cases the condition is transient and the mother returns to normal after the baby is born (NDDG 1985).

Diabetes is directly responsible for nearly 36,000 deaths each year in the United States, making it the seventh leading cause of death. It also contributes to nearly 95,000 additional deaths per year, 75 percent of which are due to cardiovascular complications (Kovar, Harris, and Hadden 1987). Mortality rates for white males and white females with Type I diabetes are 5 to 11 times greater, respectively, than for the general population. Type II diabetes prevalence is 33 percent higher for blacks than for whites, and mortality rates for blacks with this condition are twice those for whites. American Indians and Alaskan Natives have mortality rates from Type II diabetes 2.3 times that of the general population, with the highest worldwide rate of diabetes occurring among the Pima Indians in the United States (DHHS 1985).

Mortality rates increase with age. Twelve percent of patients with Type I diabetes die within 20 years of onset, primarily from acute complications below age 20 and from renal complications above this age. Type I diabetes is especially serious at younger ages; half the diagnosed cases are in children under age 20, and the condition is second only to cancer as a chronic illness in this group. The survival of persons with Type II diabetes is only 70 to 80 percent of that expected for the general population 25 years after diagnosis (NDDG 1985).

Many of the adverse health effects of diabetes derive from its complications (see Table 5-2). Diabetic ketoacidosis is responsible for 2 to 14 percent of hospitalization for diabetes and is the underlying cause of 10 percent of diabetes deaths. Diabetes is the leading cause of new cases of blindness among persons ages 20 to 74 and is responsible for one-fourth of all new cases of end-stage renal disease and 40 to 45 percent of all nontraumatic amputations in the United States. The risk of developing heart disease is about twice as high among persons with diabetes as in the general population, and ischemic heart disease is a factor in 50 to 60 percent of the recorded deaths of adults with diabetes. Lipid abnormalities occur in a substantial proportion of people with diabetes. Hypertension rates are also twice as high among people with diabetes, and the risk of stroke increases twofold to sixfold. Infants born to mothers with diabetes are at greater risk for congenital anomalies, macrosomia, respiratory distress, jaundice, and perinatal mortality (NDDG 1985). In addition, one-half of individuals with diabetes suffer serious limitations of activity and one-third are unable to work regularly. The economic cost of diabetes was estimated in 1985 to be $13.8 billion per year, or about 3.6 percent of total health care costs in the United States (NDDG 1985).

Table 5-2
Clinical Complications of Diabetes

Deaths

- Each year, diabetes is the cause of about 36,000 deaths among Americans and is a contributing cause in another 95,000 deaths.

Heart Disease and Stroke

- People with diabetes are two to four times more likely to have heart disease and two to six times more likely to have a stroke than people who do not have diabetes.

Kidney Disease

- Ten percent of all people with diabetes develop end-stage kidney disease (where a person requires dialysis or a kidney transplant to live).
- Nearly 25 percent of all new patients with end-stage renal disease have diabetes.

Blindness

- Each year, 5,000 people lose their sight because of diabetes. Diabetic eye disease is the number one cause of new blindness in people between the ages of 20 and 74.

Amputations

- Diabetes causes about 45 percent of all nontraumatic leg and foot amputations in the United States.

Sources: American Diabetes Association 1986; Kovar 1987.

Key Scientific Issues

- Role of Obesity in Type II Diabetes
- Role of Specific Dietary Factors in Diabetes
- Role of Dietary Therapy in Diabetes Management

Role of Obesity in Type II Diabetes

Obesity (see chapter on obesity) is strongly associated with the onset and severity of Type II diabetes (O'Sullivan 1982). At least 80 percent of persons with the Type II disease are more than 15 percent in excess of their desirable body weight at the time of diagnosis. Some estimates suggest that new cases of this condition could be reduced by nearly half by preventing obesity in middle-aged adults (Wood and Bierman 1986). Much of the increased risk of diabetes among black Americans and Pima Indians has been attributed to high rates of obesity and its complications in these

populations (DHHS 1985). The risk of diabetes increases with the degree of obesity and its duration (NIH 1986) as well as by the specific distribution of body fat; fat on the upper body is more associated with development of Type II diabetes than is lower body fat (Kissebah et al. 1982).

Type II diabetes is characterized by insulin resistance, which means that a given amount of insulin does not work as efficiently as it does in non-diabetic individuals. Obesity itself also can contribute to insulin resistance, and insulin resistance can be profound when obesity is combined with Type II diabetes. When this happens, the liver, skeletal muscle, adipose tissue, and other target organs for insulin action do not respond appropriately, perhaps because the number of insulin receptors has been reduced. As a result, the pancreatic beta-cells secrete greater amounts of insulin. Thus, an obese person with Type II diabetes may secrete normal to above-normal amounts of insulin, but the hormone is relatively ineffective and blood sugar levels remain high.

The specific cellular cause of the high blood glucose and other metabolic abnormalities of Type II diabetes is still uncertain, although three defects may be partially involved: a diminished pancreatic beta-cell response to glucose, reduced synthesis or function of cellular receptors for insulin, and an as yet uncharacterized defect in utilization of glucose following binding to cellular receptors (Arky 1983).

Although the relationship of obesity to these defects remains to be established, weight loss reduces insulin resistance as well as fasting and postprandial blood glucose levels in overweight persons with diabetes (Henry, Scheafer, and Olefsky 1985; Henry, Wallace, and Olefsky 1986; Henry et al. 1986). Furthermore, significant caloric restriction lowers blood glucose levels in these individuals even before weight loss occurs. Once desirable weight is achieved, control of blood sugar levels can be accomplished by consuming just enough energy to maintain it. In general, the more recent the onset of diabetes, the more responsive a person will be to the beneficial effects of weight reduction. As weight falls to desirable levels, improvements in cardiovascular disease risk factors—hypertension and high blood lipid levels—also occur (Arky 1983).

While very low-calorie diets (fewer than 800 kcal) are usually reserved for individuals with moderate to severe obesity (Stunkard 1982), diabetes and other risk factors may demand that such measures be used under a doctor's supervision. Although weight loss prescriptions are often difficult to implement (Wood and Bierman 1972), behavior modification to reduce calorie

intake and promote exercise can be effective and improves prospects for persons with diabetes (Arky 1983; NIH 1986).

Role of Specific Dietary Factors in Diabetes

Carbohydrates

A diet containing 50 to 60 percent of total calories as carbohydrate is now recommended for individuals with diabetes (ADA Task Force 1987), not only because high-carbohydrate diets improve glucose tolerance and insulin sensitivity (Brunzel et al. 1971; Brunzel et al. 1974; Thompson, Hayford, and Danney 1978), but also because the reduced fat—especially saturated fat—intake that accompanies a high-carbohydrate diet lowers cardiovascular risk. Still, some disagreement remains about the optimal percentage of carbohydrate for persons with diabetes (Reaven 1980; Jarrett 1981). Furthermore, not all of the carbohydrate in a diet need be available nutritionally; some of it can be in the form of fiber.

A more controversial issue is the relative proportion of simple and complex carbohydrates that people with diabetes should consume. Blood glucose and insulin levels sometimes respond differently to different types of simple and complex carbohydrates in the diet (Crapo 1984). This response can be expressed as a "glycemic index," which is the rise in blood glucose following ingestion of a food as a percentage of the rise that follows ingestion of a standard food. Food form, fiber type, digestibility of the starch, and cooking and preparation procedures have been shown to affect glycemic responses to foods. Even these responses may be altered when foods are combined. Some studies have suggested that glycemic responses to food combinations can be predicted from the glycemic index of the carbohydrate components (Collier et al. 1986; Wolever et al. 1985), whereas others have failed to demonstrate predicted differences (Coulston and Hollenbeck 1986; Laine, Thomas, and Bantle 1986). Although several studies have suggested that positive clinical effects are produced when persons consume diets containing low-glycemic-index foods (Kiehm, Anderson, and Ward 1976; Simpson et al. 1981; Rivellese et al. 1980), these suggestions are too preliminary to be considered a basis for therapy. Because present knowledge of food composition and physiology does not permit consistent prediction of glycemic responses, the use of glycemic index tables is not currently recommended for people with diabetes (NIH 1986).

Some studies have been interpreted as supporting the idea that consuming modest amounts of sucrose is acceptable in the diet of persons with

diabetes as long as they can maintain adequate metabolic control (ADA 1984; ADA Task Force 1987). For example, some investigators have found no significant differences in blood sugar levels among persons with diabetes consuming sucrose or starch (Bantle, Laine, and Thomas 1986), and others have reported that consumption of fructose—a constituent of sucrose—leads to only a minimal rise in blood glucose levels (Arvidsson-Lenner 1976; Bohannon, Karam, and Forsham 1978; Lamar 1959; Crapo, Kolterman, and Olefsky 1980; Crapo, Kolterman, and Henry 1986). This last observation has led to the idea that a level of up to 75 g/day of fructose in the diabetic diet may be acceptable if it does not compromise nutritional adequacy (Olefsky and Crapo 1980). In other studies, however, high-carbohydrate diets, sucrose, and fructose have all been reported to increase blood glucose, insulin, and lipid levels in persons with diabetes (Coulston et al. 1987; Hallfrisch et al. 1983). These inconsistencies have yet to be resolved. Thus, a recent consensus conference recommended that sucrose intake be permitted only in persons who are not overweight and who do not respond to sucrose intake by increasing blood lipid levels, and that in any case, sucrose not exceed 5 percent of calorie intake from carbohydrate (NIH 1986).

Fat

The traditional restriction of carbohydrate intake in persons with diabetes leads to an increased fat intake (and, usually, saturated fat) because the percent of protein in human diets typically does not vary much. This high saturated fat consumption may have contributed to the frequent cardiovascular complications seen in past years among persons with diabetes. Persons with diabetes have higher plasma cholesterol and triglyceride levels and lower levels of high density lipoproteins than nondiabetic control populations. To help reduce this increased risk for coronary heart disease, a diet low in total fat, saturated fat, and cholesterol has been recommended (ADA Task Force 1987). Although these recommendations are consistent with those of the American Heart Association (see chapter on coronary heart disease), their effectiveness in reducing the incidence and the severity of cardiovascular complications in diabetics has not been firmly established. This can be explained in part because persons with diabetes (like those with other kinds of disease) are usually excluded from participation in the major diet-heart disease intervention trials. However, because these dietary recommendations are consistent with those recommended for other adults with high blood cholesterol levels and with good nutritional practices, the person with diabetes should know about them.

Some individuals with diabetes do not maintain normal plasma lipid levels despite a fat-restricted diet, perhaps because of accompanying obesity,

uncontrolled hyperglycemia, or coexistence of a primary disorder of lipoprotein metabolism. In such cases, the physician may need to prescribe a more restrictive dietary regimen. If persons with diabetes exhibit poor control of blood glucose levels accompanied by marked hypertriglyceridemia (plasma triglyceride levels over 1,000 mg/dl), they become at risk for acute pancreatitis. This condition requires rapid treatment that may include restriction of dietary fat along with vigorous control of hyperglycemia through insulin or oral hypoglycemic agents.

Protein

The protein requirements of individuals with diabetes under good control seem to be the same as those of healthy individuals; that is, a daily intake of 0.8 g/kg of body weight for adults and somewhat higher intakes for infants, children, and pregnant or lactating women (NRC 1980). When insulin levels are normal, protein is conserved in the body and the use of amino acids for glucose synthesis is limited (Cahill 1970). In persons with poorly controlled diabetes, dietary requirements may be increased because protein is used to synthesize glucose.

Individuals with diabetes and concurrent renal insufficiency should avoid excessive protein intake. Glomerular hyperfiltration (increased blood flow and filtration across the renal glomerular capillary bed) leads to impaired renal function in persons with diabetes, and increased protein intake may exacerbate renal damage (see chapter on kidney diseases). Furthermore, protein restriction slows the rate of decline in renal function in individuals with diabetic nephropathy (Evanoff et al. 1987). Because past dietary recommendations for persons with diabetes sometimes emphasized protein, and because the average American eats more protein than is necessary to maintain health, current recommendations suggest that people with diabetes should reduce protein intake below the level consumed by Americans (ADA Task Force 1987).

Fiber

Recent studies have suggested that a higher intake of dietary fiber than is typical for Americans might improve many clinical conditions, including the abnormal glucose tolerance of diabetes (LSRO 1987). Some studies have demonstrated that diets containing higher amounts of fiber (particularly water-soluble fiber) and carbohydrate are associated with lower blood glucose and serum lipid levels (Anderson 1980; Anderson and Chen 1979; Wheeler 1982; Jenkins, Wolever, Jenkins, Lee, et al. 1983; Vahouny 1982).

Inconsistencies in the results of studies of fiber and diabetes may be due to differences in types and properties of fiber. As discussed in the gastrointestinal diseases chapter, the water-insoluble fibers, such as cellulose, lignin, and most hemicelluloses, affect gastrointestinal transit time and fecal bulk but have a limited impact on plasma glucose, insulin, or cholesterol levels (McMurray and Baumgardner 1984; Hall, Bolton, and Hetengi 1980). However, the water-soluble fibers—pectins, gums, storage polysaccharides, and a few hemicelluloses—have little influence on fecal bulk but reduce serum levels of glucose and insulin (Wheeler 1982; Anderson 1980; Anderson and Chen 1979; Vahouny 1982).

Studies also indicate that blood glucose levels immediately following a meal are more influenced by soluble than by insoluble fibers. Further study of the effects of insoluble fibers on long-term baseline blood glucose levels is needed (Cohen et al. 1980; Jenkins, Wolever, Bacon, et al. 1980; Jenkins, Wolever, Taylor, et al. 1980; Jenkins et al. 1977; Jenkins et al. 1976; Miranda and Horwitz 1978; Monnier et al. 1981). Several reports since 1976 suggest that purified fiber supplements help to control blood glucose in individuals with diabetes and that they decrease fasting serum glucose, reduce glycosuria, decrease serum cholesterol, and lower fasting serum triglyceride levels (Anderson and Tietyen-Clark 1986). Such supplements are most effective when they are mixed with food (Williams, James, and Evan 1980; Cohen et al. 1980) and when the total carbohydrate level in the diet is high (Jenkins, Wolever, Bacon, et al. 1980).

Very high-carbohydrate, high-fiber diets, providing 70 percent of calories as carbohydrate and 35 g of plant fiber per 1,000 calories, consistently improve glucose tolerance, decrease fasting plasma glucose levels, lower insulin needs, and decrease serum cholesterol concentrations. These results have been confirmed in longer term studies comparing a more moderate diet that provides 55 to 60 percent of calories as carbohydrates and 25 g of plant fiber per 1,000 calories (Anderson and Tietyen-Clark 1986; Anderson et al. 1987).

These benefits may be related more to the increased intake of complex carbohydrate than to fiber. Some studies suggest that the fiber content is not the major factor that determines, for example, the serum glucose response to consumption of cereals (Jenkins, Wolever, Taylor, Barker, and Fielden 1981; Jenkins, Wolever, Jenkins, Lee, et al. 1983). Nevertheless, increasing the level of fiber in the diet of a person with diabetes, or in the diet of someone at risk for diabetes, may help lower blood cholesterol and triglyceride concentrations (Anderson and Chen 1979; Albrink, Newman, and Davidson 1979).

The optimal amount and type of fiber that improve diabetes symptoms are not well defined. If, as evidence suggests, at least 15 g of fiber per meal (depending on total daily calorie intake) are necessary to achieve therapeutic benefits for persons with diabetes, major changes in dietary patterns are required. And the use of some of the viscous, soluble fibers is generally not practical because of their unpalatability and gastrointestinal side effects. High-fiber diets also may impair absorption of essential trace elements and be inappropriate in persons with autonomic neuropathy, a neurologic disease (NIH 1986).

Alcohol

Abstinence from alcohol is not necessarily required for adults with diabetes, but some potential problems need attention. Alcoholic beverages add calories without nutritional benefit and may need to be restricted in overweight persons. In addition, excessive alcohol consumption by a person who is fasting or undernourished may lead to hypoglycemia, which can be a serious problem in persons taking insulin or oral hypoglycemic agents. Intoxication itself may impair a person's adherence to a prescribed management plan. Finally, alcohol ingestion may raise fasting and postprandial plasma triglyceride levels. Considering the increased risk for cardiovascular disease in persons with diabetes, alcohol consumption should probably be avoided if the person has concomitant hypertriglyceridemia. When alcohol is part of the meal plan, the person's fat intake should be reduced accordingly to account for the calories (7 kcal/g of alcohol) (see chapter on alcohol).

Alternative Sweeteners

Nutritive alternative sweeteners are sugars such as fructose and sorbitol that can be used as sources of calories. Aspartame, strictly speaking, is a nutritive sweetener, but it is used in such small quantities that its caloric contribution is minimal. Non-nutritive alternative sweeteners, such as saccharin and cyclamate, provide virtually no calories in relation to their sweetness.

Alternative sweeteners may be useful for persons with diabetes consuming sugar-restricted diets, both to provide sweetness without associated hyperglycemia and, in some cases, to help reduce caloric intake in overweight individuals (Porikos, Booth, and Van Itallie 1977). The risks, benefits, and effects of the different sweeteners in individuals with diabetes have not been evaluated fully, however, and there is little general agreement about the desirability, acceptability, or usefulness of these substances in diabetes

treatment. It is not known, for example, whether alternative sweeteners contribute to better diabetes control or whether they are effective in weight reduction programs in Type II diabetes. Because persons with diabetes are likely to ingest greater quantities of alternative sweeteners than the general population, issues of side effects, safety, and risk are especially important. The American Diabetes Association's current position on use of nutritive and non-nutritive sweeteners is that they are acceptable in management of diabetes (ADA Task Force 1987).

Role of Dietary Therapy in Diabetes Management

Management Goals

Lifelong care is required to avoid or to reduce the risk factors and complications of Type I and Type II diabetes. Because strategies to control hyperglycemia are similar to those used to reduce excessive blood lipid levels, blood pressure, and body weight and their associated cardiovascular risks, dietary therapy is considered the key to diabetes management (ADA Task Force 1987). Maintaining blood glucose as close to physiologic levels as possible will prevent hypoglycemia and its consequent damage to the brain and nervous system; it will also improve the outcome of pregnancy for women with diabetes (ADA Task Force 1987). Whether control of hyperglycemia will prevent or delay the development of long-term cardiovascular, renal, retinal, or neurologic complications, however, has not been established (Wood and Bierman 1986).

In persons with Type I diabetes, the goals of dietary management are to maintain appropriate body weight and prevent hypoglycemia (as well as hyperglycemia). These are accomplished by consuming meals with an appropriate calorie content at regular intervals, coordinated with the times of insulin injection and levels of physical activity. Because individuals with this form of the disease are usually young and lean, caloric intake must be adequate to support normal growth and development.

In contrast, 80 to 90 percent of individuals with Type II diabetes are overweight, and the first goal of diet therapy for such persons is weight loss. Hence, for most of these individuals, restriction of caloric intake and increased physical activity leading to moderate weight loss may be sufficient to control blood glucose levels and to avoid the need for insulin or hypoglycemic medication (ADA Task Force 1987). Once desirable weight is achieved, people with Type II diabetes must continue to adhere to the recommended diet to maintain the reduced weight while consuming amounts of nutrients necessary to maintain normal blood glucose levels.

For persons with either type of diabetes, dietary therapy is concerned with (1) maintenance of proper nutrition, (2) the total number of calories ingested, (3) the distribution of caloric intake throughout the day, and (4) the individual food sources that make up these calories. The American Diabetes Association has issued general dietary recommendations for persons with diabetes, and these are summarized in Table 5-3. Issues related to the American Diabetes Association guidelines—patient education strategies, exchange lists, counseling—are discussed below. However, to ensure the most appropriate diet for any given person with diabetes, individual diet plans should be developed with a trained dietitian or nutritionist (Nuttal, Maryniuk, and Kaufman 1983).

Table 5-3
American Diabetes Association Dietary Recommendations for Persons With Diabetes

Dietary Factor	Recommendation
Calories	Should be prescribed to achieve and maintain a desirable body weight.
Carbohydrate	Should comprise 55 to 60 percent of the calories with the form and amount to be determined by individual eating patterns and blood glucose and lipid responses. Unrefined carbohydrates should be substituted for refined carbohydrates to the extent possible. Modest amounts of sugars may be acceptable as long as metabolic control and desirable body weight are maintained.
Protein	Should follow the Recommended Dietary Allowance (NRC 1980) of 0.8 g/kg body weight for adults, although more may be needed for older persons. Some reduction in protein intake may prevent or delay the onset of the kidney complications of diabetes.
Fat	Should comprise 30 percent or less of total calories, and all components should be reduced proportionately. Replacement of saturated with polyunsaturated fat is desirable to reduce cardiovascular risk.
Cholesterol	Should be restricted to 300 mg/day or less to reduce cardiovascular risk.
Alternative sweeteners	Both nutritive and non-nutritive sweeteners are acceptable in diabetes management.
Sodium	Should be restricted to 1,000 mg/1,000 kcal, not to exceed 3,000 mg/day, to minimize symptoms of hypertension. Severe sodium restriction, however,

Table 5-3 (continued)

Sodium (continued)	may be harmful for persons whose diabetes is poorly controlled and for those with postural hypotension (low blood pressure and consequent dizziness when first standing up) or fluid imbalance.
Alcohol	Should be moderate and may need to be restricted entirely by persons with diabetes and insulin-induced hypoglycemia, neuropathy, or poor control of blood sugar, blood lipids, or obesity.
Vitamins and minerals	Should meet recommended levels for good health. Supplements are unnecessary for persons with diabetes except when caloric intake is exceptionally low or the variety of food intake is limited. Calcium supplements may be necessary under special circumstances.

Source: American Diabetes Association Task Force on Nutrition and Exchange Lists. 1987. Nutritional recommendations and principles for individuals with diabetes mellitus: 1986. *Diabetes Care* 10:126–32. Reproduced with permission from the American Diabetes Association, Inc.

Education Strategies

Better management of diabetes reduces hospitalizations and other personal and economic costs. To achieve these benefits, persons with diabetes must practice optimal self-care, which, in turn, depends on both knowledge and support. Education of persons with diabetes is associated with improved self-care skills, dietary adherence, and control of blood glucose and blood lipid levels (Mazzuca et al. 1986; ADA 1986) and results in cost savings greater than the costs of the education program (Davidson, Delcher, and Englund 1979). Although coordinated outpatient education programs are the preferred setting for education of persons with diabetes, the lack of third-party reimbursement for such programs has impeded their development (ADA 1986).

Use of Exchange Lists. Exchange lists categorize foods into groups with similar energy, protein, carbohydrate, and fat content and indicate how they can be used in meals. Because individuals with diabetes plan meals that contain specific proportions of protein, fat, carbohydrates, and calories, the foods within each group—starch/bread, meat and substitutes, vegetables, fruits, milk, and fat—can be freely substituted (exchanged) for one another in the amounts designated. The exchange system is widely used in diet counseling and meal planning for persons with diabetes. Exchanges are not intended to be used as self-instructional materials and generally require a trained nutritionist to explain their use, to help tailor the

diet to the individual's needs, and to assess the individual's understanding of appropriate food intake (Slowie 1977).

In 1976, and again in 1986, the exchange system was revised to reflect current scientific knowledge. The 1976 version reflected recommendations to restrict intake of calories, cholesterol, and saturated fat. It identified meat exchanges with high, medium, and low saturated fat content; it included the cholesterol content of meat and fat exchanges; and it provided the relative content of polyunsaturated and saturated fats (ADA and American Dietetic Association 1976). The 1986 revision retained these features but changed the order of the exchanges to emphasize high carbohydrate and high fiber intake and to update information about the nutrient content of breads and fruits. Symbols were added to identify foods with high sodium and fiber content, and lists of combination foods and foods recommended for occasional use were added (Franz et al. 1987).

Dietary Counseling. Dietary counseling helps the person with diabetes achieve good control of blood glucose and lipid levels by consuming appropriate levels of calories and nutrients, maintaining consistency in the timing of meals and snacks, and developing meal plans appropriate to individual lifestyle and food preferences. Additional goals are to help children and adolescents achieve normal growth and development rates and to encourage adequate nutrition for the pregnant woman.

Despite the evident importance of dietary therapy, individuals with diabetes often fail to adhere to the recommended diet. This problem means that patients and physicians must understand the importance of dietary management goals and methods; in addition, practitioners must provide detailed nutrition counseling (Hauenstein, Schiller, and Hurley 1987). Although physicians have sometimes perceived dietary noncompliance as the patient's fault, persons with diabetes have reported that dietary adherence depends more on environmental factors (e.g., family, job, economic status) or on physiologic factors (e.g., visual or ambulatory restrictions) that interfere with food purchase or preparation than on personal control. Understanding these different perceptions can help individuals with diabetes to assume greater responsibility for their own care (House, Pendleton, and Parker 1986).

Meal planning for persons with diabetes can be based on several alternative approaches: (1) dietary guidelines, such as the USDA/DHHS *Dietary Guidelines for Americans,* supplemented with information specific to diabetes; (2) exchange lists (discussed above); (3) counting systems to monitor total caloric and glucose consumption; and (4) sample menus

tailored to the special needs of individuals (Green 1987). Any of these methods may be appropriate for any given individual, but development of an individual meal plan requires patient education both in principles of good nutrition and in effective implementation of these principles. For the most part, clinicians perform the initial examination, obtain a medical history (including, perhaps, something about diet), outline an overall nutritional plan, and refer the person with diabetes to a trained dietitian or nutritionist for further counseling (Nuttall, Maryniuk, and Kaufman 1983). The dietitian or nutritionist then obtains a detailed diet history, develops an appropriate meal plan, and helps the person follow it by means of followup contacts. The most effective approaches consider individual dietary, sociocultural, economic, and lifestyle characteristics and involve the person with diabetes in devising the diet plan (Nuttall, Maryniuk, and Kaufman 1983). Because behavior changes usually occur gradually, dietary counseling is also more effective when it presents information in small increments that can be readily applied (Franz et al. 1987).

Nutrition information should be presented in stages to persons with diabetes. In the first stage, counselors should teach basic food selection skills and develop simplified, individualized meal plans. In subsequent stages, the counselor can provide more detailed information that extends and reinforces existing knowledge and that helps the person to change dietary behavior. Such information needs to be reinforced by continuing education that reviews dietary management, evaluates adherence to the recommended diet, provides further motivation to improve dietary behavior, and incorporates the results of new information into the dietary management program (Franz et al. 1986).

Implications for Public Health Policy

Dietary Guidance

General Public

Obesity greatly increases the risk for developing Type II diabetes, and obesity is in turn related to caloric imbalance: excessive intake of energy and/or insufficient energy expenditure. Because dietary fat contains more than twice the calories of either protein or carbohydrate, a reduction in fat intake should lead to a more favorable caloric balance, especially when this dietary change is accompanied by appropriate levels of physical activity. Controlling obesity by reducing dietary fat intake should help reduce the prevalence of Type II diabetes and is also consistent with dietary recom-

mendations for the prevention of coronary heart disease, hypertension, and some types of cancer.

Special Populations

Overweight persons with Type II diabetes benefit substantially from weight loss and may accrue benefits when fat, salt, alcohol, and simple sugars are reduced in combination with an appropriate increase in foods containing complex carbohydrates and soluble fiber. Even moderate weight loss, accomplished by reducing caloric intake and increasing energy expenditure, reduces blood glucose and insulin toward normal levels.

Current research suggests that diets relatively low in fat and cholesterol, salt, and protein can reduce the risk of the long-term cardiovascular, hypertensive, and renal complications of diabetes, respectively. Persons with diabetes and concurrent insulin-induced hypoglycemia, neuropathy, or poor metabolic control should avoid alcohol. Although research has not unequivocally established that complex carbohydrates and fiber improve blood glucose and insulin levels in individuals with diabetes, diets higher in these substances are generally lower in fat, cholesterol, and calories, and they are associated with lower blood lipid levels and, therefore, lower risk for coronary heart disease. Such diets can help reduce high blood cholesterol levels and the risk for coronary heart disease.

Until similar uncertainties about the metabolic effects of sugar in persons with diabetes are resolved, prudence dictates caution in the amount of its use. Research on dietary management of Type I diabetes emphasizes the importance of weight maintenance, avoidance of hypoglycemia, and metabolic control by coordinating caloric intake and expenditure with the schedule of insulin administration. Information, counseling, and followup on the appropriate application of these dietary principles and guidance for dietary management should be provided to persons with diabetes by qualified health professionals.

Nutrition Programs and Services

Food Labels

The food industry should be encouraged to provide nutrition information on the labels of most food products. The information on calories, fat (especially saturated fat), and other nutrient content will help the public to control caloric intake and will help persons with diabetes to make the necessary dietary modifications their physicians recommend.

Food Services

Evidence related to the role of dietary factors in diabetes currently holds no special implications for policy changes in food service programs.

Special Populations

Persons with diabetes of either type should be provided with counseling and assistance with dietary changes to control their disease. This should be coordinated with other aspects of their health care needs such as insulin administration and levels of physical activity.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in diabetes should include investigations into:

- The role of calorie intake and physical activity, and subsequent weight control, in the prevention of Type II diabetes.
- The metabolic consequences of obesity.
- The metabolic mechanisms of intestinal and hepatic processing of dietary carbohydrate, and the effects of other nutrients and of fiber on carbohydrate metabolism.
- The influence of dietary carbohydrates on glycemic responses in persons with diabetes, and the effects of such responses on development of the cardiovascular, renal, retinal, and neurologic complications of this condition.
- The influence of specific dietary factors—fat, cholesterol, sugar, protein, fiber—on development of the cardiovascular, renal, retinal, and neurologic complications of diabetes.
- The long-term risks and benefits of non-nutritive sweeteners as aids to adherence to dietary regimens.
- The behavioral and environmental factors that influence adherence to weight loss and dietary regimens in persons with diabetes.
- The specific educational techniques that will improve acceptance of and adherence to therapeutic regimens.

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LSRO. *See* Life Sciences Research Office.

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NDDG. *See* National Diabetes Data Group.

NIH. *See* National Institutes of Health.

NRC. *See* National Research Council.

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Chapter 6

Obesity

They are as sick that surfeit with too much
as they that starve with nothing.
William Shakespeare (1564–1616)
Merchant of Venice, I.ii.

Introduction

Obesity is a condition of excess body fat. Because degree of fatness is a continuum, any definition of obesity must be arbitrary and related to a standard of normality. The standard of normality most commonly agreed upon is the weight, adjusted for height, associated with longest survival. Although the exact cutoff points for normality and the exact contribution of obesity to illness and premature death are still under investigation, obesity undoubtedly contributes to premature mortality, particularly when associated with elevated blood cholesterol levels, high blood pressure, or diabetes. Although poor health is not an inevitable consequence of obesity, excess body fat poses health risks to many Americans. Despite rapid advances in the definition and epidemiology of obesity, of adipose cell metabolism, and of the causes and consequences of obesity, disagreements still prevail on almost every key issue. Because the causes of obesity are not well understood, knowledge about how to prevent and treat it is also limited. This chapter outlines the current knowledge of the diagnosis, risks, causes, and treatment of obesity, calls attention to areas of controversy, and assesses the implications of this knowledge for public health policy.

Historical Perspective

Historians of obesity, finding few scientific records, have searched for clues in linguistics, history, and art and have concluded that obesity as it is now known did not occur in England, except in a few isolated instances, until it began to appear in the English upper classes in the 18th and 19th centuries (Trowell 1975).

One hypothesis suggests the ability to store excess calories as fat in adipose tissue was useful during prehistoric times as a protection against food shortages. However, this ability later became a handicap in industrialized societies. The industrial revolution allowed food to be available consistently and reduced the physical effort needed to obtain, process, and prepare it. Increased control of infectious diseases, modern transportation, and increasingly sedentary patterns of work and recreation contributed to the presence of the current high level of obesity in the United States.

Moderate obesity was considered a sign of health in this country until the present century, and many societies still consider it healthy. The positive attributes of body fat were extolled by early fertility symbols (e.g., the Venus of Willendorf from prehistoric times), by the ancient Greeks, and by Shakespeare. On the other hand, Dickens described the association of extreme obesity with poor health in the character of Mr. Pickwick, who suffered from the cardiorespiratory syndrome that now bears his name. These concerns eventually led life insurance companies to develop and use rate structures based on tables of body weight-for-height (Rittenbaugh 1982).

Widespread interest in studying body fat (adipose tissue) was stimulated by the publication in 1940 of "Adipose Tissue: A Neglected Subject" (Wells 1940). A subsequent prophetic observation correlated the distribution and size of body fat cells with the development of atherosclerosis: fat cells concentrated in the trunk region were more likely to be linked to heart disease than were those on the arms or legs (Bjurulf 1959). In 1965, the American Physiological Society published a large compendium of information on adipose tissue that is still a good source of information (Renold and Cahill 1965).

The first data using weight tables to predict life expectancy were collected by the life insurance industry in 1913 (Association of Life Insurance Medical Directors and Actuarial Society of America 1913), but tables of ideal or desirable weight did not appear until the Metropolitan Life Insurance Company published its first tables of ideal or desirable weight in the 1940's (Simopoulos and Van Itallie 1984). Concurrently, modern epidemiologic techniques began to identify obesity as a risk factor for some of the major diseases of modern times: cardiovascular disease, diabetes, hypertension, and cancer. The most recent epidemiologic data on obesity as a health hazard were the subject of a national conference (NIH 1985) and are reviewed in this chapter.

Significance for Public Health

Obesity is one of the most prevalent diet-related problems in the United States. It affects about 34 million adults ages 20 to 74 (NCHS 1987), with the highest rates observed among the poor and minority groups (Van Itallie 1985; Van Itallie and Abraham 1985).

Population data for heights and weights (and, therefore, obesity) among Americans derive from three national surveys: the National Health Examination Survey (NHES I) of 1960–62 (DHEW 1964), the first National Health and Nutrition Examination Survey (NHANES I) of 1971–74 (DHEW 1973), and NHANES II of 1976–80 (McDowell et al. 1981; NCHS 1987). In addition, data are available from the Framingham Heart Study (Hubert et al. 1983) and from the American Cancer Society Study of 1959–62 (Lew and Garfinkel 1979).

The 1971–74 NHANES found that 23.7 percent of men and 26.0 percent of women ages 20 to 74 were overweight. These figures were based on a definition of overweight that included persons whose weights met or exceeded the 85th percentile of the body mass index, or BMI (weight in kilograms divided by height in meters squared for men, and for women, divided by height to the power 1.5) for individuals ages 20 to 29. The BMI is discussed in more detail below. Because body weights increase with age, population rates of overweight that have been reported for adults ages 25 to 74 (and age-adjusted) are higher—26.0 percent of men and 29.4 percent of women (NCHS 1986).

NHANES II reported 25.6 percent of Americans ages 20 to 74 as overweight. Age-adjusted rates for blacks (36.6 percent) exceeded those for whites (24.6 percent), and those for females of all races (26.7 percent) exceeded those for males (24.4 percent). Although the rate for black males (26.3 percent) was only slightly higher than that for white males (24.4 percent), the rate for black females of 45.1 percent was highest of all—almost twice that of the 24.6 percent for white females (NCHS 1987). Rates of obesity in the United States appear to be higher than those observed in England, Canada, or Australia, at least among certain age groups (Bray 1985; Millar and Stephens 1987). The reasons for these differences have not been established.

The peak overweight rates for men occur from ages 35 to 64, whereas rates for women continue to increase throughout the ages in which they are

measured. The percent of adults classified as overweight increases from a low of 5.5 percent among black males ages 20 to 24 to a high of 61.2 percent among black women ages 45 to 54 (NCHS 1987).

NHANES II data also identified individuals at or above the 95th percentile BMI for a reference population ages 20 to 29. By this criterion, 9.3 percent of all Americans were classified as severely overweight, with the rate for blacks (15.5 percent) almost twice that for whites (8.8 percent). Here too, rates for females (10.6 percent) were higher than for males (8.0), with a much higher prevalence among black females than among white females (19.7 and 9.6 percent, respectively). The highest prevalence of severe overweight was the 26.3 percent observed among black females ages 35 to 44; the lowest was the 3.4 percent rate seen in white females ages 20 to 24 (NCHS 1987). When adjustments were made for differences in age distribution among populations between surveys, the age-adjusted proportions of men and women severely overweight (95th percentile by BMI) in 1976–80 significantly exceeded those in 1961–62 (Van Itallie and Abraham 1985).

The influence of poverty on the prevalence of overweight in women has been established. For example, in the 45 to 54 age range, 54.1 percent of poor women were overweight compared with 32.5 percent in the general female population (Van Itallie 1985).

Severe overweight increases the risk for high blood cholesterol, high blood pressure, and diabetes and, hence, for diseases for which these conditions are risk factors (see chapters on diabetes, coronary heart disease, high blood pressure, neurologic disorders, and kidney diseases). It also increases the risk for gallbladder disease (see chapter on gastrointestinal diseases) and for some types of cancer (see chapter on cancer). Its psychosocial consequences are significant (see chapter on behavior). The great prevalence of obesity and its physical and mental health consequences suggest that its prevention should be a high public health priority.

Perhaps for these and other reasons, many Americans try to lose excess weight. According to data from the 1985 National Health Interview Survey, 27 percent of males and 46 percent of females were trying to lose weight by reducing caloric intake, increasing physical activity, or both (Stephenson et al. 1987). The health consequences of these activities are also of public health concern and are reviewed in this chapter.

Key Scientific Issues

- Definition of Obesity
- Health Consequences of Obesity
- Causes of Obesity
- Treatment of Obesity

Definition of Obesity

An ideal, health-oriented definition of obesity would be based on the degree of excess body fat at which health risks to individuals begin to increase. No such definition currently exists. Instead, the most commonly used methods estimate body fat as a percentage of total body weight (underwater weighing), establish an index of body fat level (skinfold thickness or waist-to-hip circumference measurements), compare weight-for-height measurements (height and weight tables), or compute an index of body weight as a function of height (BMI) in reference to population standards.

Much of the scientific disagreement about the level of body fat associated with increased health risks to individuals or to populations can be attributed to the difficulties in measuring body fat content and in defining overweight and obesity. Even underwater weighing, which measures body fat as a percent of total body weight and which is too cumbersome and expensive to use in population studies, can produce inaccurate results (Barnes 1987). The easily available measurements of heights, weights, and skinfold thicknesses, which are more frequently used in epidemiologic studies for assessing obesity and its effects, can be even less accurate.

Reference Body Weight Standards

An ideal body weight-for-height based on minimal health risks has not yet been defined for either individuals or populations. Instead, weight-for-height is usually compared with standards based on survey populations. The accuracy of such determinations, therefore, depends on the size and type of the reference population, as well as on the precision and appropriateness of the measures used.

Height and Weight Tables. The reference standards most commonly used to define obesity are those based on actuarial data from the Metropolitan

Life Insurance Company (MLIC), in which "desirable" or "ideal" weight is the weight-for-height of insured persons with the longest lifespans. The original 1949 tables were revised in 1959 (MLIC 1959) based on the Build and Blood Pressure Study of 1959 (Society of Actuaries 1960), and again in 1983 (MLIC 1983) based on the Build Study of 1979 (Society of Actuaries and Association of Life Insurance Medical Directors of America 1980).

Tables of heights and body weights derived from several studies are given in Table 6-1. These tables present ranges of weight-for-height associated with the lowest mortality rates. The midpoint of the range is usually used as the standard for ideal or desirable weight. As seen in Table 6-1, Metropolitan desirable weights of 1983 are higher than those for 1959 in nearly all height categories but especially in those that are shorter. Both sets of data present as "desirable" body weights that are significantly lower than average weights measured in population surveys.

Relative Weight. Relative weight refers to actual weight as a percent of the desirable weight defined in the tables. A relative weight of 100 would thus be a desirable weight. As commonly used, a relative weight of 120 percent of that desirable is considered overweight, and relative weights of 140 percent or more are considered severely overweight (NIH 1985; Foster and Burton 1985). The desirable weights were slightly more liberal in the 1983 Metropolitan tables than in the 1959 tables, particularly for persons of short stature; weights for the shortest men in the 1983 table were heavier by 12 lb and for the shortest women by 14 lb.

These tables are handicapped by major flaws in the data from the studies on which they are based. For example, the tables present heights and weights with shoes and clothing but whether heights and weights were obtained with or without clothes and shoes was not consistent. The data for the Metropolitan tables were drawn from persons who could afford life insurance and were predominantly white and from middle-class males of young and middle age; thus, they were not necessarily representative of other groups. For these and other reasons, some experts believe that these tables are limited in value (Knapp 1983).

Body Mass Index. Ratios of weight to height estimate total body mass rather than fat mass, but they correlate highly with amount of body fat (Revicki and Israel 1986). The most commonly used ratio is known as Quetelet's index, or the BMI, and is usually defined as body weight in kilograms divided by the square of the height in meters (wt/ht^2). A simple nomogram to facilitate calculation of the BMI is given in Figure 6-1. In

population studies such as NHANES, this index is modified to reflect body composition differences between men and women.

A great advantage of such an index is the capability to evaluate and compare not only individuals but populations or subgroups within populations. Thus, various experts have recommended that the degree of obesity be defined by the BMI and have established reference standards for its use. These standards were derived from the same studies used to construct the Metropolitan tables. The BMI equivalent to a relative weight of 100 was 22 kg/m^2 for men and 21.5 kg/m^2 for women (Simopoulos and Van Itallie 1984). Table 6-2 shows the equivalent body mass indices derived from the three reference populations in common use: the 1959 and 1983 Metropolitan tables of desirable weights (MLIC 1959, 1983) and the 1976–80 NHANES (NCHS 1987). The indices in Table 6-2 are translated from the 85th and the 95th percentile weight distribution of NHANES II and from the 120 percent and 140 percent overweight cutoff points of the Metropolitan tables of 1959 and 1983. These indices are in rather close agreement. While some experts suggest that the body mass indices based on the 1959 Metropolitan tables, 26.4 for men and 25.8 for women, be considered the upper limits of normal weight (NIH 1985), others favor the higher levels derived from the more rigorous national probability sample of NHANES II (NCHS 1987).

The term overweight rather than obesity is used in this discussion because, although the BMI correlates highly with body fat, it does not distinguish between body fat and lean body tissue. While excess fat tissue is generally assumed to account for the additional weight and, therefore, the additional mortality among overweight individuals, excess weight can also include lean body mass (which weighs more than fatty tissue) (Van Itallie 1985; Forbes and Welle 1983) or a larger body frame size (Simopoulos and Van Itallie 1984). Such problems limit the use of the BMI as a standard for health risk (Garn, Leonard, and Hawthorne 1986). Its clinical significance, discussed below, has also been questioned (Callaway 1984).

Body Composition. Careful measurements of skinfold thickness made with calipers generally correlate well with body fat content. The sums of the scapular and triceps skinfolds that correspond to the 85th percentile of the NHANES II population were 45.5 mm in men and 70.1 mm in women (Van Itallie 1985). The lean body mass (or fat-free weight) can be calculated as the difference between total body weight and the weight of adipose tissue estimated from skinfold thickness or other methods. Elbow breadth and wrist circumference may be useful indicators of body frame size (Simopoulos and Van Itallie 1984).

Table 6-1
Comparison of Metropolitan Desirable Weights With Average Weights From U.S. Cohort Studies

Height (Without Shoes), cm (ft in)	Metropolitan Tables[a] (Medium Frame), Weight in Kilograms (Pounds) (Without Clothing)		Average Weight for Age 40–49 y, kg (lb)			
			Insured Lives			
	1959[a]	1983	Build and Blood Pressure Study 1959[b] (1935–1953)[e]	Build Study 1979[b] (1950–1971)[e]	American Cancer Society Study 1979[c] (1959)[e]	Health and Nutrition Examination Survey (HANES I, 1979)[d] (1971–1974)[e]
			Men			
156 (5 1)	50–55 (111–122)	57–62 (126–136)	60 (133)	61 (135)	—	—
159 (5 2)	52–57 (114–126)	58–63 (128–138)	62 (137)	63 (139)	67 (148)	66 (145)[f]
162 (5 3)	53–59 (117–129)	59–64 (130–140)	64 (141)	65 (144)	68 (149)	68 (150)[f]
164 (5 4)	54–60 (120–132)	60–65 (132–143)	66 (145)	68 (149)	69 (153)	73 (162)
167 (5 5)	56–62 (123–136)	61–66 (134–146)	68 (149)	69 (153)	71 (156)	72 (159)
169 (5 6)	58–64 (127–140)	62–68 (137–149)	70 (154)	72 (158)	73 (160)	75 (166)
172 (5 7)	59–66 (131–145)	64–69 (140–152)	72 (158)	73 (162)	74 (163)	78 (173)
174 (5 8)	61–68 (135–149)	65–70 (143–155)	73 (162)	76 (167)	77 (169)	79 (174)
177 (5 9)	63–69 (139–153)	66–72 (146–158)	76 (167)	78 (171)	78 (173)	79 (175)
179 (5 10)	65–72 (143–158)	68–73 (149–161)	78 (171)	80 (176)	80 (177)	83 (184)
182 (5 11)	67–74 (147–163)	69–75 (152–165)	80 (176)	82 (181)	83 (182)	85 (188)
185 (6 0)	68–76 (151–168)	70–77 (155–169)	82 (180)	85 (187)	85 (187)	88 (194)
187 (6 1)	70–78 (155–173)	72–78 (159–173)	84 (185)	87 (192)	87 (192)	92 (203)
190 (6 2)	73–81 (160–178)	73–80 (162–177)	86 (190)	90 (198)	90 (198)	92 (203)[f]
192 (6 3)	75–83 (165–183)	75–83 (166–182)	89 (196)	92 (203)	92 (203)	—

Women

146 (4 9)	43–48 (94–106)	48–54 (106–118)	54 (120)	52 (115)	—	58 (127)[f]
149 (4 10)	44–49 (97–109)	48–54 (106–120)	56 (123)	54 (118)	52 (115)	59 (131)[f]
151 (4 11)	45–51 (100–112)	50–56 (110–123)	57 (126)	54 (120)	55 (121)	62 (136)
154 (5 0)	47–52 (103–115)	51–57 (112–126)	59 (129)	56 (124)	57 (126)	64 (141)
156 (5 1)	48–54 (106–118)	52–59 (115–129)	60 (132)	57 (126)	58 (128)	63 (138)
159 (5 2)	49–55 (109–122)	54–60 (118–132)	62 (136)	59 (130)	60 (132)	64 (141)
162 (5 3)	51–57 (112–126)	55–61 (121–135)	63 (139)	60 (133)	62 (136)	67 (148)
164 (5 4)	53–59 (116–131)	56–63 (124–138)	65 (143)	62 (136)	63 (139)	68 (151)
167 (5 5)	54–61 (120–135)	58–64 (127–141)	67 (147)	64 (140)	64 (142)	71 (156)
169 (5 6)	56–63 (124–139)	59–65 (130–144)	68 (151)	65 (144)	66 (146)	71 (156)
172 (5 7)	58–65 (128–143)	60–67 (133–147)	70 (155)	67 (147)	68 (150)	72 (158)
174 (5 8)	60–67 (132–147)	62–68 (136–150)	73 (160)	70 (152)	71 (156)	78 (172)
177 (5 9)	62–68 (136–151)	63–69 (139–153)	75 (165)	70 (155)	73 (161)	—
179 (5 10)	64–70 (140–155)	64–71 (142–156)	77 (170)	72 (159)	75 (165)	—

[a]Not age specific: 1959 tables recommended for ages 25 and older; 1983 tables for ages 25 to 59 years.
[b]Without shoes or clothing.
[c]Values are means for age groups 40 to 44 and 45 to 49. Self-reported heights without shoes and weights with indoor clothing.
[d]Values are means for age groups 35 to 44 and 45 to 54. Measured without shoes; clothing ranged from 0.20 to 0.62 lb (not deducted from weights shown).
[e]Years when measurements taken.
[f]Estimated values obtained from linear regression equations.

Source: Manson, J.E.; Stampfer, M.J.; Hennekens, C.H.; and Willett, W.C. 1987. Body weight and longevity. A reassessment. *Journal of the American Medical Association* 257:353–58.

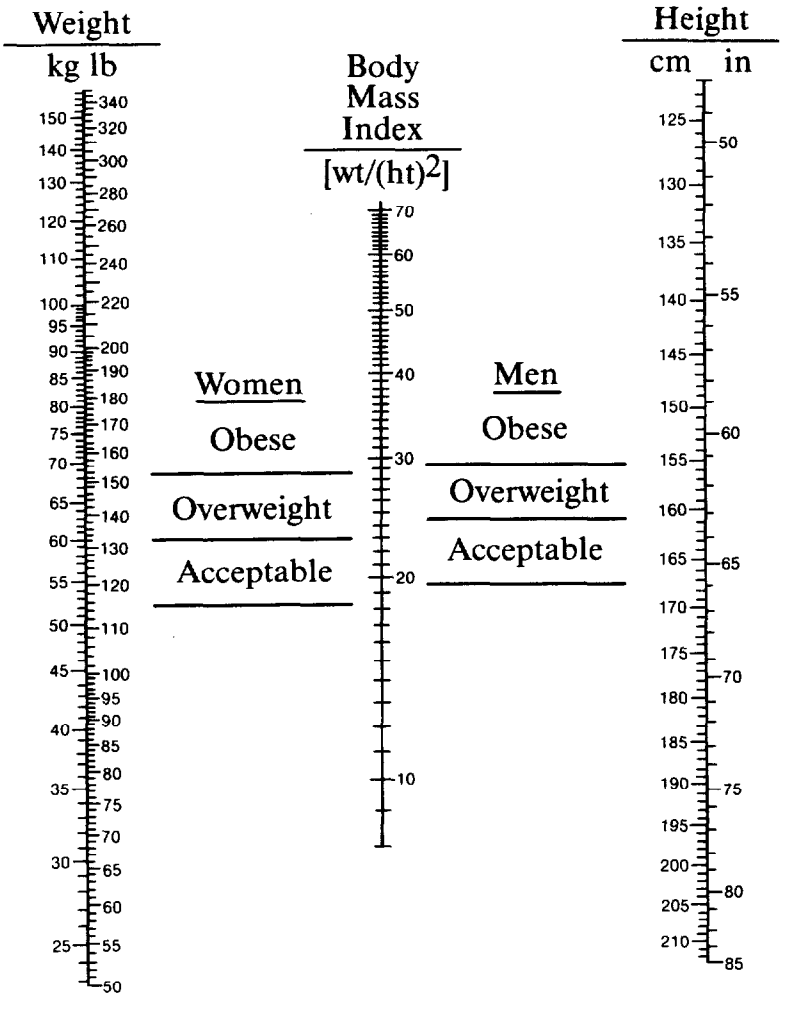

Figure 6-1. A nomogram for determining body mass index (BMI). To use this nomogram, place a ruler or other straight edge between the column for height and the column for weight connecting an individual's numbers for those two variables. Read the BMI in kg/m^2 where the straight line crosses the middle lines when the height and weight are connected. Overweight: BMI of 25-30 kg/m^2; obesity: BMI above 30 kg/m^2. Heights and weights are without shoes or clothes.

Source: Bray, G.A. 1985. Obesity: definition, diagnoses and disadvantages. *The Medical Journal of Australia* 142:S2-S8. Copyright 1985, *The Medical Journal of Australia*, reprinted with permission.

Table 6-2
Body Mass Index (kg/m^2) Used to Define Desirable Weight and Overweight According to Three Different "Ideal" Reference Populations

Study[a]	"Ideal" Reference Population	BMI for "Ideal" Reference Population					
		Mean		Overweight		Severe Overweight	
		Men	Women	Men	Women	Men	Women
NHANES II	20- to 29-year-olds	24.3	23.1	27.8	27.3	31.1	32.3
Metropolitan 1959	Desirable weight insured	22.0	21.5	26.4	25.8	30.8	30.1
Metropolitan 1983	Desirable weight insured	22.7	22.4	27.2	26.9	31.8	31.4

[a]The NHANES II data define overweight as the 85th percentile or more of the distribution of BMI for men and women ages 20 to 29 and severely overweight as the 95th percentile for that reference population (NCHS 1987). The Metropolitan 1959 data are taken from the 1959 Metropolitan Life Insurance tables. Weights and heights were adjusted to approximate those without shoes or clothing (Simopoulos and Van Itallie 1984; NIH 1985). The Metropolitan 1983 data are taken from the 1983 Metropolitan tables. Height and weight were with shoes and light clothes (Van Itallie 1985; NIH 1985). For both the 1959 and the 1983 Metropolitan data, the weights for midpoint of medium-frame persons were used, and for both studies overweight and severe overweight were defined as 20 percent and 40 percent, respectively, over desirable weight.

Types of Obesity

Hyperplastic vs. Hypertrophic. Obesity is associated with too many adipose cells (hyperplastic obesity), adipose cells that are too large (hypertrophic obesity), or both (Hirsch and Batcheloer 1976). Studies on differences and changes in fat cell sizes and numbers have led to the hypothesis that while changes in the size of adipose cells may occur at any age, the number of adult cells may be fixed and determined by weight gain during certain periods of childhood development; fat cell number is established by late adolescence (Knittle et al. 1979) and, once established, does not decline. These suggestions have been interpreted to imply that the potential for sustained weight reduction in adulthood may depend, in part, on the number of adipose cells present. That is, because people with excessive numbers of fat cells may expect only limited success in weight reduction, prevention of adult obesity should begin with limits on excessive weight gain during childhood (Hirsch and Batcheloer 1976).

This hypothesis has received limited support. Although adult-onset obesity is more commonly due to an increase in the size of a normal number

of adipose cells than to an increase in their number (Krotkiewski et al. 1983), adipose cell number also increases in response to excessive weight gain at any time throughout adult life (Sjostrom 1980). Some studies have reported better treatment outcome among hypertrophic than hyperplastic obese subjects (Bjorntorp et al. 1975), but others have not observed any such difference (Strain et al. 1984), and the clinical significance of differences in fat cell size and number remains to be determined.

Upper Body vs. Lower Body. Women generally have been observed to have more subcutaneous fat than men, but men appear to suffer a greater cardiovascular risk from a given degree of fat than women (Bjorntorp 1983). The distribution of body fat may be an indicator of this difference. More men than women accumulate large fat cells in the abdominal region. This distribution around the abdomen with increased waist-to-hip ratio, referred to as upper body obesity, is associated with increased cardiovascular risk factors such as hypertriglyceridemia and impaired glucose tolerance (Krotkiewski et al. 1983). Lower body obesity is more typical of women, who tend to accumulate fat in the hips, gluteal regions, and extremities, a distribution that does not appear to be associated with increased cardiovascular risk factors (Krotkiewski et al. 1983), perhaps because fat on the hips is not well mobilized (Rebuffe-Scrive et al. 1985). Adipose cells are insulin-resistant in the abdominal region but usually are insulin-sensitive in the gluteal region (Maugh 1982). Studies of siblings ranging in relationship from identical twins to adoptive suggest that these differences in adipose cells may be genetically determined (Bouchard et al. 1985). Accordingly, women with upper body obesity with a waist-to-hip ratio similar to that of men are, like men, at increased risk for hypertriglyceridemia, hyperinsulinemia, diabetes, and cardiovascular disease (Krotkiewski et al. 1983).

Regardless of gender, a high waist-to-hip ratio predicts an increased risk for cardiovascular disease and diabetes. Measurements made in 1967 of waist-to-hip circumference of 792 54-year-old men in Gothenberg were positively correlated 13 years later with deaths from stroke and ischemic heart disease (Larsson et al. 1984). Other indices of body fatness such as the BMI, the sum of three skinfolds, or either waist or hip circumference alone showed no such correlation. A 12-year study of 1,462 women found the waist-to-hip ratio to be a better predictor of myocardial infarction, angina pectoris, stroke, and death than any other anthropometric measurement obtained (Lapidus et al. 1984). In both of these studies, persons whose waist-to-hip ratio was in the top quintile of distribution (greater than 1.0 for men or 0.8 for women) suffered the greatest incidence of cardiovascular disease.

Childhood Obesity. Obesity and extreme obesity in children have been defined in several studies by a triceps or scapular skinfold thickness greater than or equal to the 85th or 95th percentile, respectively, of children in the same age group and sex between the baseline and a later year of measurement in national surveys (Dietz 1986). Increased weight-for-height above the 85th percentile for a defined population has also been used and can be deduced from standard growth charts (see chapter on maternal and child nutrition). Obesity in children can cause psychosocial dysfunction, orthopedic problems, abnormal glucose tolerance, hypertension, and elevated cholesterol and triglycerides that may persist into adulthood (Dietz 1986; Freedman et al. 1985). It also can increase the risk of obesity in adulthood (Garn 1985a, 1985b; Shear et al. 1988; Sorensen and Sonne-Holm 1988). According to a comparison of children studied in the NHES Cycle II and Cycle III between 1963 and 1970 and children studied later in NHANES I and II from 1971 to 1980, obesity and extreme obesity in children appear to be increasing by as much as 54 and 98 percent, respectively, in 6- to 11-year-olds and by 39 and 64 percent, respectively, in 12- to 17-year-olds (Gortmaker et al. 1987).

Health Consequences of Obesity

Excess Mortality

Numerous studies have examined the effects of excessive body weight on mortality. The best known studies include the Build and Blood Pressure Studies of 1959 and 1979 (Society of Actuaries 1960; Society of Actuaries and Association of Life Insurance Medical Directors of America 1980) and the American Cancer Society Study (Lew and Garfinkel 1979; Lew 1985). Several smaller studies include the Manitoba Study (Rabkin, Mathewson, and Hsu 1977), the Chicago People's Gas Company (Dyer et al. 1975), the Seven Countries Study (Keys 1980), the Longshoremen Study (Borhani, Hechter, and Breslow 1963), and the Provident Mutual Life Study (Blair and Haines 1966). This subject has been reviewed extensively (Simopoulos and Van Itallie 1984; NIH 1985; Manson et al. 1987).

In most of these studies, mortality increased with increasing weight. This effect can be expressed as the mortality ratio, defined as the actual number of deaths as a percent of expected deaths for the population as a whole. The mortality ratio has been shown to increase with degree of obesity, and with its duration, from 110 among persons 5 to 15 percent overweight to 227 among those 55 to 65 percent overweight (NIH 1985). Extreme (morbid) obesity, defined in this instance as either 100 percent or 100 lb over

desirable weight (Kral 1985), has been reported in one small series to be associated with a mortality ratio of 1,200 percent (NIH 1985).

Although experts generally agree that excessive body weight is associated with increased mortality (NIH 1985), the body weight associated with the lowest mortality still lacks precise definition. Several important methodologic issues contribute to this uncertainty. These include the failure to control for cigarette smoking and inappropriate control for biologic effects of overweight such as hypertension, hyperlipidemia, and hyperglycemia, for weight loss due to subclinical disease (Manson et al. 1987), for weight history, for body fatness, or for duration of the condition (Simopoulos and Van Itallie 1984).

Several studies, for example, have reported a higher mortality at the lower as well as the higher range of fatness. This J- or U-shaped curve was found in the Build Study of 1979 (Society of Actuaries and Association of Life Insurance Medical Directors of America 1980; Van Itallie and Abraham 1985), the Framingham Heart Study (Hubert et al. 1983; Garrison and Castelli 1985), the American Cancer Society Study (Lew and Garfinkel 1979), and the Hawaiian Japanese Study (Rhoads and Kagan 1983). The increased mortality at lower weights was related to several types of cancer (Lew and Garfinkel 1979). The J-shaped curve was markedly reduced but still observable when adjusted for smoking history (Garrison and Castelli 1985), as well as for serum cholesterol level, blood glucose level, and systolic blood pressure (Harris et al. 1988).

In the Build and Blood Pressure Study of 1959 (Society of Actuaries 1960), optimal weight for all ages, judged by survival, was close to that of 20- to 29-year-olds. Older cohorts were heavier, and the increase in relative weight with increasing age was associated with increased mortality. Data from the Framingham Heart Study confirm that being overweight increases health risks for older people (Harris et al. 1988). Implicit in this trend is the undesirable effect of weight gain beyond desirable weight after maturity and the suggestion that weight gain acquired during adult life might be more detrimental than the degree of overweight. In fact, one study has reported the highest rates for cardiovascular and renal disease among overweight adults who were below average weight as children but who developed late-onset obesity (Abraham, Collins, and Nordsieck 1971). However, in the Build Study of 1979, the effect of overweight on mortality was more marked in obese men issued insurance policies between ages 15 and 39 than for equally obese men issued insurance policies between ages 40 and 69. A problem with both the 1959 and 1979 studies was the rather

short average duration of time that policyholders were observed—6.6 years for the latter study. In the Build Study of 1979, the adverse effects of underweight became evident in a relatively shorter time than the adverse effects of overweight (Society of Actuaries and Association of Life Insurance Medical Directors of America 1980).

The studies that do not show increased risk from obesity, such as the Seven Countries Study and the Longshoremen Study, have limitations because they were too short in duration, too small in sample size, or did not consider the adverse effects of smoking or of preexisting illness (Simopoulos and Van Itallie 1984; Van Itallie and Abraham 1985; Manson et al. 1987). Under these circumstances, the adverse effects of overweight would be obscured and of underweight exaggerated. Prospective data from the Framingham Heart Study, in which a cohort was followed for 26 years, clearly show the adverse effect on mortality of as little as 10 percent overweight, using the 1959 Metropolitan tables (Hubert et al. 1983). Bearing in mind data limitations, minimal mortality appears to occur at a weight 10 percent below the U.S. averages as shown in Table 6-1 (Manson et al. 1987).

Other Health Consequences

Relative body weights above 100 to 109 percent of desirable are associated with increased mortality as well as morbidity from heart disease, cancer, diabetes, digestive diseases, and cardiovascular disease. The higher the relative weight, the greater the risk for these conditions (Lew and Garfinkel 1979). From the NHANES II data, rates of hypertension and diabetes were nearly tripled for persons 20 percent or more overweight, and hypercholesterolemia was 50 percent more common (Van Itallie 1985). Obesity is associated with reduced levels of high density lipoproteins but with elevated levels of triglycerides and atherogenic lipoproteins (Albrink et al. 1980). The large American Cancer Society Study found mortality from various causes to increase according to the degree of overweight. Data from this study are shown in Table 6-3. Of all obesity-related diseases, noninsulin-dependent diabetes is most clearly and strongly associated with obesity. The details of these relationships are discussed in the chapter on diabetes.

Many other serious conditions such as gallstones, sleep apnea, osteoarthritis, and other disabling disorders of locomotion bear a direct relationship to obesity, although causality is not necessarily proved by these associations.

Table 6-3
Mortality Ratios for All Ages Combined in Relation to the Death Rate of Those 90 to 109 Percent of Average Weight

		Weight Index						
	Sex	<080	080–089	090–109	110–119	120–129	130–139	140+
Total deaths	M	1.25	1.05	1.00	1.15	1.27	1.46	1.87
	F	1.19	0.96	1.00	1.17	1.29	1.46	1.89
Coronary heart disease	M	0.88	0.90	1.00	1.23	1.32	1.55	1.95
	F	1.01	0.89	1.00	1.23	1.39	1.54	2.07
Cancer, all sites	M	1.33	1.13	1.00	1.02	1.09	1.14	1.33
	F	0.96	0.92	1.00	1.10	1.19	1.23	1.55
Diabetes	M	0.88	0.84	1.00	1.65	2.56	3.51	5.19
	F	0.65	0.61	1.00	1.92	3.34	3.78	7.90
Digestive diseases	M	1.39	1.28	1.00	1.45	1.88	2.89	3.99
	F	1.58	0.92	1.00	1.66	1.61	2.19	2.29
Cerebral vascular disease	M	1.21	1.09	1.00	1.15	1.17	1.54	2.27
	F	1.33	0.98	1.00	1.09	1.16	1.40	1.52

Source: Lew, E.A., and Garfinkel, L. 1979. Variations in mortality by weight among 750,000 men and women. *Journal of Chronic Diseases* 32:563–76. Copyright 1979, Pergamon Press, Ltd., reprinted with permission.

Causes of Obesity

The causes of obesity are incompletely understood, so that effective treatment is difficult. Obesity is the net result of an excess of energy consumption over expenditure. Factors that must be considered as contributing to causation are: (1) heredity, (2) primary overeating, (3) altered metabolism of adipose tissue, (4) defective or decreased thermogenesis (the process by which calories are converted into heat), (5) decreased physical activity without an appropriate reduction in food intake, and (6) certain prescribed medications. These potential causes can interact with one another. Of the six factors, individuals may have some control of overeating and underactivity.

Genetic Causes

Some studies of incidence of obesity among population groups, and among individuals within population groups, suggest that the tendency for obesity is inherited. On the other hand, separating genetic from cultural and environmental contributions is difficult—a fact brought out by studies of American Indians and blacks (Van Itallie and Abraham 1985; Van Itallie

1985), two populations that display higher levels of obesity than other groups. To explore the question of environment versus heredity, investigators have examined the weight characteristics of twins and adopted siblings. In addition, studies of reduced energy expenditure in overweight infants and adults, as reviewed later in this chapter, have provided evidence in support of a genetic basis for obesity.

One study measured the body fatness of 871 biologic and adopted siblings of French descent, including 87 pairs of monozygotic twins, and found that the amount and distribution of fat were related to the closeness of the genetic relationship. Similarities were not observed between adopted siblings. The genetic effect was particularly noted in measurements of skinfold thicknesses and in lean body mass. At the same time, a substantial environmental, or cultural, effect was also observed (Bouchard et al. 1985). Aerobic capacity in response to submaximal exercise also appeared to be at least partially genetically determined because similarities were greater among twins than among siblings or adopted siblings (Bouchard et al. 1984). Although these findings do not entirely rule out effects of early learned practices, they do make it tempting to speculate that for genetic reasons, some persons are less able to benefit from exercise and are thus more susceptible to obesity than others.

Another recent study provided even broader evidence for the genetic determination of obesity. In a study of 4,071 pairs of twins, investigators estimated that 80 percent of the contribution to obesity could be explained by genetics (Stunkard, Foch, and Hrubec 1986). Evidence for a smaller but still substantial genetic contribution was provided by investigations on 540 Danish adoptees (Stunkard et al. 1986). In this latter study, the BMI of the adoptees correlated strongly with that of their biologic parents but not at all with that of their adoptive parents, an observation that suggests that in this Danish population, early family environment had apparently little influence in determining the degree of fatness.

Overeating

Overeating is clearly a prominent contributor to obesity. Yet, obese persons do not necessarily consume more calories for their weight than lean individuals. Nutrient intake, established by dietary interview of a probability sample of 6,219 male and nonpregnant female adults selected from NHANES I, did not correlate with the degree of obesity (Braitman, Adlin, and Stanton 1985). Although underreporting of food intake by the obese could not be ruled out, the authors suggested that factors other than overeating, such as decreased levels of physical activity, be given increased consideration in the etiology of obesity.

Additional factors include complex controls of feeding behaviors at the biologic and behavioral levels. At the biologic level, feeding behavior is regulated in part by the brain hypothalamus (Dallman and Bray 1986) and its interactions with brain neurotransmitters, nervous impulses from the intestinal tract or from higher brain centers, circulating nutrients absorbed from the intestinal tract, and certain hormones. While anatomic or biochemical lesions in the brain can cause obesity, more frequent and likely causes of overweight are improper signals coming to the brain, particularly those from the adipose tissue and the intestinal tract (Stricker 1984).

Feeding behavior occurs in response to hunger and to appetite induced by the presence of food. Satiety and the resulting cessation of eating occur in response to certain hormones, nervous impulses, and absorbed nutrients signaling the brain (Dallman and Bray 1986). Whether specific foods affect feeding and satiety and, consequently, over- or undereating is uncertain. Laboratory animals overeat and become obese if offered highly palatable foods, especially those high in fat and sugar and low in fiber. The same may be true of some humans (Herman and Polivy 1984). Foods low in fat and high in naturally occurring fiber appear to induce satiety in humans at lower levels of caloric intake than do high-fat, low-fiber foods (Heaton et al. 1983; Duncan, Bacon, and Weinsier 1983).

Psychologic and behavioral factors also influence eating behavior, although their precise role has been difficult to define. Suggestions that obese persons were more dependent on external cues than internal signals of physiologic hunger (Schachter 1971) or were more restrained (and, therefore, overcompensated) in their eating behavior (Herman and Polivy 1984) have not proved as useful in diagnosis and treatment as was once thought (Stunkard and Messick 1985). The effects of peer pressure (Herman 1978) are also not well established.

Altered Adipose Cell Metabolism

Obesity might result from a metabolic error in energy balance in which an unusually high proportion of available dietary calories is directed to adipose tissue for storage. In humans and in many animals, adipose tissue is not as active in fat synthesis as other tissues but instead depends largely on circulating triglycerides for its fat content. These, in turn, originate from chylomicrons derived from absorbed dietary fat or from very low density lipoproteins synthesized by the liver from excess nutrients not immediately needed as fuel.

Lipoprotein Lipase. The removal of circulating triglyceride and its deposition in adipose tissue depends on lipoprotein lipase, an enzyme in adipose tissue. In studies of genetically obese strains of experimental animals, the observed increase in fat mass at the expense of lean body mass, even with caloric restriction, has been attributed to an excess of adipose tissue lipoprotein lipase (Greenwood and Vasselli 1981). Too much of this enzyme appeared to "pull" triglyceride into the adipose tissue, cause deprivation of other tissues (such as muscle), and lead to overeating. Thus, the overproduction of adipose tissue lipoprotein lipase might account for human obesity. Increased synthesis of lipoprotein lipase has been observed in the adipose tissue of obese persons who are losing weight, which could explain the rapid regain of weight lost with dieting (Schwartz and Brunzell 1981). However, other observers have reported no increase of adipose tissue lipoprotein lipase activity in response to caloric restriction. Instead, they report a decline in the enzyme with reduced calories and an increase with return to higher caloric intake (Rebuffe-Scrive, Basdevant, and Guy-Grand 1983). Until these inconsistencies can be resolved, the role of lipoprotein lipase in human obesity remains uncertain.

Hormones. In times of caloric need, as in fasting or during exercise, lipoprotein lipase is inactivated and adipose tissue is mobilized. Many hormones stimulate lipolysis (breakdown of lipid), but epinephrine released from the adrenal medulla and norepinephrine released from sympathetic nerve endings are probably the chief activators of lipolysis during exercise and stress, respectively. A genetic component to epinephrine-stimulated lipolysis has been identified (Despres et al. 1982), which suggests that an inherited impairment of epinephrine response during exercise could account for the observed failure of obese individuals to lose weight with exercise (Ribeiro et al. 1984).

Insulin is another hormone that modifies energy balance and may contribute to obesity (Dallman and Bray 1986). Hyperinsulinemia and insulin resistance, for example, can occur in all types of obesity and may be a link between hypertension, obesity, and glucose intolerance (Modan et al. 1985). Plasma insulin, which increases in response to feeding, promotes uptake of circulating triglycerides by adipose tissue and inhibits fat mobilization, thereby favoring storage of excess calories as fat. These reactions are reversed during fasting, when insulin levels are low. As discussed in the diabetes and high blood pressure chapters, weight loss often is followed by a correction of these abnormalities; when weight is regained, the problems return.

Whether human obesity is caused by a primary abnormality in adipose tissue or in the hormones that regulate its deposition is unknown at this time. However, adipocyte precursors obtained from massively obese subjects release a factor that, when added to rat adipose cells in tissue culture, causes cells to multiply (Lau, Roncari, and Hollenberg 1987). This finding suggests that metabolic effects may indeed play a role.

Altered Thermogenesis

Set Points. The weight of most people remains remarkably stable over the adult years, despite large fluctuations in dietary intake. Experiments in animals indicate that body weight is stabilized at a specific set point that is maintained without conscious control by variations in metabolic rate in response to food intake (Keesey 1986). A possible mechanism for such stability is a change in body heat production, or thermogenesis, to compensate for changes in energy intake (James 1983). Although human body weight often appears to be regulated at a set point, its controlling mechanism has not yet been demonstrated.

Heat production is an accurate measure of energy expenditure or metabolic rate. Because measurement of actual heat production is cumbersome and expensive, metabolic rate is usually determined by indirect calorimetry, which converts measurements of oxygen consumption into calories, ideally expressed per unit of lean body mass. Lean body mass is the body compartment containing the most metabolically active tissues and accounts for most energy expenditure. Thus, accurate methods for estimating lean body mass are essential (Horton 1983) as are those for measuring the degree of physical activity.

Metabolic Rate. The measure of the energy used for running the body's essential metabolic machinery and for maintaining body temperature is the resting metabolic rate (RMR), obtained when the subject is resting comfortably several hours after the last meal or physical activity. The basal metabolic rate (BMR) is the energy the body needs when the subject is at complete rest, before arising in the morning and 12 hours or more after the last meal (Horton and Danforth 1982). The RMR is much more convenient to obtain, and although it is slightly higher than the BMR, it provides a reasonable estimation of the BMR. At stable body weights, BMR and RMR are higher in obese persons than in normal-weight persons because of the increased body size. It is uncertain, however, whether the RMR of the obese is the same (Himms-Hagen 1984; Blaza and Garrow 1983) or lower (Danforth 1983) than that of normal-weight persons when it is expressed in terms of lean body weight.

Diet-Induced Thermogenesis. The energy generated metabolically when food is digested, called diet-induced thermogenesis, rises with increased food ingestion. Adaptive thermogenesis is the increase in RMR that occurs with increased food intake. Together, these forms of thermogenesis account for only about 10 percent of total energy expended. Failure to increase thermogenesis with overeating could result in obesity, but whether obese persons have defective thermogenesis has not been established. In the Vermont Prison Study, thin prisoners required many more calories to increase their body fat than could be calculated from the caloric value of the food ingested (Sims et al. 1973). These results suggest that in normal-weight individuals, extra calories are readily metabolized to heat when they are not needed.

In persons of normal weight, thermogenesis increases following a meal and is proportional to meal size (Rothwell and Stock 1986). The type of carbohydrate consumed may affect heat production; sucrose appears to be more thermogenic than glucose in normal-weight—but not obese—persons (Sharief and Macdonald 1982). Other macronutrients may also be important. The thermogenic effect of dietary protein, carbohydrate, and fat has been estimated to be 25, 10, and 3 percent of calories ingested, respectively (James and Trayhurn 1981). The small amount of heat lost when fat is processed may account for the importance of dietary fat as an inducer of obesity. Despite these findings, other investigators found a very small increase in total heat output with overfeeding and have concluded that any such adaptation to carbohydrate (but not fat) intake is very small (James 1983).

Effect of Weight Loss. In studies using continuous indirect calorimetry, reduced glucose-induced thermogenesis was found after obese subjects lost 9 to 33 kg (compared with controls), suggesting that defective thermogenesis is one of the factors causing relapse of obesity after weight loss (Schutz et al. 1984). In another study, energy expenditure was measured in a respiration chamber before and during weight reduction in obese subjects, and it declined as fat was lost; results were based on lean body mass (Ravussin et al. 1985). Other investigators analyzed the caloric content of measured liquid formula diets fed to obese and lean (never obese) patients during long-term hospital stays of many months' duration under metabolic ward conditions. They found that obese and lean subjects required similar amounts of energy per square meter of surface area per day. After weight loss and stabilization to a lower body weight, the obese subjects showed a 28 percent decrease in calories required to maintain body weight at the new level (Leibel and Hirsch 1984).

Other researchers, however, have identified problems with methodology or experimental design in such studies of defective thermogenesis in the obese (James 1983). For example, measurement of thermogenesis over periods of time longer than a few hours is only feasible where calorimetry chambers are available. Although people can reside in such chambers and move about freely for days at a time, activity is far from normal. Moreover, the need to express oxygen consumption in terms of lean body mass presupposes accuracy of methods of measuring body composition. Changes in heat production when dieting subjects are re-fed also complicate these studies. Although some evidence favors the hypothesis that adaptive thermogenesis occurs with weight change and is mediated by thyroid activity and the sympathetic nervous system (Danforth 1983; Landsberg and Young 1983; Horton 1983), the effect appears to be small and the role of thermogenesis in weight loss must be considered unsettled.

Lack of Exercise

Various studies have shown that physical inactivity in adult life shortens life expectancy (Paffenbarger et al. 1986), perhaps because underactivity without concomitant decrease in food intake can result in obesity. The very large difference in caloric expenditure between the most inactive and most active occupations, 2,300 to 4,400 kcal daily (Joint FAO/WHO Ad Hoc Expert Committee 1973), suggests that exercise could help manage and prevent obesity. Obesity may be a disease of inactivity, but that hypothesis has been difficult to prove (Stern 1984). Direct methods of measurement of daily physical activity are lacking, and current methodology for evaluating activity at home cannot detect whether inactivity contributes to obesity (Garrow 1978). Most studies that have compared the activity patterns of lean and obese subjects are based on questionnaires.

Epidemiologic data from the Lipid Research Clinics Prevalence Study show relatively low energy intakes to be coupled with increasing body weight, particularly in women (Dennis et al. 1985). Other epidemiologic data support this finding (Braitman, Adlin, and Stanton 1985). These and other investigators attribute the finding to decreased activity level. In another study, persons who participated in vigorous weekend activity were leaner than those who did not (Morris et al. 1980). A correlation also has been reported in young adolescents between degree of obesity and number of hours of television watched per week (Dietz and Gortmaker 1985).

Another interesting, but as yet unvalidated, aspect of the relationship between physical activity and body weight is involuntary movement—spontaneous fidgeting or moving, which varies widely from individual to

individual. In one study, for example, that measured energy expenditure in unselected subjects, very large individual differences in energy—100 to 800 kcal/day—were attributed to differences in spontaneous activity (Ravussin et al. 1986). Among infants, energy expenditure at age 3 months was more than 20 percent lower in those who became overweight than in infants whose weight remains normal (Roberts et al. 1988). A reduced 24-hour energy expenditure in adults correlated strongly with subsequent weight gain in southwestern American Indians with a high prevalence of obesity (Ravussin et al. 1988). Much is still to be learned about the relationship among physical movement, caloric expenditure, and body weight, but the cumulative effects of physical activity over time could be important in preventing or correcting obesity (Black 1983).

Prescribed Medications

Many drugs prescribed for clinical conditions other than obesity may cause weight gain. Such drugs include propranolol, clonidine, and related medications prescribed for hypertension and other cardiovascular diseases that may change metabolic rates and decrease levels of energy expenditure. Adrenal steroids such as prednisone, prescribed as anti-inflammatory agents, cause hypertrophic obesity. Some people experience weight gain with tranquilizers such as amitriptyline and diazepam, certain antihistamines such as cyproheptadine, and birth control pills. These and other issues related to medications are reviewed in the chapter on drug-nutrient interactions.

Treatment of Obesity

To lose weight, one must decrease caloric intake, increase caloric expenditure, or do both. Thus, the chief approaches to weight reduction involve behavior change related to diet and exercise, drugs to decrease hunger or increase satiety, and surgical or mechanical intervention designed to reduce food intake. To date, none of these methods has proved to be entirely effective, and none is without risk.

Weight loss reduces health risks in the obese. In theory, it should be accomplished easily, but in practice, traditional diet therapy has not been very successful; people who lose weight tend to gain it back (Stunkard 1986). Thus, a combination of diet and exercise seems the most sensible approach to treatment (Stricker 1984). Because obesity is a condition requiring continuous attention, any behavior changes required to maintain weight loss must be lifelong.

Behavior Modification

Behavior changes to induce weight loss were based initially on the theory that faulty eating behavior caused obesity and could be corrected by a program of record keeping, stimulus control, and reinforcement of appropriate behaviors. The early programs focused on the importance of eating behavior and introduced specified behavioral procedures to change eating patterns. Weight losses, however, were modest, and behavior therapy is now used as part of broader programs that include nutrition education, exercise, and cognitive restructuring (Stunkard 1987). Such programs form the basis of many commercial efforts that treat a substantial number of mildly obese people in this country (Brownell 1986). Current approaches are trying to increase the amount and duration of weight loss by combining various behavior modification techniques with low-calorie diets (Wadden, Stunkard, and Brownell 1983). The results have not been evaluated from a long-term perspective.

Drugs and Surgical Methods

Thus far, no drug therapy has induced long-term weight loss. Drugs are aimed at decreasing hunger or increasing satiety, usually by mimicking certain neurotransmitters or hormones that play a physiologic role in feeding behavior (Sullivan and Triscari 1985). One problem is that weight lost with drug therapy is more often regained than with other methods, suggesting that appetite-suppressant drugs lower the set point level at which body weight is regulated and only secondarily suppress appetite (Stunkard 1982). Regardless, weight loss would be expected to occur only during the period of drug therapy, suggesting the need for chronic treatment.

Surgical intervention appears appropriate only for selected persons with massive obesity or with its severe complications who have not responded to more conservative treatment. Jejunoileal bypass has been largely abandoned because of unfavorable side effects. Other procedures such as gastric balloons and gastric surgery, which reportedly cause substantial weight loss—although rarely to ideal weight—in morbidly obese persons (Kral 1985), require further study before their long-term effects are known.

Dangers of Dieting

Extremely low-calorie diets, 300 or 400 kcal per day, have resulted in deaths due, at least in part, to the effects of dietary deficiencies on the heart muscle (Van Itallie and Abraham 1985). Short-term studies indicate that the same problems are less likely to occur with diets higher in calories (range of

800 kcal) and with better quality protein (Wadden, Stunkard, and Brownell 1983). Nevertheless, such higher calorie diets still require careful medical supervision.

Another possible risk of dieting is the effect of repeated attempts on long-term prospects for weight loss. One study of rats has suggested that cyclic weight reduction may increase the difficulty of losing weight. Obese rats subjected to two repeated episodes of weight reduction and weight gain lost less weight during the second cycle and regained it more easily and with a lower food intake (Brownell et al. 1986). Whether similar effects occur in humans is as yet uncertain.

Fad weight loss regimens of unscientific merit have been estimated to cost consumers $5 billion annually (Herbert 1981). While such diets attract many people's attention they may be dangerous, especially when they provide less than the full complement of essential nutrients (Dwyer 1985). This danger is discussed in greater detail in the chapter on dietary fads and frauds.

Depression brought on by dieting is a serious condition affecting many obese persons (Stunkard and Rush 1974). Preoccupation with being thin may lead to two related and often serious eating disorders, anorexia nervosa and bulimia, that occur most commonly in adolescent girls (Herzog and Copeland 1985). Anorexia nervosa is characterized by an extreme fear of becoming obese, with severe diet restriction and weight loss sometimes to the point of cachexia and death. Bulimia is a syndrome of secretive binge eating followed by self-induced vomiting or purging. These conditions are discussed in detail in the chapter on behavior.

Implications for Public Health Policy

Dietary Guidance

General Public

Excess weight or overweight occurs when too few calories are expended and too many consumed for individual metabolic requirements. The extraordinarily high prevalence of obesity in the United States—one-fourth of American adults are overweight and nearly one-tenth are severely overweight—coupled with its role as a risk factor for diabetes, hypertension, coronary artery disease and stroke, gallbladder disease, and some types of cancer, suggests that a reduction in the average weight of the general

population would improve the Nation's health. Americans, in general, would benefit from a lifestyle that includes more physical activity and a diet containing fewer calories.

Because fat contains more than twice the caloric value per gram of either protein or carbohydrate, the general public would benefit from reduced fat intake. In addition, it may be difficult to meet essential vitamin and mineral requirements on low-calorie diets. Because sugar and alcohol provide calories from carbohydrate but no other nutrients, individuals seeking to attain and maintain desirable body weight should use these substances sparingly.

Evidence indicates that exercise burns calories, increases the proportion of lean to fat body mass, and, therefore, raises the metabolic rate. Therefore, increased levels of physical activity are important for attaining desirable body weights among the general population.

Special Populations

Qualified health professionals should evaluate overweight persons for the presence of chronic disease risk factors—especially elevated blood cholesterol, blood glucose, or blood pressure. Such evaluation is important for individuals whose excess body fat is distributed mainly on the abdomen. This pattern is more typical for men than for women, and it increases risks for diabetes, high blood pressure, hyperlipidemia, and heart attacks.

Health professionals should work with obese persons to restrict caloric intake and to increase caloric expenditure. Such advice should also be provided to overweight persons, with or without other significant risk factors, to help reduce their risk for heart disease, stroke, some kinds of cancers, and many other diseases and to prevent or reduce psychosocial complications of obesity. Professional guidance is recommended because many popular means to reduce weight may themselves pose risks to health and because unsupervised efforts to control obesity usually fail over the long term. Although excess body fat is difficult to lose, current research suggests that long-term individual or group programs that facilitate behavioral changes in diet and exercise are most likely to be effective. The intensity of these programs and the precise goal for weight loss should depend on the patient's degree and distribution of overweight, weight history, chronic disease risk factors, health status, and personal choices.

Current evidence is insufficient to recommend similar programs for overweight children. Obesity in infancy and childhood increases the risk for

adult obesity, but most overweight children will not become obese. Because no method now exists to predict which children will develop obesity as adults, because research has not yet identified effective methods to prevent adult obesity, and because children require adequate energy and nutrients to develop and grow normally, low-calorie diets should not be generally recommended for this group. Instead, they should be reserved for children with elevated risk factors for chronic disease. For most overweight children and their families, qualified health professionals should provide counseling and assistance in developing diets that contain adequate, but not excessive, calories and social and physical activities in which the child enjoys participating.

Nutrition Programs and Services

Food Labels

Evidence related to the role of diet in obesity indicates that calorie information should be provided on most food product labels.

Food Services

Evidence related to the role of diet in obesity suggests that service programs should include a variety of foods low in calories in their menus.

Food Products

Evidence related to the role of diet in obesity suggests that the food industry should continue to develop food products low in calories and with adequate nutrient content.

Special Populations

Overweight patients should be provided with counseling and assistance in the development of diets low in calories and high in essential nutrients, as well as lifestyle modifications that include high levels of physical activity to achieve appropriate weight goals.

Research and Surveillance

Research and surveillance issues of special priority related to the role of nutrition and exercise in obesity and weight management should include investigations into:

- Determination of ideal or desirable body weights for individuals or for the population of various ages.

- Determination of the health risks associated with various degrees of overweight in children and adults.
- Identification of an effective means to measure total body fat and its regional distribution in individuals and in the population.
- Identification of the types of obesity most associated with increased chronic disease risk.
- The contribution of genetic and metabolic factors to obesity, including the molecular and genetic basis of energy metabolism and the nature of genetic aberrations in human obesity.
- The effects of diet, exercise, and weight loss on metabolism and thermogenesis.
- The effects of physical activity on maintenance of desirable body weight.
- The identification of dietary, behavioral, environmental, or genetic factors that predict development of obesity or the ability to lose weight successfully.
- Identification of the dietary, behavioral, environmental, social, or genetic factors that increase the risk of overweight in high-risk population groups.
- The health consequences of repeated cycles of weight gain and loss.
- The most effective individual, group, and community intervention strategies for weight management.
- The most effective intervention strategies for use with high-risk groups.
- The most effective means by which to educate individuals and the public about the factors predisposing to weight gain and loss.
- The most effective ways in which to promote increased physical activity in the population.
- The long-term effectiveness of existing weight control programs.

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Chapter 7

Skeletal Diseases

For the women of this city do not possess sufficient devotion to look after everything as the purely Greek women do. If nobody looks after the movements of the infants the limbs of the majority become distorted, as the whole body rests on the legs . . . [when] the bones have not yet become strong.
Childrearing advice to the women of
Rome, Soranus of Ephesus
in second century A.D. (Temkin 1956)

Introduction

Historical Perspective

Major skeletal diseases influenced by nutrition include rickets, osteomalacia, and osteoporosis. Among all the nutritionally related skeletal diseases, rickets, the "softening" of bones in children, is probably the most well known. Rickets and its adult form, osteomalacia, traditionally viewed as urban diseases, have been largely eradicated in the industrialized world by milk fortification, enrichment of infant foods with vitamin D, the use of vitamin D supplements by children, and improved environmental conditions that promote adequate exposure to sunlight. Rickets is still prevalent in the developing world and is occasionally found elsewhere, especially where rapid urbanization has created conditions similar to the Industrial Revolution when social conditions and air pollution prevented adequate exposure to sunlight.

Hippocrates was the first to describe rickets. In the fifth century B.C., he observed children whose ". . . legs and arms attain full size, but the body will not grow correspondingly at the spine." Not until 1645 was the first formal description of the condition published; the classic study *De Rachitide* by Glisson, who traced its origin to the Greek word rachitis, or spinal disease, followed soon after (Guggenheim 1981).

The incidence of rickets increased with the Industrial Revolution. Rickets became known as the "English Disease," although it was prevalent throughout Northern Europe, where overcrowding and substandard living

conditions had become the norm. The disease was astonishingly widespread. For example, in 1907, half of the children between ages 6 months and 3 years admitted to Paris hospitals were reported to suffer from rickets, and in 1921, perhaps three of every four infants in New York City were affected.

Understanding developed slowly about the relationship between vitamin D deficiency and rickets. Cod liver oil was prescribed as treatment as early as 1807, but it was only in the late 1800's that rachitic lion and bear cubs at the London Zoo were cured when fed bone meal, milk, and cod liver oil (Todhunter 1973). The preventive powers of sunlight were observed in 1890.

It was not until this century that researchers untangled the complex interactions among vitamin D, sunlight, social conditions, and the disease. The isolation of vitamin D from fats and oils and the understanding of its activation in skin by ultraviolet radiation finally provided the keys to rational public health prevention of rickets and osteomalacia.

Today, osteoporosis—loss of bone mass—has become the most important bone disease in Western countries. The studies of early skeletons by Trotter and international comparisons by Nordin established that bone loss in aging persons occurs in every population. Such studies, coupled with population-based evidence suggesting a dietary contribution, stimulated current work on the role of diet in the prevention of age-related bone disease (Nordin 1984).

Significance for Public Health

Osteoporosis

The major skeletal disease in which nutrition may play a role is osteoporosis, characterized by a decrease in the amount of bone often so severe that it leads to fractures after even minimal trauma. Osteoporosis may be classified into primary and secondary forms. Primary osteoporosis, specifically involutional osteoporosis, may occur in two types: Type I (postmenopausal) osteoporosis (accelerated decrease in bone mass that occurs when estrogen levels decline after menopause), and Type II (age-related) osteoporosis, the inevitable loss of bone mass with age that occurs in both men and women (Riggs and Melton 1986). Secondary osteoporosis may develop at any age as a consequence of endocrinologic and gastrointestinal conditions or metabolic disorders, as well as prolonged bedrest and states of weightlessness, that result in bone demineralization.

Osteoporosis afflicts 15 to 20 million Americans, causing each year an estimated 1.3 million fractures of the vertebrae, hips, forearms, and other bones in those 45 years of age and older (Consensus Development Panel 1984). The risk of hip fractures is about twice as great in women as in men. Because women live longer than men, the absolute incidence is even higher. One-third of women 65 years and older have vertebral fractures, the most common break caused by osteoporosis. By age 90, one-third of women and one-sixth of men will have suffered hip fractures, leading to death in 12 to 20 percent of these cases and to long-term nursing home care for many of those who survive (Riggs and Melton 1986). Millions of other older Americans find their mobility restricted and the quality of their lives diminished by the consequences of osteoporosis. The total direct and indirect costs of osteoporosis to the U.S. economy were estimated to be between $7 and 10 billion in 1986 (Peck, Riggs, and Bell 1987).

Without effective measures to prevent the development of this disease, the costs of osteoporosis to the United States will increase because of the rapid increase in the number of older Americans. Prevention of osteoporosis is especially important, not only because of the costs of the disease, but also because treatment of osteoporosis, once fractures have occurred, is relatively ineffective and the functional limitations and deformities that develop are often irreversible. Precisely why certain individuals develop osteoporosis and others do not is incompletely understood. Aging itself, the loss of sex hormones at menopause, and genetics all play a role. To date, estrogen-replacement therapy is the best documented method of preventing osteoporosis in postmenopausal women. Although this treatment has been associated with increased risk of developing endometrial and other cancers, this association may not be significant especially at lower doses of estrogen (Ettinger, Genant, and Carn 1987). Table 7-1 lists factors that increase or decrease the risk for developing osteoporosis. Although much is yet to be learned about how diet can affect the development of this disease, sufficient scientific evidence now exists to make nutrition a focus of programs to prevent or to treat osteoporosis.

Rickets and Osteomalacia

Two other important diet-related bone diseases are rickets, which affects growing children, and osteomalacia, which affects adults. Both are characterized by an inadequate mineralization of bone. In osteoporosis, both the mineral and protein components of bone are lost; the remaining bone is thinner but normal in composition. In rickets and osteomalacia, the protein matrix is poorly mineralized, so the bone that remains is rubbery or soft.

Table 7-1
Scientific Validity of Risk Factors

Well Established	Moderate Evidence	Inconclusive or Inadequate Evidence
Obesity (−)	Alcohol (+)	Moderate physical activity
Black ethnicity (−)	Cigarette smoking (+)	Asian ethnicity
Age (+)	Heavy exercise (−)	Parity
Premenopausal oophorectomy (+)	Low dietary calcium (+)	Diabetes
Consumption of corticosteroids (+)		Thiazide diuretic use
Estrogen use (−)		Progestin use
Extreme immobility (+)		Drinking water fluoride
		Caffeine use

(+) = increased risk; (−) = decreased risk.

Source: Peck, W.A.; Riggs, B.L.; Bell, N.H.; Wallace, R.B.; Johnston, C.C., Jr.; Gordon, S.L.; and Shulman, L.E. 1988. Research directions in osteoporosis. *American Journal of Medicine* 84:275–82. Copyright 1988, *American Journal of Medicine*, reprinted with permission.

Although clinical cases of rickets and osteomalacia are relatively uncommon in the United States today, they are important for public health consideration because they can be prevented or treated.

Scientific Background—Bone Physiology

Bone is a spongy protein matrix in which crystals of calcium and phosphorus salts are embedded. From birth until death, bone tissue is continually being formed, broken down, and reformed in a process called remodeling. The cells that break down bone are called osteoclasts, and those that build bone are called osteoblasts.

From infancy through young adulthood, the activity of the osteoblasts normally predominates over that of the osteoclasts, resulting in the steady accumulation of bone mass. By the fourth decade, this process levels off and the amount of bone mass achieved at this time is called peak bone mass. Men develop a peak bone mass 30 percent more dense than that of women, and blacks about 10 percent more dense than that of whites (Consensus Development Panel 1984). Hence, although all individuals lose bone as they get older, women are more susceptible to osteoporosis than men, and whites more than blacks. Men in general and blacks as a group can sustain a greater loss of bone before the onset of fracture because they have a greater bone mass at skeletal maturity. However, differences in

bone mass do not fully explain the differences in osteoporosis rates between the sexes and races. Differences in bone architecture and structure must also be important.

Usually between the ages of 30 and 40, the balance of bone remodeling activity then swings over to the osteoclasts and adults begin to slowly lose bone mass. Mineral is lost more readily from trabecular bones, found in the vertebrae and pelvis, than from the cortical bones that form the limbs. The decline in estrogen production after menopause is associated with the period of most rapid bone loss in women.

The nutritional controls of bone mineralization have yet to be identified fully. At present, the only established nutritional determinants of mineralization are calcium, phosphate, and vitamin D.

Several recent reviews summarize present knowledge of nutrition and bone metabolism (Aloia et al. 1985; Chan and Alon 1985; Chan, Alon, and Hirschman 1985; Favus 1985; Heaney 1986; Heaney et al. 1982; LSRO 1981; Marcus 1982; Parfitt et al. 1982; Peck, Riggs, and Bell 1987; Raisz 1982, 1988; Raisz and Kream 1983; Riggs and Melton 1986; Riggs, Seeman, et al. 1982; Riggs, Wahner, et al. 1982). The following sections cite only a few key articles and recent studies that are not included in these reviews.

Key Scientific Issues

- Role of Calcium in Skeletal Disease
- Role of Vitamin D in Skeletal Disease
- Role of Phosphate in Skeletal Disease
- Role of Calories and Protein in Skeletal Disease
- Role of Alcohol in Skeletal Disease
- Role of Other Minerals in Skeletal Disease
- Role of Other Vitamins in Skeletal Disease
- Role of Exercise in Skeletal Disease

Role of Calcium in Skeletal Disease

Ninety-nine percent of the body's calcium is found in the bones and teeth, where it is essential for their formation and maintenance; the remaining 1 percent in fluids and soft tissue is critical for proper functioning of every

nerve and muscle cell. Because of calcium's importance throughout the body, constant skeletal remodeling most likely evolved to provide a continuous supply of calcium.

Despite the evident physiologic importance of calcium, remarkably few studies have documented the effects of dietary calcium on peak bone mass reached by different populations, and none explains how different levels of dietary calcium affect age-related bone loss.

Such studies are complicated by the difficulties of studying large groups of people over long periods of time. In the United States, variations by age, sex, and season in calcium intake are thought to reflect the consumption of dairy products, which are also major sources of protein and phosphate, nutrients that may affect calcium metabolism. Moreover, the availability of calcium for building and maintaining the skeleton is determined not only by the amount of calcium in the diet but also by how much of that calcium is absorbed and how much is retained by the body.

Calcium Absorption

Calcium absorption is determined by (1) the amount of dietary calcium that goes into solution, (2) the interaction of calcium with other dietary substances within the small intestine, and (3) the level of activity of active and passive transport systems that move calcium across the intestinal wall and into the body. The amount of calcium in solution in the intestinal tract is influenced by the physical and chemical form of calcium consumed (Recker 1985; Recker and Heaney 1985). Calcium salts in food or supplements are usually soluble in the stomach's acidic environment. Persons who cannot produce gastric acid may absorb calcium poorly (Recker 1985) and may require calcium supplements (e.g., calcium carbonate, calcium gluconate, calcium citrate), which should be ingested with meals.

Calcium is a cation, a positively charged molecule, that can react with negatively charged molecules, called anions, to form complexes. Some of these calcium complexes are insoluble and cannot be absorbed. For example, the anion oxalate, which is found in spinach, rhubarb, and other plant foods, reacts with calcium to form calcium oxalate, which is quite insoluble. Other food anions, particularly polyphosphates, can also impair absorption.

Calcium is transported across the intestine principally by calcium-binding proteins, whose concentration is regulated by the active hormonal form of vitamin D. Factors that diminish the availability and metabolism of vitamin

D also diminish the absorption of calcium from the small intestine. Many drugs can interfere with calcium absorption. Examples include tetracyclines, which bind with calcium to form insoluble complexes, and antiepileptic drugs that impair intestinal transport of calcium and inhibit activation of vitamin D.

Calcium Retention

Calcium is lost from the body primarily in the urine and in the feces. Renal excretion, an important determinant of calcium balance, is regulated by hormones and is influenced by dietary protein intake. Increasing the level of protein in the diet seems to increase the amount of calcium lost in the urine (Margen et al. 1974; Allen, Oddoye, and Margen 1979), and epidemiologic data show that hip fractures and protein intake are positively correlated (Hegsted 1986). Secretion of calcium into the intestine, on the other hand, is probably not regulated by hormones but reflects the rate of production of intestinal juice in the digestive process, all of which can be influenced by diet.

Calcium and Peak Bone Mass

Peak bone mass is determined by several factors. Calcium deficiency does not ordinarily cause selective impairment of mineralization. Instead, there is increased bone resorption or breakdown due to excessive parathyroid hormone (PTH) secretion (secondary hyperparathyroidism) and decreased bone formation. A rickets-like syndrome has been reported in infants on extremely low calcium intakes (Kooh et al. 1977), but it differs somewhat from the rickets produced by vitamin D and phosphate deficiency.

Genetic determinants of peak bone mass are important (Farmer et al. 1984). For example, the larger bone mass in blacks than in whites in the United States can be detected in the fetus and may be due to differences in the vitamin D endocrine system (Bell, Greene, et al. 1985). On the other hand, lactase deficiency, which is more common in blacks, has been associated with a decreased calcium intake and an increased likelihood of developing osteoporosis in whites (Newcomer et al. 1978). This inconsistency suggests a strong role for genetic factors in the incidence of osteoporosis, although current observations need to be evaluated with a closer assessment of the magnitude of individual variations within a given group.

The role of dietary calcium in determining peak bone mass is uncertain. Populations of similar ethnic backgrounds have been observed in which there are differences in calcium intake but no difference in bone mass. For

example, one study reported that Guatemalans and Panamanians have similar peak cortical bone mass, although calcium intake is thought to be considerably higher in Guatemalans (Garn et al. 1969).

Other population studies, however, suggest that calcium intake does affect peak bone mass. In two regions of Yugoslavia, where dairy product intakes differ, average bone mass was higher in the area with the higher calcium intake. Because dairy products also contain substantial amounts of phosphate and protein, calcium may not have been the only determinant of this difference. Nevertheless, the difference in peak bone mass seems to affect skeletal disease; the incidence of hip fractures was substantially lower in the group consuming more dairy products (Matkovic et al. 1979). One investigator in the United States has reported that women with a greater calcium intake because of a high calcium concentration in the water supply also had a greater bone mass, but only if they also had an adequate intake of vitamin D (Sowers, Wallace, and Lemke 1985).

These data are not entirely consistent, but they suggest the importance of peak bone mass in skeletal health and the need for further research on the nutritional determinants that affect the skeleton up to age 35. Presumably, persons with greater bone mass in early adulthood are able to resist the effects of age-related bone loss.

One reason for uncertainty about the influence of dietary calcium intake on bone mass is that young individuals can adjust to a decreasing calcium intake by an increased efficiency of calcium absorption. This compensation is mediated by calcitriol (1,25-dihydroxyvitamin D), the active hormonal form of vitamin D. However, this compensatory response is blunted with age.

Nevertheless, a low calcium intake could interfere with the adolescent growth spurt and could compromise the subsequent consolidation of skeletal mass that occurs up to the age of 35. From 1976 to 1980, the median calcium intake for boys ages 12 to 14 was 1,024 mg, which is close to the Recommended Dietary Allowance (RDA) of 1,200 mg for that age group. In contrast, median calcium intake of 793 mg for girls in that age group was below the RDA (Carroll, Abraham, and Dresser 1983). More recent data on the calcium intakes of men and women 19 to 50 years of age indicate that while calcium intakes have increased slightly from 1977 to 1985 and are above the RDA of 800 mg for men, they fall below the RDA of 800 mg for women (Marston and Raper 1987). Thus, the influence of this level of intake on peak bone mass in women is of great interest.

Calcium and Age-Related Bone Loss

At present, studies of the effect of calcium supplementation on age-related bone loss are inconclusive. Some reports indicate that a sufficiently high calcium intake can reverse a negative calcium balance and thereby suppress bone loss (Horsman et al. 1977; Recker, Saville, and Heaney 1977). Other studies have found that daily calcium supplementation as high as 2,000 mg/day is of little or no help in preventing bone loss in postmenopausal women (Nilas et al. 1985; Riis, Thomsen, and Christiansen 1987). However, it should be noted that the Danish women in this study were consuming an average of 950 mg/day before entry into the study (Riis, Thomsen, and Christiansen 1987). This intake is well above the RDA for calcium of 800 mg/day, making it difficult to extrapolate these results to American women, many of whom consume less than 500 mg/day in their diet.

Understanding the influence of calcium intake on age-related bone loss is complicated in that age itself may influence both the intestinal absorption of calcium and the skeleton's subsequent utilization of calcium. It is not clear when age-related decreases in calcium absorption first begin. Decreases in absorptive ability may begin as early as age 30 or as late as age 60 (Heaney et al. 1982). Decreased absorption may result from the kidney's decreased ability to synthesize calcitriol (the active form of vitamin D) and decreased intrinsic absorptive capacity. Treatment of older individuals with calcitriol regularly increases calcium absorption (Gallagher et al. 1982), but whether this means that osteoporosis could be caused by an inadequate supply of vitamin D is debatable. Osteoporotic persons have somewhat lower calcitriol levels in their blood. Although older people may have a reduced ability to synthesize calcitriol in response to PTH, one study has found no difference between postmenopausal women with osteoporosis and age-matched healthy postmenopausal women in response to PTH (Riggs, Hamstra, and DeLuca 1981). Differences in calcitriol synthetic ability in response to PTH stimulation may explain differences in the underlying pathologies of Type I and Type II osteoporosis. A recent study reported impaired calcitriol synthesis in aging women with age-related osteoporosis (Tsai et al. 1984), while others (Riggs, Hamstra, and DeLuca 1981) reported no differences in postmenopausal osteoporotics relative to their age-matched controls. Trials with calcitriol have failed to demonstrate its safety and efficacy for treatment of osteoporosis (Ott and Chesnut 1987; Falch et al. 1987; Aloia et al. 1988).

At least two possible mechanisms might explain why calcitriol synthesis and intestinal absorption both decrease with age. One mechanism may be

important to the pathogenesis of Type I (postmenopausal) osteoporosis, while the other may be more important in the pathogenesis of Type II (age-related) osteoporosis (Riggs and Melton 1986). In the first, the reduced inhibition of estrogen on bone resorption at menopause increases the supply of calcium released from bone into the blood and reduces PTH secretion, which in turn reduces calcitriol synthesis in the kidney, and, as a result, decreases calcium absorption in the intestine. The failure to respond to decreased calcium intake could then be attributed to an unregulated increase in bone resorption and loss.

This sequence does not explain the age-related bone loss associated with an increasing PTH level that occurs in both men and women. Although the increasing level of immunoreactive PTH might be due to impaired renal excretion of inactive metabolites of this hormone, measures of PTH biologic activity also show an age-related increase. These findings were confirmed in several recent studies that reported an increase in the biologically active form of the hormone with age (Forero et al. 1987; Young et al. 1987). Hence, a second hypothesis explains age-related bone loss in both sexes in terms of the kidney's decreased ability to synthesize calcitriol (Tsai et al. 1984) and (probably) the intestine's decreased intrinsic ability to transport calcium (Francis et al. 1984). These two conditions would result in secondary hyperparathyroidism, but because of the renal abnormality, there would be blunted or minimal increase in calcitriol synthesis, persistent impairment of calcium absorption, and negative calcium balance.

Both hypotheses may be true in different individuals or in the same individual under different circumstances, but whichever mechanism holds, calcium supplementation could theoretically decrease bone loss. If bone resorption increases because of decreased estrogen, the effect of increased calcium should be inhibition of bone resorption, but only to the extent that calcium supplementation either decreases PTH secretion or increases calcitonin secretion. If the primary event is decreased calcitriol synthesis, then calcium loading should be effective only to the extent that it increases passive absorption.

Whatever the role of calcium in achieving and maintaining skeletal mass, calcium intake is superimposed on genetic and age-related changes in bone cell function. Calcium may also affect bone formation directly by increasing either the replication or differentiation of bone cells. Even when calcium supplies are adequate, an age-related decrease in osteoblastic bone formation may occur. This change is demonstrated by the fact that the packets of new bone formed on remodeling surfaces are thinner or smaller in older individuals (Courpron 1981).

Calcium Toxicity

Excessive calcium intake can cause inappropriate mineralization, particularly in the soft tissues. Many years ago, large amounts of calcium carbonate were regularly prescribed for patients with peptic ulcer. A small proportion of them developed milk-alkali syndrome, characterized by hypercalcemia, deposits of calcium in the kidneys, and progressive impairment of renal function. This disorder is now rare (Carroll and Clark 1983). Moreover, the prescribed doses were much larger than the 1 to 2 g of calcium per day that have been suggested for women in the general population.

Nevertheless, some people who have a defective intestinal barrier to calcium absorption may absorb too much calcium and develop soft tissue calcifications or renal stones (see chapter on kidney diseases). Therefore, when calcium supplements are recommended to pre-or postmenopausal women who are at high risk for development of renal stones, they should be screened for excessive urinary concentrations of calcium to determine the appropriate dose. A high fluid intake (i.e., at least 2 liters of water per day) should be encouraged when calcium supplements are used. High calcium intakes may also cause constipation in some individuals.

Role of Vitamin D in Skeletal Disease

The role of vitamin D in preventing rickets and osteomalacia is well established (Jacobs 1979). Subtle abnormalities in vitamin D metabolism can affect the development and maintenance of bone mass in the absence of these two diseases.

Vitamin D is synthesized in the skin in response to sunlight. In the body, the vitamin is transformed first by the liver to 25-hydroxyvitamin D and then by the kidneys into its active hormonal form, called 1,25-dihydroxyvitamin D or calcitriol. This active form helps to increase the absorption of calcium by stimulating intestinal formation of the calcium-binding proteins that transport calcium across the intestinal wall into the body. Vitamin D also acts directly on bone: in low doses it stimulates deposition of new bone, but at high doses it stimulates resorption of bone.

The supply of vitamin D can easily be limited or its activation to calcitriol impaired. Although only a few minutes of exposure to sunlight produces the daily requirement of vitamin D in the skin, many people do not receive this exposure, particularly in the winter. This deficiency can be overcome by consuming foods fortified with vitamin D; however, some individuals

who are on vegetarian diets that limit dairy products and who have limited intake of these foods may not obtain enough vitamin D from their diets (Hellebostad, Markestad, and Halvorsen 1985).

Various diseases may impair the conversion of vitamin D to calcitriol. Hepatic disease, for example, may lead to decreased synthesis of the intermediate 25-hydroxyvitamin D. Impairment of intestinal mucosal function decreases absorption of vitamin D and calcium. Too rapid intestinal transit and impaired fat absorption also decrease calcium and vitamin D absorption. Loss of vitamin D metabolites through enterohepatic circulation may be less important because there is no clear evidence that conjugated vitamin D metabolites excreted in the bile are conserved by reabsorption (Arnaud 1982). Although gastrointestinal disorders might be expected to lead to impaired bone mineralization, most persons with gastrointestinal disease and decreased bone mass have osteoporosis rather than osteomalacia. Moreover, diminished bone mass in persons with gastrointestinal disease often fails to respond to treatment with vitamin D in any form (Arnaud 1982). Other nutritional elements such as protein, and other factors from the liver and intestine such as somatomedin or insulin-like growth factors and enteroglucagon, may be as important as, or more important than, vitamin D in the bone loss that accompanies gastrointestinal disease.

Osteoporosis

Perhaps the most important question concerning vitamin D supplementation is its use in the prevention and treatment of postmenopausal and age-related osteoporosis. Ten to fifteen years ago, patients with osteoporosis were given vitamin D supplements in doses of 50,000 to 150,000 IU a week in addition to other forms of therapy such as calcium, estrogen, and fluoride supplements. Retrospective analysis of these studies indicates that large doses of vitamin D have no significant effect on the incidence of vertebral compression fractures (Riggs, Seeman, et al. 1982). Thus, current recommendations are that vitamin D intake be adequate—400 to 1,000 IU/day—but not increased.

The possibility that impaired activation of vitamin D into 1,25-dihydroxyvitamin D or calcitriol, rather than vitamin D supply, is the limiting factor in older persons and in people with osteoporosis has inspired several experiments with calcitriol supplementation. Calcitriol supplements can increase calcium absorption and may increase the body's stores of calcium, but effects on bone mass and the incidence of bone fractures are as yet unknown. Some studies argue that calcitriol supplementation actually decreases bone mass (Jensen et al. 1985), a finding that is consistent with

previous observations that excessive 1,25-dihydroxyvitamin D has a direct catabolic effect on bone. On the other hand, those studies were done in embryonic bone cultures and may have limited *in vivo* application. Because most of these studies do not show an increase in bone mass, yet some suggest that the incidence of fractures decreases (Gallagher et al. 1982), calcitriol supplementation may improve the quality rather than the quantity of bone.

Some data suggest that a decreased availability of 25-hydroxyvitamin D also could be important in osteoporosis, particularly in the older population. Before vitamin D is converted to calcitriol in the kidneys, it is transformed to 25-hydroxyvitamin D in the liver. An inadequate amount of the liver precursor could lead to an insufficient amount of calcitriol formed in the kidneys. Blood levels of 25-hydroxyvitamin D are reduced in older subjects, particularly in those who have limited exposure to the sun (Lamberg-Allardt 1984). These individuals are at especially high risk for developing hip fractures. Many patients with hip fractures also have low levels of 25-hydroxyvitamin D.

Maintaining an adequate supply of vitamin D, either through exposure to sunlight or from dietary sources, may help to reduce the incidence of hip fractures in older persons, but it is difficult to judge how great that effect might be.

Rickets and Osteomalacia

Vitamin D deficiency rarely causes rickets and osteomalacia in the United States because most Americans get enough sunlight and ingest sufficient amounts of vitamin D available in fortified foods and dietary supplements. Nevertheless, rickets and osteomalacia due to vitamin D deficiency do occur and need to be prevented.

Rickets occurs most often in children who stay indoors and who are breastfed and not given vitamin D supplements (Edidin et al. 1980). The incidence may be somewhat higher in black children, who make less vitamin D for a given amount of sun exposure than do white children. Socioeconomic factors may also be important. Children with vitamin D-deficiency rickets often do not have adequate health care, or they are affected by unusual practices that limit sun exposure or vitamin D intake.

The most common cause of osteomalacia in the United States is an inherited or acquired defect in the metabolism of vitamin D (Jacobs 1979). Formation of 25-hydroxyvitamin D in the liver is usually not the problem,

because only a relatively small amount of hepatic tissue is required to supply adequate amounts. A failure to form 1,25-dihydroxyvitamin D in the kidney is a much more serious problem. As indicated above, this problem may occur in a subtle form with aging.

Deficient absorption of vitamin D also causes rickets and osteomalacia in the United States. Gastrointestinal disease impairs absorption, but it is more likely to cause osteoporosis than osteomalacia, probably because general nutritional deficits decrease bone formation, increase bone resorption, and deplete the protein matrix. Causes of deficient absorption include pancreatic insufficiency, nontropical sprue, or intestinal bypass surgery (Passmore and Eastwood 1986). In patients with these conditions, vitamin D as well as calcium and other nutrients may be poorly absorbed. Vitamin D metabolism may also be abnormal after gastrectomy (Nilas, Christiansen, and Christiansen 1985). Clear-cut osteomalacia due to vitamin D deficiency is also rare, but it occurs occasionally in older individuals who remain indoors and eat inadequate diets.

In renal failure, impaired vitamin D hydroxylation to the biologically active form may lead to marked impairment of mineralization (see chapter on kidney diseases). Most patients in the United States with renal failure do not develop typical osteomalacia, but instead develop osteitis fibrosis cystica, a condition characterized by resorption of bone due to marked secondary hyperparathyroidism (Dunstan et al. 1985), failure to form 1,25-dihydroxyvitamin D, and impaired intestinal absorption of calcium. In chronic renal failure, however, sufficient calcium may be obtained through dialysis or from increased resorption of bone to maintain mineralization even though dietary sources are reduced.

In renal osteodystrophy, some observations suggest that 1,25-dihydroxyvitamin D is not always sufficient to produce mineralization in patients with osteomalacia. Although it has been suggested that the lack of 24,25-dihydroxyvitamin D, another renal metabolite, causes this condition, administration of this metabolite does not consistently cure osteomalacia. The role of other substances such as aluminum and magnesium is also uncertain.

Osteomalacia can also result from prolonged ingestion of anticonvulsant medication, particularly phenytoin, perhaps due to impaired formation of 25-hydroxyvitamin D in the liver or to a direct effect on intestinal calcium transport. This problem is usually associated with marginal intakes of vitamin D or limited sun exposure and can be overcome by moderate vitamin supplementation (Mosekilde et al. 1977).

Finally, osteomalacia can occur in renal tubular acidosis associated with such disorders as the Fanconi syndrome (Chan and Alon 1985). Other defects, including impaired vitamin D hydroxylation to the biologically active form and low tubular reabsorption of phosphate, may be present as well. It is not clear that acidosis by itself impairs mineralization, although it certainly decreases skeletal mass and impairs bone growth.

Inherited or acquired defects in vitamin D metabolism produce some forms of rickets. In vitamin D-dependent rickets, for example, 1,25-dihydroxyvitamin D does not form in the kidney. This defect can be treated effectively by replacement doses of calcitriol. Other kinds of rickets resist treatment with large doses of vitamin D because of defects in the function of cellular receptors for 1,25-dihydroxyvitamin D.

Other vitamin D metabolites may play a role in mineralization. In several experiments, 25-hydroxyvitamin D or 24,25-dihydroxyvitamin D has been used successfully to treat certain patients who failed to respond to calcitriol. These compounds are bound more tightly to vitamin D-binding protein than is calcitriol and retain activity for longer time periods. In animal studies and *in vitro*, some evidence indicates that 24,25-dihydroxyvitamin D can stimulate cartilage growth. On the other hand, none of the vitamin D metabolites is essential to rats for normal growth and mineralization of the skeleton when adequate calcium and phosphate are supplied by dietary manipulations or by continuous subcutaneous infusion (Underwood and DeLuca 1984). At present, it is uncertain whether 25-hydroxyvitamin D or 24,25-dihydroxyvitamin D has a specific role in maintaining skeletal mineralization (Brommage and DeLuca 1985). Thus, the major role of vitamin D in mineralization appears to be its effect on the intestine and, perhaps, on renal tubular reabsorption of phosphate in the kidney.

Vitamin D Toxicity

Excessive amounts of vitamin D are potentially toxic and can cause bone loss by increasing resorption or breakdown and by impairing bone growth and mineralization (Coburn and Brautbar 1980; Holmes and Kummerow 1983), although the moderate increases in intake that occur through dietary supplementation seem unlikely to have such adverse effects.

Role of Phosphorus in Skeletal Disease

Phosphorus is the second most abundant mineral in the body, exceeded only by calcium. About 85 percent of the body's phosphorus is in bone as bone mineral, principally hydroxyapatite crystals containing about two

atoms of phosphorus for every three atoms of calcium. All plant and animal foods are rich in phosphorus, and except for the prematurely born infant who is fed human milk, nutritional deficiencies of phosphorus are rare. Human breast milk contains enough phosphorus to nourish a full-term infant but not, apparently, to support the growth requirements of preterm infants.

Phosphate is important in mineralization both in animal models and in clinical disease. In rats, rickets occurs only with a combined deficiency of vitamin D and phosphate relative to calcium, but in people, rickets can be produced by phosphate deficiency even in the presence of a high concentration of 1,25-dihydroxyvitamin D (Rowe et al. 1979). Phosphate's role in mineralization is obvious in persons with phosphaturic osteomalacia or vitamin D-resistant rickets. In these persons, a combination of frequent administration of phosphate plus large doses of vitamin D restores bone growth and mineralization to an extent that cannot be achieved by either agent alone. Even with the use of calcitriol, phosphate supplementation is needed to mineralize bone in this condition (Chan, Alon, and Hirschman 1985).

Some forms of phosphate, such as plant phytates, are poorly absorbed and can also bind calcium, increasing calcium excretion in the feces. Increased phytate in the diet may contribute to osteomalacia but does not necessarily influence bone mass. When large amounts of aluminum hydroxide antacid gels are ingested, phosphate depletion can also occur because of the formation of aluminum phosphate, which is insoluble and unabsorbable. The clinical significance of these interactions has not been established.

Many studies indicate that phosphate regulates bone formation and resorption (Raisz and Kream 1983). *In vitro* studies have shown that increasing phosphate concentration beyond the physiologic range can inhibit bone resorption (Lorenzo, Holtrop, and Raisz 1984). Although osteoclast activity may decrease, morphologic studies suggest that the osteoclasts are less effective rather than inactivated.

Increasing the phosphate concentration in cultures of bone-forming cells increases both collagen synthesis and deposition of mineral. *In vitro* mineralization may require the addition of an organic phosphate compound such as beta-glycerol phosphate. Organic phosphate may provide a constant delivery of phosphate that does not precipitate, or it may provide more effective organic forms because they are hydrolyzed locally in the matrix.

The enzyme alkaline phosphatase can cleave organic phosphate compounds in bone, thus raising the local concentration of inorganic phosphate and promoting mineralization. Although the precise role of alkaline phosphatase is uncertain, mineralization is impaired when this enzyme is deficient, as in the disease familial hypophosphatasia.

Some *in vivo* studies also indicate that phosphate promotes bone growth. The rate of bone formation across animal species is generally proportional to their serum phosphate concentration. For example, rats with high serum phosphate levels also have high rates of skeletal growth. Within species, serum phosphate levels are also higher at times of rapid bone formation, as in early infancy and puberty in humans. Hormones may be more likely than nutrition to control these changes in serum phosphate concentration. An inadequate intake of phosphorus could, in theory, impair skeletal growth as well as soft tissue growth, but phosphates are so abundant in foods that a seriously deficient intake would probably indicate decreased intake of other nutrients.

While phosphate deficiency can lead to decreased bone mass, excessive phosphate intake can also harm the skeleton. The adverse effects of high phosphate intake have been studied extensively in animals (LSRO 1981; Jowsey, Reiss, and Canterbury 1974). Excessive dietary intake of phosphate produced bone disease in animals, particularly if the diet was also low in calcium. The current American diet is quite rich in phosphorus; this imbalance might affect bone health adversely, but that hypothesis has not been proved.

Recent studies suggest that the adverse effects of excessive phosphate are largely mediated through secondary hormonal responses or through toxic effects of phosphate deposition in soft tissues. Excessive phosphate intake reduces serum calcium concentration, particularly when the calcium intake is low, because some of the phosphate carries calcium with it into soft tissue. The resulting hypocalcemia stimulates PTH secretion, which leads to increased bone resorption and increased phosphate excretion in the urine. Because the effect of PTH on the kidney continues after the phosphates have been absorbed, fasting hypophosphatemia is common in persons consuming large amounts of phosphate, presumably due to secondary hyperparathyroidism (Herbert et al. 1966; Reiss et al. 1970; Sherwood et al. 1968). High phosphate intakes can also decrease calcitriol production in the kidneys, impairing calcium absorption and producing further secondary hyperparathyroidism (Portale, Halloran, and Morris 1987).

The aforementioned sequence of events occurs in experiments and may also occur in persons with renal failure who cannot excrete phosphate efficiently; whether nutritional phosphate excesses in American diets produce similar changes in the healthy population is in question. Bone mass may be lower in people who consume diets that contain a relatively high ratio of phosphorus to calcium as compared with vegetarians, for whom this ratio is substantially lower (Marsh et al. 1980). The difference is small, however, and many other uncontrolled variables may be involved. Some young adults have elevated PTH activity with a high phosphorus intake (Bell et al. 1977). More recently, direct measurement of increased PTH level and action with high phosphorus intake was reported in young adults consuming ordinary foods (Calvo, Kumar, and Heath 1988).

Role of Calories and Protein in Skeletal Disease

An adequate intake of calories and protein is essential for the growth and maintenance of a healthy skeleton. Calories support the synthesis of bone tissue and also "spare" the body from using for energy the protein that is needed to form bone matrix. In children, insufficient calorie or protein consumption inhibits skeletal growth. Adults who consume insufficient calories or protein may also lose bone mass and become susceptible to bone fractures.

Calories

Changes in calorie consumption may affect hormone production. In children, the decreased skeletal growth associated with malnutrition is probably mediated, at least in part, by decreased production of somatomedin or insulin-like growth factors. In adolescents and adults, calories may also affect the production of sex hormones (Cuttler et al. 1985), as demonstrated in adolescent women (whose growth spurt is associated with menarche). The onset of menses may depend on a certain body weight or level of fat stores, that, in turn, depends on adequate nutrition, including calories. Healthy women who lose large amounts of weight may stop menstruating, although factors other than calories may also be involved. In persons with anorexia nervosa, menstrual disorders may occur earlier than can be accounted for simply by weight loss (Drossman, Ontjes, and Heizer 1985).

The combination of decreased intake of calories, calcium, and other nutrients and decreased production of estrogen may be responsible for reduced density of bone mass in persons with anorexia nervosa (Rigotti et al. 1984). Female athletes, particularly runners and ballet dancers, who have

very low body fat content, a low intake of calories and calcium, and amenorrhea also have decreased bone mass (Drinkwater et al. 1984; Marcus et al. 1985).

Low body fat, which presumably reflects a low calorie intake, may also cause reduced bone mass in postmenopausal women (Dequeker, Goris, and Uyterhoeven et al. 1983). One hypothesis suggests that after menopause, body fat provides a continued source of estrogen that retards bone loss in obese women. Another possibility is that women who weigh more put more stress on the skeleton and stimulate bone mass to increase, perhaps through an effect on the vitamin D-endocrine system (Bell, Epstein, et al. 1985). Cigarette smoking seems to affect bone mass adversely, but this finding may be related to the lower caloric intake and decreased estrogen production observed in women who smoke (Rundgren and Mellstrom 1984).

Protein

Adequate dietary protein is essential for bone growth; the skeleton is second only to muscle in terms of total body protein content. Abnormal protein nutrition may cause osteoporosis, and a decreased protein intake could contribute to the decline in bone mass observed in alcoholics, although nutritional factors other than the direct effects of alcohol may also be involved.

High protein intake may also cause bone loss. In young individuals, increasing dietary protein intake increases calcium excretion in urine and produces a negative calcium balance (Heaney et al. 1982; Hegsted 1986). Under ordinary circumstances, increased phosphate intake accompanies increased protein intake; high-protein foods are often high in phosphate as well. If dairy products are the source of protein, calcium intake may also rise. Thus, whether moderately high-protein diets have an adverse effect on bone mineralization has not yet been established (Heaney and Recker 1982).

Why calcium loss results from high protein intakes is also uncertain. The acid content of the diet may be a major factor because much of the calcium loss from a high-protein diet can be reproduced by administering the sulfur-containing amino acids that were in that diet (Tschope and Ritz 1985). Increased acidity induces calcium loss by increasing renal excretion directly as well as by increasing the dissolution of mineral from the skeleton and impairing mineral deposition.

Role of Alcohol in Skeletal Disease

Excessive alcohol intake is a risk factor for osteoporosis (see Table 7-1), but the basis for this relationship has not been established (Consensus Development Panel 1984). In women, the incidence of hip fractures has been observed to increase with increasing alcohol consumption (Paganini-Hill et al. 1981). The association between alcohol and bone loss was first described more than 20 years ago in a population of young male alcoholics (Saville 1965). More recent radiographic evidence has confirmed extensive bone loss among alcoholic patients ranging in age from 24 to 62 (Spencer et al. 1986). Other studies have reported significant bone loss, decreased bone density, increased bone resorption, and increased fracture incidence among alcoholics (Nordin 1984).

Why alcohol induces bone loss is uncertain. The main hypotheses include poor nutrition, alcohol-induced calcium diuresis, secondary effects of liver disease, and induction of excessive PTH secretion. Malabsorption of calcium has been observed in some studies (Nordin 1984) but not in others (Spencer et al. 1986). The current lack of information on mechanism of action, the effects of excessive alcohol intake on bone loss in women of different ages, and the effects of moderate alcohol intake on bone metabolism suggest a need for further research.

Role of Other Minerals in Skeletal Disease

The skeleton is a storehouse for relatively large amounts of sodium, magnesium, copper, silicon, and other minerals, whose intake may affect mineralization of the skeleton.

Fluoride

The effects of fluoride on bones and teeth have been observed and studied for nearly 100 years. Fluoride is incorporated into tooth enamel, and its beneficial effect in reducing the incidence of caries is well established (see chapter on dental diseases).

Fluoride could be a possible treatment for osteoporosis because it is rapidly and extensively accumulated into bone mineral. It stimulates osteoblast activity and new bone growth, particularly that of trabecular bone, the type most susceptible to fracture. Animal studies have not produced consistent data about the effect of fluoride on experimentally induced osteoporosis (Bikle 1983). Human epidemiologic studies show that subjects living in areas where water is fluoridated have greater bone densities than those

living in low-fluoride areas (Bernstein et al. 1966; Simonen and Laitinen 1985); however, other epidemiologic studies suggest that small amounts of fluoride have no consistent effect on fracture incidence (Kanis and Meunier 1984). Nevertheless, human clinical studies have demonstrated an improved calcium balance with short-term administration of large doses of fluoride, increased bone mass when fluoride was administered for at least a year, and an increased volume of trabecular bone and a decreased incidence of fractures in groups treated with fluoride for at least 2 years (Bikle 1983).

Consequently, fluoride in relatively high doses of 50 to 100 mg of sodium fluoride daily has been used to treat osteoporosis. These doses increase bone mass in a substantial proportion of persons and may decrease fractures (Riggs, Seeman, et al. 1982). Such high intakes of fluoride, however, produce skeletal abnormalities such as osteophytes (bony overgrowths) and stimulate bone matrix formation at inappropriate sites. Fluoride therapy without supplemental calcium and vitamin D may produce osteomalacia, and gastrointestinal and rheumatic side effects have also been reported (Bikle 1983). Controlled prospective trials of fluoride in the treatment of osteoporosis are currently under way in the United States.

Aluminum

The effect of consuming large amounts of aluminum hydroxide in antacids was mentioned earlier in the phosphates section. Aluminum hydroxide's role in impairing bone growth and mineralization is complex because it affects phosphate absorption, osteoblast function, and mineral deposition itself. Whether aluminum causes impaired mineralization in renal osteodystrophy or whether it accumulates as a result of this condition is uncertain (Quarles et al. 1985).

Magnesium

Bone recycling may be impaired by the direct effects of magnesium on bone cells (Johannesson and Raisz 1983) as well as by the decreased production of PTH and hypocalcemia that develop in severe magnesium deficiency (Rude et al. 1978). The high levels of circulating magnesium observed in renal failure are associated with impaired mineralization *in vitro* and can slow the formation of hydroxyapatite. Changes in dietary magnesium, however, do not significantly affect the regulation of bone metabolism.

Sodium

High sodium intakes can cause increased loss of calcium in the urine and could affect age-related bone loss (Breslau et al. 1982; Goulding 1983). The

issue of sodium in the diet is discussed in the chapter on high blood pressure.

Trace Elements

Other ions may affect mineral metabolism. Zinc and silicon, which are deposited in bone, are important factors in bone mineralization (Calhoun, Smith, and Becker 1974; Carlisle 1981). Circadian variations in serum zinc concentration parallel serum calcium changes (Markowitz, Rosen, and Mizruchi 1985). Copper has been shown to inhibit bone resorption (Wilson, Katz, and Gray 1981). Low boron intake may also be a risk factor for osteoporosis (Nielsen et al. 1987). The clinical importance of these substances in bone metabolism is unknown.

Role of Other Vitamins in Skeletal Disease

Vitamin A deficiency can alter bone remodeling in animals but is not a major cause of bone disease in humans. Excessive levels of vitamin A, obtained from animal foods or supplements (but not as beta-carotene from plants), can produce hypercalcemia and skeletal abnormalities, with thinning of the cortex and fractures in some areas and overproduction of bone in other areas.

Vitamin C deficiency is associated with osteoporosis but is not a major factor in the disease in the United States (Lynch et al. 1967). There is no evidence that megadoses of vitamin C adversely affect the skeleton.

Vitamin K-dependent proteins, particularly osteocalcin, have recently been identified in bone. At present, their metabolic roles are not clearly defined. Their current importance as clinical indicators for bone turnover is difficult to assess (Delmas et al. 1983; Slovik et al. 1984; Cole and Gundberg 1985; Price, Parthemore, and Deftos 1980). Depressed circulating levels of vitamin K have been reported recently in patients with osteoporosis (Hart et al. 1985), and vitamin K deficiency produces hypercalcemia in rats (Robert et al. 1985). Warfarin, an anti-coagulant that blocks the action of vitamin K, can reduce bone mineral in vitamin D-treated rats (Price and Sloper 1983). Further investigations are needed to explain this interaction between vitamin K and bone mineralization.

Role of Exercise in Skeletal Disease

Although not strictly a nutritional issue, the role of exercise in skeletal disease is important. That physical activity affects maintenance of skeletal

mass was first noted in spinal injury patients (Freedman 1949) and has since been confirmed in patients who require bed rest, in normal volunteers who stay in bed for long periods of time, and in astronauts who work in gravity-free environments (Anonymous 1983).

Whether exercise prevents osteoporosis has not yet been established. Although the evidence from cross-sectional and prospective studies suggests that physical exercise may increase the peak bone mass achieved at maturity and may also reduce losses of bone mass after maturity, many of these studies have methodological flaws (Block et al. 1987). Nevertheless, until better information becomes available, 3 to 4 hours of weight-bearing exercise per week is potentially beneficial to the skeleton and could represent a safe, low-cost method for maintaining bone mass.

Implications for Public Health Policy

Dietary Guidance

General Public

The prevalence, health consequences, and expense of osteoporosis among Americans make it a compelling public health priority. Dietary factors of particular concern are calcium, phosphate, vitamin D (and its hormonally active form calcitriol), protein, sodium, calories, and alcohol. How these factors affect peak bone mass development is important and requires further investigation. Other lifestyle factors that may decrease the risk for osteoporosis include increased exercise and decreased cigarette smoking. In postmenopausal women, estrogen-replacement therapy has been the best documented method of preventing osteoporosis.

The dietary factors associated with bone mass, the universality of bone loss with age, the interaction of diet and lifestyle with genetic factors, and the difficulties in measuring bone loss in populations make defining the relationship between diet and osteoporosis difficult. However, evidence suggests that, particularly during the first three to four decades of life, ingesting adequate calcium, maintaining appropriate body weight, exercising, restricting alcohol, and avoiding cigarette smoking are appropriate public health strategies for prevention of osteoporosis.

Most interest in the dietary control of osteoporosis focuses on calcium. Although current epidemiologic and clinical evidence is uncertain, chronic low calcium intake may decrease peak bone mass, especially during adolescence. Surveys indicate that dietary calcium intake of adolescent girls is

one-third or more below the 1,200 mg/day recommended for this population and that adult women of reproductive ages also consume less than the recommended 800 mg/day. Although the ideal level of calcium intake for development of peak bone mass is unknown, and although it has not yet been established whether increased calcium intake will prevent osteoporosis, females, particularly adolescents and young adults, in the United States should increase food sources of calcium. The public should also be educated about the calcium content of various foods, particularly low-fat dairy products, and should maintain adequate calcium intake at all ages.

Additional study of the epidemiologic association between diets high in protein and increased prevalence of osteoporosis is required to make further conclusions.

Special Populations

Children, pregnant and lactating women, and older people have special needs for calcium based on, respectively, the extra skeletal demands of growth, milk production, or the age-related decrease in absorption of calcium. Older Americans consume amounts of calcium that average as much as 40 percent below current recommendations of 800 mg/day. Postmenopausal women should receive counseling on supplemental use of estrogen, and all groups should receive information about calcium-rich foods. People who take calcium supplements also need education on appropriate use, side effects, the forms in which they are best absorbed, and interactions with other medications.

Nutrition Programs and Services

Food Labels

Present evidence on the role of dietary factors in skeletal disease has no special implications for change in policy related to food labeling. However, nutrition labeling, which lists calcium and other nutrient content, should be encouraged on most food products.

Food Services

Aside from the special populations noted below, evidence related to the role of dietary factors in skeletal diseases currently holds no special implications for change in policy related to food service programs.

Food Products

Foods abundant in calcium are widely available in the United States. However, the diversity of U.S. dietary patterns suggests the possibility of calcium fortification of a limited number of foods. These additions should be carefully selected to avoid excessive calcium in the food supply. Fortification should be chosen based on the frequency of consumption of a food by the targeted populations, and the calcium should be in a physiologically available form. It is important to continue fortification of suitable foods with vitamin D because this has been instrumental in reducing the prevalence of rickets and osteomalacia in the United States.

Special Populations

Food services offered to children, adolescents, and young adults should provide diets with sufficient calcium to enhance achievement of peak bone mass. Persons who are unable to convert vitamin D to its active form may require supplementation with calcitriol. Those with chronic malabsorption syndromes may require supplementation with calcium or calcitriol.

Whether calcium, vitamin D, or calcitriol should be provided to older women to prevent or delay postmenopausal bone loss is as yet uncertain. Although evidence for the precise role of physical activity in prevention of osteoporosis is still emerging, it seems reasonable to include exercise as a component of any program to enhance the skeletal integrity of older Americans. Older persons should be encouraged to maintain regular activities such as walking and other weight-bearing exercise.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in skeletal diseases should include investigations into:

- Changes in calcium and phosphate requirements throughout life.
- The effects of altering proportions of phosphate and protein on calcium requirements and bone mineralization.
- The effects of increased calcium intake on peak bone mass and on prevention of postmenopausal bone loss.
- Potential toxicities of high-dose supplements of calcium.
- The development of calcium sources with improved bioavailability.
- Safe and adequate levels of vitamin D added to the food supply.

- The relationship of vitamin D and its metabolites to calcium in the development of peak bone mass and prevention of bone loss.
- The levels of vitamin D and its metabolites, fluoride, and calcium that are safe and adequate for the treatment of osteoporosis.
- The effects of moderate and excessive alcohol intake on bone mineral metabolism.
- The effects of various levels of physical activity on loss of bone mass.
- The relationship of other vitamins and minerals to peak bone mass and to prevention of bone loss.

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Chapter 8

Dental Diseases

Sweet things are bad for the teeth.
Jonathan Swift
Polite Conversation, Dialogue II (1738)

Introduction

Historical Perspective

Descriptions of the oral manifestations of scurvy and various single and multiple B-complex deficiencies in humans were among the earliest contributions to nutrition knowledge (Jolliffe 1962). Recognition of the oral signs of nutrient deficiency was facilitated by the pain associated with pathology in the mouth and the easy access to the mouth for examination.

Early research on oral pathology was controversial because of diverse results from laboratory research and the lack of basic knowledge about the complexity of nutrition and the interrelationships among nutrients. Experimental diets were crude by today's standards and often resulted in multiple nutrient deficiencies. Moreover, pure nutrients were not available for supplementation of deficient diets, and dietary supplements rarely contained the full complement of essential nutrients. Early experimental design also differed significantly from naturally occurring conditions that might predispose to nutritional disorders.

Controversy especially centered on dental caries (tooth decay) observed in rats in early studies. Two schools of thought developed, with one emphasizing that decay was a result of environmental influences on the tooth surface and the other maintaining that lesions were evidence of systemic nutritional deficiencies. Neither perspective considered the role of microorganisms in decay processes until much later (Shaw 1952).

Role of Sugars

The relationship between sweet foods and tooth decay was observed by the ancient Greeks. Aristotle, for example, associated rotted teeth with consumption of soft figs. In the 15th century, Arculanus recommended avoidance of sweet and sticky foods to prevent tooth loss. The experimental demonstration of tooth demineralization in the presence of carbohydrates (but not meat) mixed with saliva occurred in 1890 (Newbrun 1982). These studies foreshadowed the many animal and human studies of sugar and caries incidence that have led to our current understanding of the etiology of this condition.

Role of Fluoride

One of the first descriptions of mottled enamel appeared near the turn of this century when the tooth enamel of immigrants to America from Naples was observed to be speckled with white areas or to be mottled, pitted, or discolored (Eager 1901). This condition, called *denti di Chiaie*, was thought to result from local geologic conditions, and a change in the source of water was suggested as the reason for the lower incidence of this abnormality among the children of these immigrants.

A similar phenomenon was observed in children living in Colorado Springs (Black and McKay 1916; McKay and Black 1916) and other locations by investigators who noted that the mottled teeth of these children, although apparently inadequately mineralized, were more resistant to dental caries than normally calcified teeth (McKay 1929). Studies in the 1930's demonstrated the relationship of water-borne fluoride to the prevention of tooth decay (Smith, Lantz, and Smith 1931; Dean 1938) and led to early suggestions that dental caries might be controlled by increasing the fluoride concentration of drinking water. More conclusive evidence of the inverse relationship between fluoride in the water supply and dental caries was provided by early surveys (Dean, Arnold, and Elvove 1942) that were later confirmed (Russell and Evolve 1951; Englander and Wallace 1962; Adler 1970).

Results of the epidemiologic surveys of the 1930's established the fluoride concentrations in natural water that provided near maximal caries protection without producing objectionable mottling of teeth (fluorosis). The first clinical trial to add fluoride to communal water supplies began in Grand Rapids, Michigan, in 1945, where fluoride concentration was adjusted to 1 part per million (ppm). After 6.5 years of fluoridation, caries prevalence in 4- to 6-year-old children in Grand Rapids was about 50 percent of that in the nonfluoridated (less than 0.2 ppm) neighboring community of Muskegon.

After 15 years of fluoridation, children 12 to 14 years of age, born and raised in Grand Rapids, had about 55 percent lower caries scores than children of the same age prior to fluoridation (Arnold et al. 1962). Many other studies demonstrated that controlled fluoride supplementation of community water supplies could reduce dental caries without causing undesirable side effects (Galagan and Vermillion 1957; Dean et al. 1950; Ast and Chase 1953; Knutson 1970; Hutton, Linscott, and Williams 1956; Connor 1970).

Significance for Public Health

Dental caries and periodontal disease are important and widespread public health problems in the United States. They are rarely life threatening but can cause substantial expense, pain, restriction of activity, and work loss (Corbin, Kleinman, and Lane 1985). Although dental caries among children, as well as some forms of adult periodontal disease, appear to be declining, the overall prevalence of these conditions imposes a substantial burden on Americans. Of the 13 leading health problems in the United States, dental disorders rank second in direct costs (Carter Center Health Policy Task Force 1984). Dental care cost $21.3 billion in 1985 (U.S. Department of Commerce 1986).

Dental Caries

Dental caries, or tooth decay, is caused by a progressive dissolution of mineral from tooth surfaces by acid produced by oral bacteria. Advanced disease can result in tooth loss. The National Health and Nutrition Examination Survey (NHANES) of 1971–74 reported that Americans ages 1 to 74 years had an average of 1.3 decayed, 5.3 missing, and 6.4 filled teeth. Because people normally have a total of 28 to 32 permanent teeth (depending on the presence of the four wisdom teeth), nearly half of the teeth in the average American mouth were filled, missing, or decayed at that time (NCHS 1979). A more recent survey (NIDR 1987) summarized the prevalence of coronal caries by the mean number of decayed and filled permanent surfaces (DFS). As shown in Figure 8-1, the mean DFS (which does not include missing teeth) for age 18–19 is 12, and for employed adults over age 40, the mean DFS is 29. The average for all ages was 23 DFS out of 128 possible surfaces. Comparing mean decayed and filled teeth (DFT) in the recent National Institute of Dental Research survey (NIDR 1987) with the National Center for Health Statistics (NCHS) household survey (NHANES I) conducted in 1971–74, the employed persons in the recent NIDR survey had a lower mean DFT through age 34. Beyond that age, tooth loss prevents any meaningful comparisons with earlier data.

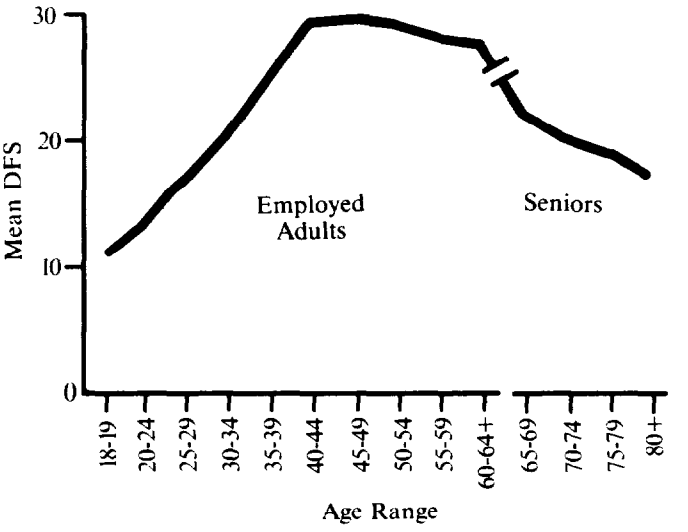

Figure 8-1. The distribution of mean decayed and filled coronal surfaces (DFS) by age as determined from the NIDR survey of employed adults and seniors.

Source: National Institute of Dental Research 1987.

The mean number of root surface lesions by age is shown in Figure 8-2. Decay of tooth roots (root caries) was three times higher in persons 65 years and older than in employed adults, 63 percent as opposed to 21 percent, and only half of such lesions had been filled. The higher prevalence in older persons results from increased exposure of root surfaces due to age-related gum recession or periodontal disease.

The number of decayed, missing, and filled permanent teeth increases steadily with age. In 1980, the average child had at least 1 carious lesion in a permanent tooth by age 8, 4 by age 12, and 11 by age 17 (NIH 1981). In the 1971–74 NHANES, the number increased from an average of 1.7 in children 6 to 11 years to 22.2 in adults 65 to 74 years (NCHS 1979). The number does not differ by sex, but blacks overall tend to have fewer decayed, missing, and filled teeth during adulthood.

Within the past two decades, the incidence of dental caries in children has been declining, perhaps by as much as 30 to 50 percent. This decline has been attributed largely to increased intake of fluoride from drinking water, food, toothpastes, mouth rinses, and topical application, although decreased intake of cariogenic foods and improved dental hygiene and care have also been suggested as contributory factors (Leveille and Coccodrilli 1982; Navia 1985; Corbin et al. 1987).

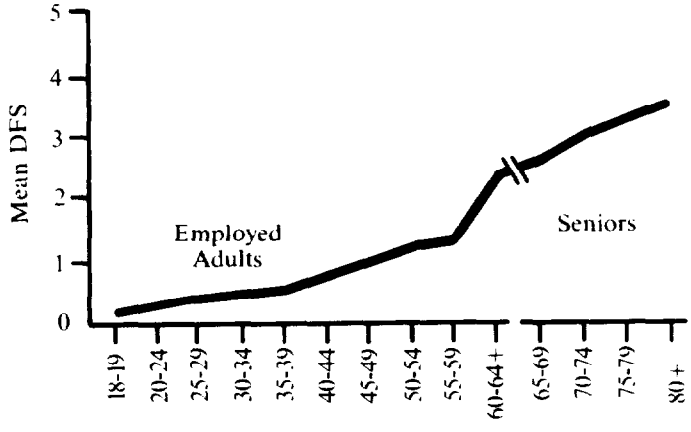

Figure 8-2. The distribution of mean decayed and filled root surfaces (DFS) by age as determined from the NIDR survey of employed adults and seniors.

Source: National Institute of Dental Research 1987.

Both the benefits and the safety of water fluoridation have been carefully examined and endorsed by many professional and scientific organizations and by U.S. Surgeons General since the mid-1940's. More than 120 million people in 8,000 U.S. communities currently are provided with optimally adjusted fluoridated water. An additional 10.7 million people in 3,000 communities drink water with naturally occurring fluoride (Center for Prevention Services 1985; Ismail et al. 1987). Nevertheless, despite the proven benefits of fluoride, only 61 percent of the U.S. population on public water supplies now receive fluoridated water (Löe 1986).

Periodontal Disease

Periodontal disease includes a spectrum of pathologic conditions ranging from minor gum inflammation (gingivitis) to severe loss of the bone structure supporting the teeth (periodontitis). Advanced disease results in loosening of and eventual loss of teeth. In national surveys of the early 1970's, 23 percent of children ages 6 to 17 years had gingivitis (NCHS 1979). Subsequent statewide surveys have reported rates varying from 19 to 44 percent in this group (Corbin, Kleinman, and Lane 1985).

National surveys of adult periodontal disease found little change in prevalence of periodontitis between 1960–62 and 1971–74. The National Adult Dental Health Survey of 1985–86 reported gingival bleeding in 43 percent of employed adults and 47 percent of persons over age 65. Seventy-seven

percent of all adults, and 95 percent of older persons, had at least one site in the mouth with periodontal attachment loss of 2 mm or more. More severe periodontal destruction, 4 mm or more attachment loss, was observed in 24 percent of adults and 68 percent of older persons. The percent of persons by severity of loss of attachment and age group is shown in Figure 8-3. For both working adults and older persons, the severity of periodontal disease increases with age, and it is more prevalent among males than among females (NIDR 1987). Periodontal disease is a major cause of tooth loss, and efforts to prevent this condition are desirable (Rank et al. 1983).

Loss of Teeth

The two major causes of tooth loss are dental caries and periodontal disease. Toothlessness limits individual selection of foods to those that require little biting or chewing, therefore influencing the nutritional intake of affected individuals.

In the 1971–74 NHANES, about 15 percent of the adult population ages 18 to 74 years had lost all permanent teeth. Another 9 percent had lost all of their upper or their lower permanent teeth, and by the ages of 65 to 74, 46 percent of Americans were edentulous (NCHS 1979). Nevertheless, these figures represent a significant decline from surveys taken in 1960–62 (Ismail et al. 1987).

This favorable trend for decreased tooth loss has continued. The 1985–86 survey of employed adults showed that toothlessness has almost been eliminated in this group; only 4 percent were missing all their teeth, and half had lost none or at the most one tooth. However, as shown in Figure 8-4, toothlessness increases with age and remains a major problem among older Americans. The survey indicated that 42 percent of Americans over age 65 were edentulous and that only 2 percent have retained all 28 permanent teeth. Comparing the prevalence of tooth loss in the recent survey to that reported by the NCHS survey in 1960–62, the current sample had less tooth loss at every age interval.

Scientific Background

Normal Tooth Development

The tooth is a very specialized structure important for the proper initial processing of solid foods. A schematic cross-section of a tooth is presented in Figure 8-5. People normally develop two sets of teeth, 20 deciduous, or primary, teeth and 32 permanent, or secondary, teeth. Each tooth develops from a tooth bud that forms in the area of the jaw. Each tooth bud contains a

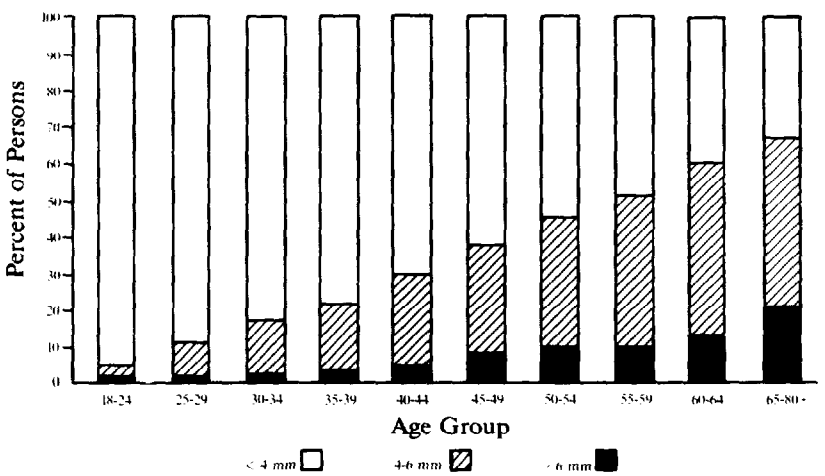

Figure 8-3. Percent of persons by severe loss of periodontal attachment (pocket depths measuring 4 mm or more) and age groups as determined from the NIDR survey of employed adults and seniors.

Source: National Institute of Dental Research 1987.

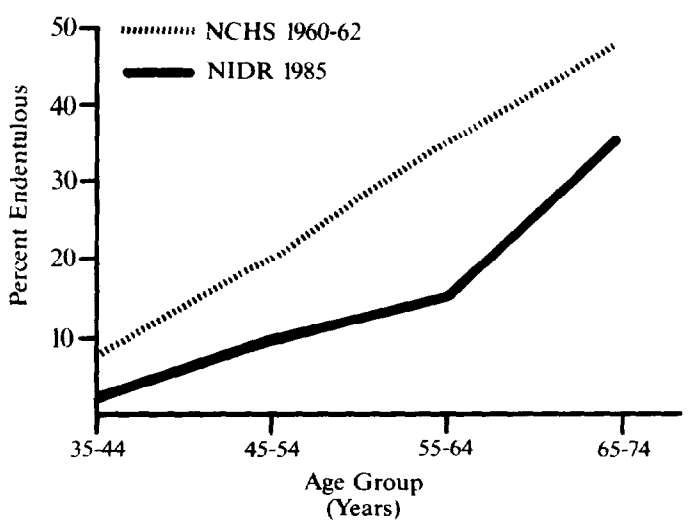

Figure 8-4. Comparison of the percent of edentulous persons in the 1985-86 NIDR survey to that reported from the NCHS survey of 1960-62.

Source: National Institute of Dental Research 1987.

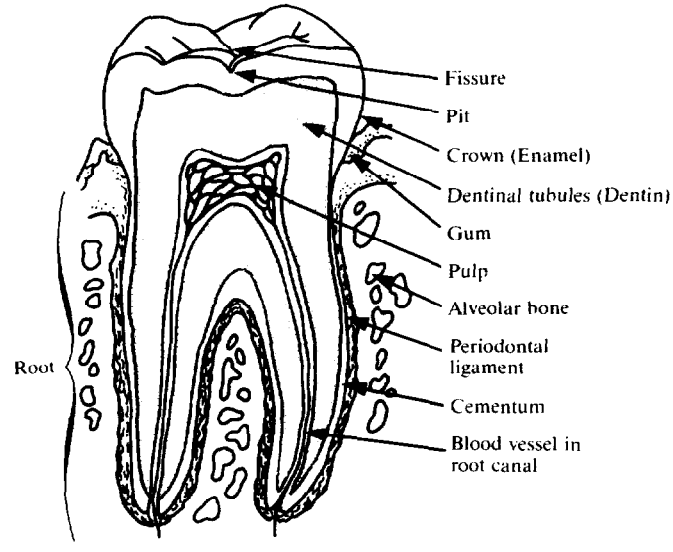

Figure 8-5. Schematic cross-section of a typical mandibular tooth. The gums recede with age, exposing the cementum of the tooth root.

dental organ that produces the tooth enamel and a dental papilla that produces the tooth pulp and the dentin. Cells from the dental follicle form the cementum and periodontal ligament after the tooth has formed.

The deciduous teeth begin forming at about 6 weeks *in utero*, when cells in the primitive oral cavity differentiate to form the dental lamina—the site of development of the tooth buds. The dental lamina is active from the second month of embryonic development, when the first buds for the deciduous teeth are formed, until about the age of 5 years, when the buds for the last permanent molars are initiated.

The formation of the tooth crown begins with the secretion of a dentin matrix containing collagen fibrils. Mineral ions then enter the matrix to form small crystals on or between the fibrils. Successive layers of dentin are formed. Enamel formation begins as soon as the first dentin layer has been laid down. Cells of the enamel organ secrete successive layers of a matrix that is chemically different from dentin matrix. Mineral crystals appear in each layer as it is secreted and grow larger as more mineral enters the tissue; matrix proteins and water are removed. This so-called maturation of the enamel continues after the full thickness of enamel matrix has

been laid down. These events occur at different times for the various deciduous and permanent teeth, beginning from a few months before birth until late adolescence.

As the tooth erupts into the mouth, it loses the layers of cells and blood vessels that covered the enamel. The enamel, however, continues to mature during the period immediately after tooth eruption and to incorporate minerals (including fluoride) into its structure from saliva, food, and drinking fluids. Otherwise, the enamel of fully erupted teeth is not known to have any metabolic dependence upon nutrients consumed in the diet. The inner surface of dentin adjacent to the pulp remains lined with the cells that formed it, and these cells continue to form secondary dentin at a very slow rate throughout the life of the tooth.

Thus, there are different periods in the developmental history of the tooth. During the preeruptive period when the crowns are forming in the jaws (which, for the wisdom teeth, continues into late adolescence), the developing enamel and dentin of the crowns are subject to nutritional deficiencies or imbalances in the same way as other tissues. In fact, in the enamel the preeruptive period can be divided into two phases, the secretory and the maturation stage. Nutritional deficiencies or excesses may affect either stage separately or both. Hypoplastic lesions in the enamel reflect disturbances affecting the secretory process. Hypomineralized defects, such as the white spot lesions of fluorosed enamel, give evidence of interference with the maturation process. After eruption, when the crown of the tooth has emerged from the jaw and the enamel is bathed instead by the saliva as well as exposed to micro-organisms and their byproducts, sloughed cells, and food debris, nutritional deficiencies or excesses and dietary habits may affect teeth in a totally different manner.

The development and maintenance of the soft tissues and bone that anchor and support the teeth (the periodontium) are also subject to nutritional deficiencies. The periodontium comprises the gingiva (the tissue that covers the alveolar bone process and surrounds the top of the tooth), the periodontal ligament (the soft connective tissue that surrounds the roots of the teeth and joins the root cementum and the alveolar bone), the root cementum (a specialized calcified tissue that covers the tooth root), and the alveolar bone (the bone that forms and supports the sockets of the teeth). The bony tissue of the alveolar process is dependent on the presence of teeth. The alveolar bone grows in response to dental eruption, is modified by dental changes, and resorbs when the teeth are lost as a result of

advanced dental caries and/or periodontal disease. The resorption of alveolar bone ridges (residual ridge resorption) has been described as an oral disease entity (Atwood 1971).

Throughout life, the oral soft tissues undergo rapid rates of turnover and repair, and the continued presence of optimum levels of nutrients is necessary to maintain proper oral health and to resist disease.

Dental Caries

Once a tooth is fully erupted, it becomes subject to the influence of chewing, acids in the mouth, and bacterial plaque. Dental caries begins with dissolution of the mineral surface of the tooth by acid produced from fermentable carbohydrate (e.g., sugar) by dental plaque bacteria. Next, the dissolution advances further into the enamel, first appearing as a white spot, and subsequently into the dentin and eventually into the pulp. If left untreated, the result is destruction of the crown and root system, tooth loss, and resorption of the surrounding bone (Newbrun 1978). The decay that begins in pits and fissures, on the smooth surfaces, or on exposed roots of the teeth is invariably due to the combined effects of bacterial infection and host and dietary factors over time (Wei, Fomon, and Anderson 1977; Shaw 1978, 1987). Patients with reduced salivary flow are also at increased risk (Mandel 1983).

Of the many bacteria found in tooth plaque, *Streptococcus mutans* is considered the primary etiologic agent in coronal caries (Loesche 1986; Shaw 1987). This bacterium is unique in that it produces enzymes that convert table sugar (sucrose) into long sticky polysaccharides. The polysaccharides promote firm attachment and accumulation of the bacteria in dental plaque (Gibbons and van Houte 1978). If not removed, the bacteria metabolize sugars (including sucrose) and produce acids that dissolve minerals from the teeth and begin the decay process. Root caries, decay of tooth root cementum following recession of gum tissues, has been regarded as an independent type of caries (Nikiforuk 1985). However, a relationship between root caries and coronal caries has been reported recently (Vehkalahti 1987). Decay also occurs around restorations where plaque is difficult to remove.

Whereas sugars facilitate the action of cariogenic bacteria, saliva is a major impediment to the pathogenesis of these bacteria (Vogel 1985; Mandel 1986). This fluid, secreted by the major and minor salivary glands, coats the tissues of the mouth and provides protection against bacteria that cause disease. The saliva contains molecules that when adsorbed to the tooth can influence attachment of bacteria to this surface and, when present in the

fluid, can clump bacteria together such that they cannot attach to the teeth but rather are cleared from the mouth by swallowing. Saliva also contains enzymes and proteins with antibacterial activity that inhibit bacterial growth or kill bacteria. In addition to these defense mechanisms, saliva can contain antibodies that attack specific kinds of bacteria. Another important function of saliva is that it supplies the calcium and phosphorus, minerals important in the remineralization of tooth surfaces that have lost mineral due to acid attack.

Several types of interventions might prevent tooth decay. The most important diet-related interventions are fluoridation of drinking water and control of sugar intake, but other approaches such as oral hygiene, application of plastic sealants, use of topical fluorides, and various chemotherapeutic agents have also been shown to be effective (Navia 1985). The efficacy of a caries vaccine that would prevent infection by cariogenic bacteria is under investigation (Navia 1985; Krasse, Elmilson, and Gahnberg 1987).

Periodontal Disease

Periodontal disease encompasses pathologic changes of the gingiva, periodontal ligament, cementum, and alveolar bone that make up the attachment and supporting tissues of the teeth (Lindhe 1983). The destruction of these tissues (the periodontium) results in the loosening and loss of the teeth. The etiology of this disease, like that of dental caries, is multifactorial, involving bacterial infection, host factors, diet, and duration of infection. The accumulation of bacterial plaque near the gum line can cause a nondestructive inflammation of the gingival tissue (gingivitis). Early studies (Löe, Theilade, and Jensen 1965; Theilade et al. 1966) showed that dental plaque caused clinical gingivitis and that when the plaque was removed the disease was reversed or prevented. If the inflammation persists, the disease can progress and destroy the gingival connective tissue and underlying tissues to form a subgingival or periodontal pocket. As the pocket depth increases, the alveolar bone (bone supporting the tooth) is resorbed and the tooth is lost. The primary etiologic agents for periodontal disease are subgingival bacteria (Socransky 1977).

The bacteria make and release toxic substances, destructive enzymes, and antigenic molecules that cooperate in the destruction of periodontal tissues. Large amounts of bacterial products can directly damage tissues or can cause overstimulation of the immune system with resulting tissue damage; under normal oral conditions, the immune system is protective against bacterial challenge (Nisengard 1977; Seymour 1987). Other factors that can decrease host defense mechanisms and, therefore, promote periodontal disease are immunologic defects, metabolic problems, endocrine

dysfunctions, and nutritional deficiencies. Reduced salivary flow is also a risk factor (Mandel 1983).

Key Scientific Issues

- Role of Diet in Tooth Decay
- Role of Diet in Periodontal Disease
- Role of Diet in Other Dental Conditions
- Effect of Tooth Loss on Nutritional Status

Role of Diet in Tooth Decay

Although diet is indicated as one of the main direct determinants of dental caries, it is also linked to each of the other determinants of causation, prevention, and treatment. Dietary factors are important for the host's normal tooth development, host resistance, and salivary composition; for selection and maintenance of the microbial population; and for the amount of time teeth are in contact with sugars and their acid byproducts (Alfano 1980). Sugars are the most important dietary factors in the causation of dental caries; fluoride is most important in its prevention. The role of other dietary components such as fats, protein, and minerals in modulating these effects is also of much current interest.

Role of Sugars

Despite the complex etiology of dental caries, the causative role of dietary sugar—especially sucrose—is well established (Keyes and Jordan 1963). Caries-producing bacteria have a rather high need for a range of simple sugars (glucose, fructose, lactose, maltose, and sucrose) that they readily metabolize into acids that demineralize teeth. The unique role of sucrose, however, depends on its ability to be converted by mouth bacteria into extracellular polymers of glucose or fructose that adhere firmly to the tooth surfaces (Gibbons and van Houte 1978; Doyle and Ciardi 1983). Together with the micro-organisms that secrete them, these extracellular products facilitate the further attachment to teeth and proliferation of bacteria.

Food sugars, such as glucose and fructose that diffuse into this plaque, nourish the micro-organisms. Food starches are converted to a limited extent by salivary enzymes to soluble glucose that can be used by plaque bacteria. Although saliva readily neutralizes organic acids, it has limited access to the acids generated at the tooth surface beneath the plaque.

Recent reviews of extensive animal studies and human epidemiologic and clinical observations during the past 30 years have thoroughly documented the role of sucrose and other sugars in tooth decay (Newbrun 1982; Glinsmann, Irausquin, and Park 1986). Studies in rats, for example, have demonstrated a direct relationship between the amount of sucrose in the diet and caries incidence that reaches a plateau when the sucrose concentration is 8 to 40 percent by weight. Such studies have also demonstrated the importance of the consistency and composition of the diet. Sucrose has been shown to have a greater cariogenic effect than glucose, fructose, or other simple sugars. Caries incidence increases directly with the frequency of sugar consumption (Bowen et al. 1983).

Despite methodological difficulties in assessing population-wide sugar intake, human epidemiologic studies have generally indicated an association between sugar intake and tooth decay (Sreebny 1982) as well as increasing rates of tooth decay among populations whose sugar intake is increasing (Burt and Ismail 1986). Human clinical studies have demonstrated a virtual absence of tooth decay and much lower concentrations of cariogenic bacteria in the mouths of children with inherited metabolic disorders (e.g., fructose intolerance) that prevent sucrose consumption (Newbrun 1982).

Other clinical studies show the importance of frequency of sugar consumption and the form in which it is consumed. Sugars in solution are more readily cleared from the mouth than sugars in solid foods and, therefore, are more likely to have only a transient influence on plaque acidity. Foods that adhere to the teeth are more cariogenic than those that wash off quickly (Gustafsson et al. 1954). In addition, people eat foods in different ways. It appears that any increase in the length of time food remains in the mouth is likely to increase the initiation and progression of caries (Newbrun 1978).

Metabolism of sugars by mouth bacteria results in acid production concomitant with a pH drop in dental plaque from a level near neutral to about 5. This effect lasts 20 to 30 minutes until buffering agents in saliva restore the normal pH. Recurrent exposures to such episodes for extended time periods lead to dissolution of the enamel. The presence of calcium, phosphate, fluoride, and other minerals in the saliva permits remineralization when the pH is neutral. Thus, the tooth is exposed to alternating cycles of dissolution and remineralization. If the balance favors dissolution, clinical carious lesions occur, and if it favors remineralization, early lesions are repaired and advanced caries does not develop.

Research into the cause of caries has not entirely overcome problems in measurement of sugar intake, the confounding effects of other dietary components, and secular trends in dental hygiene and fluoride consumption. Evidence exists that sugars as they are consumed in the average American diet contribute to the development of dental caries. Current average daily intake levels in the United States are 62 to 143 g, or 18 to 32 percent of total caloric intake (Glinsmann, Irausquin, and Park 1986). Reduction of dietary sugar would be expected to reduce levels of tooth decay in the population, in particular at the time of tooth eruption (Loesche 1985).

Nursing Bottle Caries

A special example of the importance of the duration of contact between fermentable sugars and teeth is nursing bottle caries (Gardner, Norwood, and Eisenson 1977; Ripa 1978; Dilley, Dilley, and Machen 1980; Kelly and Bruerd 1987). This unique pattern of dental caries, where the upper incisors become badly decayed, has been described in young children. In severe cases, the chewing surfaces of the molars become affected, but the lower incisors rarely develop lesions. The lesions on the upper incisors begin as a generalized demineralization on the third of the crown next to the gums and progress so that the tooth is encircled by a ring of decay that may become so deep that the crown breaks off just above the gum.

This condition occurs when children are put to bed with a bottle of milk, formula, juice, or sweetened beverages. These practices allow sugars in milk or other fluids to remain in contact with the tooth surfaces for extended periods. The position of the upper incisors makes them especially vulnerable, while the lower incisors are usually protected by the tongue. These carbohydrates are metabolized to acids by the oral micro-organisms that are always present on tooth surfaces, and this action is compounded by the infrequent swallowing and reduced salivary flow that occur during sleep.

Role of Fluoride

The efficacy of fluoride in the prevention of tooth decay is well established. It is generally assumed to prevent caries by decreasing the solubility of tooth enamel, promoting remineralization of the enamel surface, modifying the chemical interactions in plaque, or inhibiting lactic acid production by cariogenic bacteria (Navia 1985).

Since 1945, when fluoride was first added to community water supplies, more than 35,000 published scientific papers have attested to the efficacy,

safety, and cost-effectiveness of fluorides in prevention of tooth decay (Richmond 1985). Many of these studies demonstrate reductions in dental caries of 50 percent or more when fluoride is added to a community water supply.

One focus of research in the 1930's and 1940's was to determine the optimal level of fluoride in drinking water. This concentration is about 1 ppm for temperate regions. Current recommendations for optimum fluoride concentrations vary from 0.7 to 1.2 ppm, depending on regional variation in prevailing air temperature because the amount of water consumed tends to be less in colder climates. Caries incidence increases when drinking water contains less than the optimum level of fluoride, but mild forms of fluorosis (the mottling of tooth surface) can begin to occur at about twice the optimum level. Fluorosis occurs only when developing teeth are exposed to excess fluoride, generally over a period of months; once a tooth is fully formed, continuing fluoride exposure may promote the remineralization process.

For children living in areas with inadequate concentrations of fluoride in the water, dental authorities recommend fluoride supplements at dosages that depend on the natural fluoride content of the local water supply and the age of the child. The dosages currently recommended by the Council on Dental Therapeutics of the American Dental Association and the American Academy of Pediatrics are provided in Table 8-1. The effectiveness of prenatal fluoride supplementation, however, is uncertain because clinical studies of its effects on subsequent caries incidence have been equivocal (Driscoll 1981).

Table 8-1
Supplemental Fluoride Dosage Scheduled (in mg F/day[a]) According to Fluoride Concentrations of Drinking Water

	Concentration of Fluoride in Water (ppm)		
Age (years)	Less than 0.3	0.3 to 0.7	Greater than 0.7
Birth to 2	0.25	0	0
2 to 3	0.50	0.25	0
3 to 13	1.00	0.50	0

[a]2.2 mg of sodium fluoride contain 1 mg of fluoride.

Source: Council on Dental Therapeutics 1984.

Another area of uncertainty concerns current levels of fluoride intake. When the optimal level of about 1 ppm was originally established, the primary source of fluoride for human consumption was the water supply. Today, fluoride is also available from toothpastes, mouth rinses, and soft drinks and foods prepared with fluoridated water. These sources have increased the availability of fluoride beyond that originally envisioned, perhaps to levels that might induce fluorosis (Horowitz et al. 1984). Several recent studies have observed an increased incidence of mild (barely noticeable) tooth mottling among children taking fluoride supplements or living in communities where water is fluoridated. Although there is no evidence that this condition is harmful, these observations have led some authorities to suggest reevaluation of previously accepted standards for optimal fluoride use (Navia 1985; Leverett 1982).

Controversy about water fluoridation is not new. Despite the preponderance of community studies conclusively demonstrating the effectiveness of both naturally occurring and purposefully supplemented fluoride in drinking water, opposition has been raised on grounds of effectiveness, safety, and individual rights (Taves 1979; Watson and Schrotenboer 1983). However, studies have failed to show any relationship between fluoride and increased risk for heart disease, brain lesions, liver disease, allergies, kidney disease, mental retardation, cancer, or mutagenicity (Richmond 1985). Indeed, studies of one chronic disease, osteoporosis, suggest a protective effect for fluoride (Simonen and Laitinen 1985; see chapter on skeletal diseases). Based on the scientific evidence, the courts have consistently ruled that States and municipalities have the right to implement fluoridation as a public health procedure (Block 1986; Löe 1986).

Role of Other Dietary Factors

Protein. Experimental data show certain critical periods in the development of the teeth of young rats, during which a marginal protein deficiency exerts striking effects (Nakamoto, Mallek, and Miller 1979a, 1979b). When low-protein diets were fed to rats at any time throughout pregnancy and lactation, the molars of their offspring were altered in shape and were significantly smaller than the molars of offspring from control rats (Shaw and Griffiths 1963; Holloway, Shaw, and Sweeney 1961). Although the change in tooth size occurred without a reduction in enamel thickness, minor cusps of the third molars of the offspring from these protein-deficient females frequently did not develop, suggesting that nutritional deficiencies can prevent normal tooth development. Caries incidence was higher in the offspring of protein-deficient females than in control offspring when both were fed the same caries-producing diet after weaning. The offspring from

protein-depleted females had abnormalities of the salivary glands (decreased DNA, RNA, and protein concentrations, and decreased net weight) and the saliva (greatly reduced salivary flow and small increase in salivary protein concentration), which may partially explain their increased caries incidence (Menaker and Navia 1973a, 1973b, 1974).

Supplementing the diet of pregnant and lactating rats with 1 percent DL-methionine (the limiting amino acid of casein) prevented almost all of the abnormalities, but supplementation begun at weaning was ineffective (Shaw and Griffiths 1963). That the deficient nutrient was protein, but not calories or other nutrients, was demonstrated when protein supplements alone prevented these abnormalities (Menaker and Navia 1973a, 1973b, 1974).

In humans, protein-energy malnutrition is often associated with poor dental health. Delayed tooth eruption and impaired tooth development are common findings among children in developing countries where protein, calories, and other nutrients are inadequate (Steggerda and Hill 1942; Sweeney 1966). Abnormal lesions on the teeth of younger children in less developed nations have been reported to be highly susceptible to tooth decay even when children consume lesser amounts of sugar-containing foods and consume foods less frequently than children in more highly developed nations (Sweeney et al. 1969; Sweeney, Saffir, and de Leon 1971). Nevertheless, the permanent teeth in older children and adults in developing countries are not more susceptible to caries than those in older children and adults in industrialized countries (Russell 1966). At present, there is no evidence to indicate that an increase in caries incidence accompanies delayed tooth eruption. Little information on the influence of protein deficiency on the rate of salivary flow or on saliva composition in humans is available (Vogel 1985).

Fat. In animal studies, increasing the concentration of fat in a diet with the carbohydrate concentration held constant reduces the caries-producing potential of the diet (Shaw 1950). This may have to do with the sequence in which foods are eaten. When dietary sugar is followed by a food such as cheese (which is high in fat), the usual acid-forming response is blunted and less acid is present in plaque (Edgar 1981; Edgar et al. 1982; Schachtele and Jensen 1983). The significance of these observations for human tooth decay, however, has not yet been established.

Vitamin A. Studies of the continuously erupting incisor of the rat showed that a severe deficiency of vitamin A impairs tooth formation (Wolbach and

Howe 1925, 1933; Boyle and Bessey 1941; Schour, Hoffman, and Smith 1941). The observed changes resembled the effects of vitamin A deficiency on tissues of ectodermal origin elsewhere in the body. Bones formed entirely during a period of vitamin A deficiency contain reduced amounts of calcium, suggesting an effect on bone mineralization and the resulting bone structure. A deficiency of vitamin A for a limited time before tooth eruption has been shown to increase the susceptibility of rat molars to caries (Harris and Navia 1980; Navia and Harris 1980). Other studies, in which the third molars of rats were cultured, showed that vitamin A deficiency delays tooth formation and interferes with mineralization of both enamel and dentin (Navia et al. 1984). Vitamin A deficiency has also been observed to disrupt normal differentiation of rat tooth-forming cells and to alter the distribution of certain molecular components of dentin and pulp (Punyasingh et al. 1984).

Vitamin D and Calcium. In early studies of rickets, deficiencies of a fat-soluble vitamin, later identified as vitamin D, resulted in the softening and discoloration of the enamel of developing teeth, delayed tooth eruption, and an irregular tooth arrangement in the jaw (Mellanby 1918; Mellanby 1919). These defects were also seen in the offspring of pregnant animals given a vitamin D-deficient (rickets-producing) diet but not in animals that received daily supplements of cod liver oil (Mellanby 1928). Calcium deficiency resulted in less severe defects in the enamel and dentin, but deficiencies of both calcium and vitamin D resulted in very poorly formed enamel and dentin (Mellanby 1923). These early studies indicated the need during tooth development for adequate dietary intake of calcium and vitamin D.

In a series of clinical trials in England in which children received vitamin D supplements to their regular diet, modest reductions in dental caries were observed both for secondary teeth that had erupted before the trials began and for teeth that erupted during the trial (Committee for the Investigation of Dental Disease 1936). Despite evidence for a beneficial role of vitamin D in tooth development, clinical trials to determine whether vitamin D supplements reduce dental caries have yielded varied results (Shaw 1952), and this area remains uncertain.

A long-term study of dental abnormalities in children showed that the inherited conditions of vitamin D-dependent rickets or hypoparathyroid syndrome, both of which reduce levels of plasma calcium, are associated with abnormal lesions in tooth enamel but normal dentin. Children with low plasma levels of phosphorus but normal levels of plasma calcium developed normal enamel but abnormal dentin. Those with low plasma levels of both

calcium and phosphorus developed abnormalities in both enamel and dentin (Nikiforuk and Fraser 1979). The implications of these observations for dietary intake in normal children are unknown.

Phosphate. An increasing amount of phosphate in the diet reduces experimental caries incidence in rats (Nizel and Harris 1964), but supplementation of the diet of children with phosphate has not been shown to produce benefits (Stralfors 1964; Ship and Mickelsen 1964; Averill and Bibby 1964). Phosphate supplementation of chewing gum is reported to produce a reduction in caries incidence (Baron and Bilotti 1979; Finn et al. 1978; Jamison 1979; Richardson 1979).

Trace Elements. Certain epidemiologic surveys and experimental animal studies have suggested that some trace elements such as molybdenum, vanadium, strontium, and iron can inhibit caries development and that other elements such as selenium, magnesium, and cadmium can accelerate caries development. None of these studies has demonstrated either an independent action of these elements or an action that either augments or decreases the influence of fluoride (Curzon 1983; Navia 1970).

Other Food Components. Foods containing salts or acids can stimulate salivary flow, alter its buffering capacity, or decrease microbial acid production. Food components such as lectins (Gibbons and Dankers 1981, 1982), tannins (Kashket, Paolino, and van Houte 1985), and other less well-characterized substances (Madsen 1970) can inactivate bacteria or influence their metabolism and reproductive ability and, in these ways, may affect caries incidence.

Alternative Sweeteners. Sucrose and other simple carbohydrates can be replaced by polyols or non-nutritive sweeteners in many kinds of foods. The benefits of such products must take into account the quantities of cariogenic sweeteners that must be replaced to achieve significant caries reduction, the relationship of a food's overall chemical composition and physical properties to its cariogenicity, and the possibility of other nutritional or health effects (Hoskins 1978).

Role of Diet in Periodontal Disease

Periodontal disease is an infection of the gums and supporting structures caused mainly by the microbial flora that adhere to dental plaque. Like dental caries, the etiology of this disease includes specific microbiologic, environmental, and systemic components. The gingival sulcus (the space

between the gums and the teeth) harbors bacteria that directly and indirectly affect the formation of periodontal lesions and the later destruction of periodontal tissues and their cellular components. Environmental influences on the gums include dietary sugars and other factors that promote the formation of plaque on tooth surfaces, entrapment of food in periodontal lesions, and poor dental hygiene. Systemic influences on the initiation and progression of periodontal lesions are less well defined and more difficult to investigate, although there is considerable evidence that persons who are diabetic, immunosuppressed, or genetically susceptible are especially prone to periodontal disease. In general, only severe nutritional deficiencies or extreme endocrinologic imbalances appear to adversely affect the resistance of the gums. Diet may influence periodontal disease not only through its effects on plaque formation, but also through stimulation of salivary flow, antigenic stimulation of immune mechanisms, and enhancement of host repair and defense mechanisms (Alfano 1976; Navia 1985); however, its precise role is as yet undefined.

Role of Calcium

Calcium is a necessary mineral in the formation of all calcified tissues, including those of the periodontium. In adult dogs, a low-calcium diet produces radiologic evidence of loss of alveolar bone within 2 months and a periodontal syndrome within 1 year (Henrikson 1968). When the diet was supplemented with calcium, the periodontal disease reversed within 6 months.

It has been proposed that periodontal disease is caused by internal resorption of bone due to an imbalance of dietary calcium-to-phosphorus ratio (Krook et al. 1972). A more recent study (Svanberg et al. 1973) using similar conditions failed to confirm those results. Most scientists believe that periodontal disease is initiated by subgingival bacterial infection. Additional studies are necessary before the role of calcium in the etiology of periodontal disease can be ascertained.

Role of Vitamin C

A diet deficient in vitamin C (ascorbic acid) causes scurvy in humans. Advanced disease produces gingival changes and loosening of the teeth. Scurvy and some types of periodontal disease in humans are similar to experimental scurvy in the guinea pig and in both Old and New World monkeys, with bleeding of the gingiva, destruction of the periodontal membranes, and loosening and ultimate loss of teeth (Alvares et al. 1981; Boyle and Bessey 1941; Glickman 1948). There is ample evidence that ascorbic acid, which is required for the formation of collagen in connective

tissues, is necessary for the repair and maintenance of periodontal tissues. Only severe deficiencies result in aggravating periodontal disease.

Role of Folate

Folate is a member of the vitamin-B complex necessary for the normal production of red blood cells. Folate deficiency is a common type of hypovitaminosis in humans. In experimental gingivitis studies in humans, folate supplementation resulted in significantly less inflammation of gum tissues (Vogel and Alvares 1985). Its role in gingivitis and periodontal disease is under investigation.

Role of Other Nutrients

Various periodontal abnormalities have been produced in experimental animals as a result of nutritional deficiencies of protein (Chawla and Glickman 1951), tryptophan (Bavetta and Bernick 1956), calcium (Becks and Weber 1931), magnesium (Klein, Orent, and McCollum 1935), vitamin A (King 1940), vitamin D (Becks and Weber 1931), and B-complex vitamins (Becks, Wainwright, and Morgan 1943; Tomlinson 1939). However, in these studies, only severe deficiencies resulted in periodontal destruction, and most of these experiments were carried out in grown animals.

On the basis of current knowledge, nutritional deficiencies or imbalances do not seem likely to exert major influences on the prevalence or severity of periodontal disease in the general population. However, the ability of individuals with nutritional abnormalities to resist the progression of periodontal lesions initiated by microbiologic and environmental influences may be reduced. Severe protein malnutrition might alter the immunologic system in such a way as to render the host unusually susceptible to infection.

Role of Diet in Other Dental Conditions

Residual Ridge Resorption

The alveolar ridge (the bony ridge in which teeth are positioned) is vulnerable to the resorption or loss of mineral subsequent to tooth loss. This process results in a progressive change in the shape and a reduction in the size of the ridge that greatly affects the stability and retention of dentures (Atwood 1971, 1979; Tallgren 1972). While some patients adapt to ill-fitting dentures and contend that they can eat anything, many patients adapt by changing their diet (Yurkstas and Emerson 1964).

Resorption of the residual ridge results from an imbalance of bone resorption and bone formation, as does osteoporosis, leading to speculation about a possible relationship between these conditions. The role of calcium in the prevention and treatment of osteoporosis, either alone or in combination with vitamin D, estrogen, or fluoride, has received much attention, and calcium deficiency has been reported to be a factor in both osteoporosis and residual ridge resorption (Barzel 1979; Menczel et al. 1982). A study of 44 toothless patients found a relationship between a history of reduced dietary calcium intake and severe accumulated ridge reduction (Wical and Swoope 1974). Denture patients who were given daily supplements of calcium and vitamin D in a 1-year double-blind controlled study had 36 percent less bone loss than the group that received a placebo (Wical and Brussee 1979). However, the wide overlap of bone loss in the treatment and control groups suggested considerable individual variation and the need for further research in this area. Approaches available to minimize residual ridge resorption or restore lost bone are the following: use of implants, bone rebuilding with calcium phosphate preparations, and prevention of tooth loss.

Oral Cancer

In its earliest stages, oral cancer is painless and may present no overt symptoms. Because dentists see many people regularly, and because dentists have access to the oral cavity, they are in a unique position to provide early identification of suspicious lesions and signs of tobacco habits that put people at risk for oral and other diseases.

Although alcohol and chewing tobacco are known to increase risk, the role of nutrition in oral cancer in humans is less well established (see cancer chapter). In part, this is because epidemiologic studies on the relationship of nutrients to cancers elsewhere in the body have not been extended to include oral lesions. However, animal models have been developed for the experimental production of oral cancer that take advantage of the easy accessibility of the tongue and the mucosa of the oral pouch of the hamster for the application of suspected carcinogens and for later observation of their effects (Marefat and Shklar 1977; Shklar 1972).

These models permit the evaluation of nutritional influences in cancer formation. In several studies, animals whose diets were supplemented with derivatives of vitamin A developed oral tumors that were fewer, smaller, and later in appearance on exposure to the carcinogen 9,10 dimethyl-1,2 benzanthracene (DMBA) than those in animals that had not received the supplement (Shklar, Marefat, et al. 1980; Shklar, Schwartz, et al. 1980;

Burge-Bottenbley and Shklar 1983). A similar test of vitamin E (DL-L-tocopherol) produced fewer and smaller tumors in the animals that received it (Shklar 1982; Schwartz et al. 1985; Odukoya, Hawach, and Shklar 1984). More study of these issues is needed. Similarly, results from small studies on the influence of nutrients on the course of head and neck cancer suggest the need for further investigation (Dwyer et al. 1986).

Effects of Tooth Loss on Nutritional Status

The loss of teeth in adulthood should not be considered a normal or an inevitable event, but a pathologic result of disease or trauma that affects the normal physiologic process of the jaws, teeth, muscles, and nerves of the mouth.

Chewing Ability

The loss of natural teeth as a result of dental caries, periodontal disease, or trauma significantly reduces the ability to chew foods, as demonstrated by a variety of chewing-efficiency tests (Manly and Vinton 1951; Yurkstas, Fridley, and Manly 1951; Kapur, Soman, and Yurkstas 1974; Rissin et al. 1978; Kapur and Garrett 1984; Perez, Kapur, and Garrett 1985). Other studies suggest that tooth loss leads to reduced force in chewing such foods as carrots, meats, raw vegetables, and peanuts; markedly lower chewing performance (Manly and Vinton 1951; Kapur and Garrett 1984); and avoidance of certain hard-to-chew foods (Yurkstas and Emerson 1964). Patients with reduced salivary flow may be unable to wear removable dental prostheses due to lack of lubrication (VA 1986).

Swallowing Ability

Dentures can cause a loss of sensation in the mouth that can lead to problems in swallowing. In a study of 584 individuals who had to have a foreign object removed from the esophagus, the absence of natural teeth was considered a major factor (Ray and Vinson 1958). Dentists are urged to warn all patients provided with partial or complete dentures about this hazard and about the need for care in the preparation and chewing of food. Of 16 patients seen during 1 year because of impaction of a foreign body in the throat, only 3 had normal teeth (Wengraf 1969).

Choking on food was reported to be the sixth most common cause of accidental death in the United States in 1979, with 700 of 2,900 fatalities occurring among people 75 years or older (NSC 1979). Studies of choking victims have found that many have poor dental status (Haugen 1963;

Anderson 1977), and poorly fitting dentures are frequently suspected to be a factor in the blockage of airways with inadequately chewed and swallowed food.

Effect on Food Selection

In addition to reduced chewing efficiency, various studies have demonstrated that loss of natural teeth, even when replaced with dentures, can cause the following impairments: diminished ability to discriminate food particle size and texture, such as ability to differentiate between soggy and crisp wafers (Kapur and Collister 1970); increased flow of stimulated salivary gland secretion (Kapur, Collister, and Fischer 1967; Kapur and Garrett 1984); and diminished ability to perceive subtle differences in the sweet taste of certain solid foods (Giddon et al. 1964).

Effect on Nutritional Status

Some early studies reported that inadequate dental function as a result of toothlessness or inadequate prosthetic devices contributed to the establishment and maintenance of nutritional deficiencies (Mann, Mann, and Spies 1945; Greene, Dreizen, and Spies 1947; Ruikka, Sourander, and Kasanen 1967; Makila 1968, 1969a, 1969b). However, dietary intake can be adequate in an individual with reduced chewing provided that food is selected carefully and prepared appropriately (Geissler and Bates 1984).

Implications for Public Health Policy

Dietary Guidance

General Public

Dietary factors of principal interest in dental diseases are sugars and fluoride. Frequent consumption of sugars, especially sucrose, promotes formation of dental plaque, the key predisposing cause of both caries and periodontal disease. In the United States, the daily intake of sugars ranges on average from 62 to 143 g, or 18 to 32 percent of total caloric intake. Evidence exists that sugars as they are consumed in the average American diet contribute to the development of dental caries, suggesting that the general public should reduce its sugar consumption.

The role of fluoride in prevention of tooth decay is also well established from animal studies and from human epidemiology and clinical trials. Although fluoride is present in foods, the most efficient source of this nutrient for the general public is community drinking water that naturally

contains fluoride at an optimal level or to which fluoride is added to achieve the optimal level. Most, but not all, water supplies can be fluoridated, and current recommendations for optimum fluoride concentrations vary from 0.7 to 1.2 ppm depending on regional variation according to prevailing air temperature. Conclusive evidence shows that such levels of fluoride are safe.

Although other nutrients such as vitamin A, vitamin C, calcium, and phosphate may also be associated with prevention of dental diseases, evidence is insufficient at this time to recommend changes in dietary patterns on the basis of their relationship to these conditions for the general public.

Special Populations

Persons with diminished salivary flow are at special risk for caries and periodontal disease. They also may be unable to wear removable dental prostheses due to the lack of lubrication by saliva. Artificial saliva preparations containing fluoride and topical fluoride gels help to prevent tooth decay in such persons and can be recommended as an adjunct to sugar-restricted diets and appropriate dietary counseling. Children over the age of 6 months are at risk for nursing bottle caries, and their parents and caregivers should receive guidance in dietary and behavioral approaches to prevent this condition. Evidence related to the benefits of fluoride consumption by pregnant women on subsequent tooth development of the fetus and caries in the offspring is insufficient to recommend fluoride supplementation during pregnancy. Individuals with diabetes are especially prone to periodontal infections and should take special care to use available dietary and therapeutic means to control disease.

Nutrition Programs and Services

Food Labels

The presence and relative amount of added sugars, especially sucrose, contained in processed foods, as indicated by ingredient lists on food labels, should continue to play an important role in identifying dietary factors associated with dental disease.

Food Services

Evidence related to the role of dietary factors in dental disease suggests that food service programs should provide optimally fluoridated drinking water and promote noncariogenic foods, especially in programs for populations at high risk for dental diseases.

Special Populations

Persons with an active history of dental caries or with reduced salivary flow and parents of young children should be provided with counseling and assistance in developing diets low in cariogenic foods and in accessing appropriate sources of fluoride. Persons with diabetes are especially prone to periodontal infections and should take special care to use available dietary and therapeutic means to control their disease (see chapter on diabetes).

Research and Surveillance

Research and surveillance issues of priority related to the role of diet in dental diseases should include investigations into:

- The definition of critical periods of development of dental tissues that may be sensitive to nutrient intake.
- The role of nutritional factors in the maintenance and repair of the periodontium and oral tissues.
- The relationship between nutritional imbalances during tooth development and the formation of tooth lesions or defects that may increase caries susceptibility in children.
- The role of nutrition and nutritional status in the etiology and pathogenesis of dental diseases in older persons and other high-risk populations.
- The relationship between nutrition and both the immune and the nonspecific defense mechanisms of oral tissues and fluids.
- The most effective means to educate the public on the role of water fluoridation, diet, and dental care in preventing dental diseases.
- The mechanisms of fluoride action in the prevention of dental disease or osteoporosis.
- The effect of dietary factors such as vitamin A, vitamin E, and alcohol on the initiation and progression of oral cancers.
- Epidemiologic methods to determine the correlation between malnutrition and dental caries and/or periodontal disease.
- The role of calcium in the etiology and/or prevention of residual ridge resorption and periodontal disease.
- Estimation of the levels of fluoride from all sources in the diets of children.
- Estimation of the extent of dental fluorosis in the population.

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Chapter 9

Kidney Diseases

Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep, without immediately endangering our survival; but should the kidneys fail . . . neither bone, muscle, gland, nor brain could carry on.
Homer W. Smith (1895-1962)
From Fish to Philosopher, Ch. I

Introduction

Historical Perspective

For centuries, it has been known that dietary intake affects the composition of urine (see, for example, the discussion in the chapter on diabetes) and must, therefore, have an effect on kidney function. The idea that protein restriction might prevent further loss of kidney function in people with chronic renal insufficiency emerged during the first half of the 20th century (Addis 1948). Early studies in experimental animals suggested that excretion of urea by the kidney required "renal work." This idea received support from studies demonstrating that animals fed high-protein diets for prolonged time periods have enlarged kidneys as well as increased urea excretion. Early investigations also revealed significant increases in renal blood flow and glomerular filtration rates when meat was substituted for dietary carbohydrate or when extra protein was added to the diet (Brenner, Meyer, and Hostetter 1982).

These studies suggested that high-protein diets might stress the kidney workload to the point of failure. They also suggested that protein restriction might minimize the work required of kidneys that were already diseased and, thereby, prevent futher functional losses (Addis 1948). Additional research indicated that protein restriction could retard the progression of renal failure (Blatherwick and Medlar 1937; Farr and Smadel 1939; Addis 1948). However, the data supporting these observations were derived from rats, the study design was often faulty, and the applicability of these findings to humans—while of great interest—was uncertain.

In later decades, the development of kidney dialysis and transplantation techniques focused attention on methods—including manipulation of diet—to treat renal disease rather than to prevent it. Today, as more is learned about the progression of chronic renal disease, the role of diet in the etiology of this condition has become increasingly apparent.

Significance for Public Health

End-stage renal disease (ESRD) occurs when the kidneys are chronically unable to function sufficiently on their own, so that dialysis or kidney transplantation becomes necessary to maintain life. ESRD occurs in about 19,000 people each year in the United States (Schmidt, Blumenkrantz, and Wiegman 1983), and blacks are disproportionately affected as a result of hypertension-induced ESRD. Currently, about 80,000 persons undergo maintenance hemodialysis two or three times a week and another 11,000 persons undergo continuous ambulatory peritoneal dialysis (HCFA 1984). Approximately 9,000 kidney transplants were performed in 1986.

The estimated annual cost for maintenance hemodialysis and peritoneal dialysis treatment in the United States, including the expenses incurred by Medicare, State and private insurers, and Veterans Administration, military, and public health hospitals, is well over $2 billion (HCFA 1984). This estimate does not include the costs for pensions and from lost income, nor does it include the expenses for ancillary hospitalization, which is a frequent occurrence. A maintenance dialysis patient spends an average of approximately 15 to 16 days a year in the hospital (Blagg, Wahl, and Lamers 1983; Carlson et al. 1984). In addition to the financial costs of ESRD treatment, the patient and the patient's family often endure great physical and emotional suffering from the ravages of chronic renal failure, the frequent superimposed illnesses, and the burden of the treatment regimens.

Nutrition may affect persons who have, or are at risk for developing, ESRD in two ways. First, evidence shows that the intake of certain nutrients may influence the rate of progression of renal failure in persons with underlying renal disease. Second, individuals with advanced renal failure and those who undergo maintenance dialysis treatment often suffer from malnutrition and other nutritional disorders. It is possible, but not proved, that these nutrition-related complications may contribute to the debility, high incidence of superimposed illnesses, and poor rehabilitation typical of this condition.

Scientific Background

Functioning kidneys regulate the composition and volume of body fluids within very narrow limits. They do so by balancing intake and excretion of body fluids and the waste products derived from metabolic processes. If the kidneys fail to maintain homeostasis, a wide range of potentially lethal metabolic disorders can develop throughout the body.

Each human kidney contains about 1.2 million separate functional units called nephrons (Tisher and Madsen 1986), each with a glomerulus that removes ("clears") unwanted salts, waste products, and other chemicals from plasma along with the water in which they are dissolved. Normally, very little protein is removed. These substances are excreted from the kidney through a tubule that is connected to each glomerulus. The tubule can reabsorb back into the circulation most of the filtered water and some of the chemical substances, and it can actively remove other chemicals from blood. The fluids and chemicals that are not reabsorbed by the tubules drain into collecting ducts, flow through the ureter, and are stored in the bladder for eventual excretion as urine. The rate at which the glomeruli clear the blood of waste products is called the glomerular filtration rate (GFR).

Kidney Stones

When the concentration of certain salts in urine exceeds the limits of solubility, the salts can crystallize and form stones within the kidney or other parts of the urinary tract. The substances found most frequently in kidney stones include calcium, oxalate, phosphate, uric acid, and cystine (Smith, Van den Berg, and Wilson 1979). Although these substances derive from foods, oxalate and urate are also synthesized endogenously, and excessive dietary intake has not been shown to cause stone formation in healthy people. Instead, the supersaturated concentration of these substances in urine is the critical factor that set the stage for stone formation together with inadequate production of crystallization inhibitors (Kok, Papapoulos, and Bijvoet 1986) or inborn errors of metabolism that produce large amounts of the relevant metabolites.

Treatment of these conditions by diet or drugs is aimed at reducing the concentration of stone-forming substances in urine. The principal means to this end is to increase urine production to at least 2,500 ml per 24 hours by encouraging patients to drink water throughout the day unless on a low-fluid regimen (Smith, Van den Berg, and Wilson 1979).

Additional dietary measures to treat patients with chronic stone-forming conditions depend on the composition of the stones as well as on the genetic defect. For example, some persons who excrete excessive amounts of calcium in their urine reduce these levels in response to a low-calcium diet (Coe 1984); other persons increase calcium excretion, apparently because they compensate by synthesizing greater amounts of 1,25-dihydroxyvitamin D, absorbing more calcium, and increasing the release of calcium from bone (Broadus et al. 1984).

Dietary measures to reduce oxalate excretion include restriction of oxalate-rich foods, such as rhubarb, spinach, chocolate, and tea, and restriction of excessive intake of ascorbic acid (vitamin C), which is metabolized to oxalate. Uric acid stones have been treated with diets low in purine-rich foods, such as organ meats, fish, shellfish, and legumes. Persons with cystine-containing stones have responded successfully to low-protein diets (Sherrard 1983). Calcium phosphate stones have been treated successfully, if paradoxically, with high-phosphate diets that increase urinary excretion of pyrophosphate, an inhibitor of calcium crystallization (Smith, Van den Berg, and Wilson 1979). Reports that low-carbohydrate, low-protein, high-fiber, or vegetarian diets prevent stone formation have not been confirmed (Anonymous 1983).

Chronic Renal Failure

Chronic renal failure is permanent kidney damage with an associated depression of the GFR; it results in retention of waste products, abnormal plasma biochemistry, and symptoms ranging from lassitude to convulsions to death. Chronic renal failure is the consequence of longstanding and progressive renal damage and is usually irreversible. It may result from chronic glomerular disease (e.g., glomerulonephritis), chronic infections, polycystic kidneys or other congenital anomalies, vascular diseases, obstructive processes such as kidney stones, certain systemic or endocrine diseases, drug reactions, or hypertension.

The early stage of renal insufficiency occurs when the GFR falls to about 40 to 70 ml/min from a normal level of about 80 to 130 ml/min. Studies in animals with renal injury indicate that when the loss of kidney function causes renal insufficiency, the remaining functioning nephrons enlarge and the GFR increases (Deen et al. 1974; Hostetter et al. 1981). As a result of these adaptive changes, the loss of kidney function is proportionately less than might be expected from the loss of nephrons. In the injured or diseased kidney, increases in capillary blood flow and in the blood pressure gradient across the capillary wall have been reported (Hostetter, Troy, and Brenner

1981). Also, the chemical, electrical, and physical barriers to the movement of plasma proteins across the glomerulus into the renal tubule may be impaired (Olson et al. 1979, 1982).

For many years researchers have known that chronic renal disease often progresses to ESRD (Mitch et al. 1976; Rutherford et al. 1977; Adler and Kopple 1983; Klahr, Buerkert, and Purkerson 1983). Furthermore, the progressive loss of renal function occurs even in persons in whom the underlying cause of the renal disease has disappeared or abated—for example, in persons who have had relief of urinary tract obstruction, control of hypertension, or partial recovery from certain types of acute renal failure (McCormack et al. 1958; Kleinknecht et al. 1973; Rodriguez-Iturbe et al. 1976; Senekjian et al. 1979; Torres et al. 1980). Although the rate of progression of renal failure varies greatly among individuals, the decline in kidney function is constant in many individuals so that remaining function declines in approximately linear fashion (Mitch et al. 1976; Rutherford et al. 1977; Barsotti et al. 1981). It is not known in what percentage of persons with renal insufficiency will progress to renal failure, but the suspicion is that most people who lose more than 50 percent of their GFR will experience continued progression of the disease.

Chronic renal failure causes pervasive disorders in appetite as well as in the body's absorption, excretion, and metabolism of many nutrients. Consequently, nutritional therapy is essential in managing this condition. These disorders include: the accumulation in blood of urea and other waste products of protein metabolism and the clinical consequences of this accumulation (nausea, vomiting, and weakness leading to convulsions and coma) (Kopple 1978); a decreased ability of the kidney to either excrete a large salt load or to conserve salt when dietary sodium is restricted (Gonick et al. 1966); impaired ability to excrete water, potassium, magnesium, acids, and other compounds (David et al. 1972); a tendency to retain phosphorus (Bricker 1972; Coburn et al. 1977); decreased intestinal absorption of calcium (Coburn et al. 1977) and possibly iron (Lawson et al. 1971); and a high risk for developing certain vitamin deficiencies—particularly vitamin B_6, vitamin C, folic acid, and the active form of vitamin D, 1,25-dihydroxycholecalciferol, which is synthesized by the kidney (Kopple and Swendseid 1975).

The chronic renal failure patient is also likely to accumulate certain potentially toxic chemicals that normally are ingested in small amounts and excreted in the urine. Aluminum is such a toxin; it can cause severe bone disease, dementia, muscle weakness, and anemia in persons with kidney

failure (Elliott, MacDougall, and Fell 1978; Drueke 1980; Kaiser et al. 1984; Polinsky and Gruskin 1984). Currently, common sources of aluminum are the antacids aluminum hydroxide and aluminum carbonate, which persons with kidney disease frequently ingest to reduce intestinal absorption of phosphorus. Formerly, hemodialysis solutions contaminated with aluminum often caused aluminum toxicity, but such contamination has now been eliminated.

Acute Renal Failure

Acute renal failure is a general term used to describe a sudden decrease in the GFR, often to less than 2 percent of normal. Its early signs result from the accumulation of urea and other nitrogenous wastes. Electrolyte imbalance, metabolic acidosis, and other severe effects follow, as the person becomes increasingly uremic and other body systems are disrupted. Its most common causes are shock, severe infection, trauma, drugs, obstruction, and certain types of glomerulonephritis. In most instances, the condition is reversible if the person survives the underlying disease (Mitch and Wilmore 1988).

Despite the many advances in medical care during the past few decades, morbidity and mortality from acute renal failure remain high (Brezis, Rosen, and Epstein 1986). When associated with obstetrical complications, the mortality rate is about 17 percent; acute renal failure associated with surgery or trauma has a mortality of 51 to 53 percent (Brezis, Rosen, and Epstein 1986; Mitch and Wilmore 1988), and that caused by shock or sepsis accompanied by inadequate nutrition has a mortality rate of about 85 percent (Feinstein et al. 1981; Feinstein et al. 1983).

Protein-Energy Malnutrition in Renal Disease

One of the most prevalent nutritional complications of chronic renal failure is wasting, or protein-energy malnutrition (Kopple 1978, 1984). There are many causes for this wasting. Dietary intake, particularly of calories, is often inadequate (Kluthe et al. 1978; Kopple 1978; Salusky et al. 1983; Wolfson et al. 1984) because of loss of appetite due to the accumulation of toxins in kidney failure, the unappealing diets prescribed in renal failure, emotional depression, the debilitating effects of chronic illnesses, and the effects of acute superimposed illnesses on the patient's ability to eat or to accept intestinal tube feeding. The high incidence of superimposed illnesses can cause protein breakdown and wasting (Blagg, Wahl, and Lamers 1983; Carlson et al. 1984; Kopple 1984), as can the dialysis procedure itself. During dialysis, many biologically valuable nutrients may be lost (Kopple 1978), including amino acids, peptides, proteins (with peritoneal dialysis),

glucose (during hemodialysis with glucose-free dialysate), and certain water-soluble vitamins. The hemodialysis procedure also seems to increase net protein breakdown by unknown mechanisms (Borah et al. 1978; Farrell and Hone 1980). Renal failure patients sustain blood losses from frequent laboratory testing, occult gastrointestinal bleeding (very common in renal failure patients), and the sequestration of blood in the hemodialysis equipment (Linton et al. 1977). Because blood is rich in protein, these losses may cause serious protein depletion.

Patients with acute renal failure also demonstrate varying degrees of protein wasting. In some individuals, the net rate of protein breakdown (i.e., the difference between the total rate of protein degradation and protein synthesis in the body) may be very low—as little as 25 to 30 g/day, but in others, it may be as high as 240 g/day (Feinstein et al. 1981; Feinstein et al. 1983). For comparison, the total protein mass in a typical male is only about 6,000 g, excluding collagenous, or structural, fibrous protein (Cahill 1970). Patients with acute renal failure are often unwilling or unable to eat because of uremic poisoning or underlying illnesses such as abdominal infection, trauma, and surgical wounds. Thus, starvation often accompanies acute renal failure unless specific steps are inaugurated to nourish the patient.

In the United States, dialysis treatment is readily available for most patients with acute renal failure. Hence, patients with this condition do not often die from uremic poisoning; rather, death comes from complications such as infection associated with failure to heal wounds. Because, as discussed in the chapter on infections and immunity, protein-energy malnutrition may reduce the body's resistance to infection and impair wound healing, the profound wasting typical of acute renal failure may contribute to the high morbidity and mortality of this condition.

Dietary Management of Renal Failure

Diseased kidneys cannot clear metabolic waste products from the blood, maintain fluid and electrolyte balance, or convert vitamin D to its active form. The resulting elevated levels of nitrogenous wastes, electrolytes, and other metabolites can depress appetite and impair absorption of essential nutrients, thus establishing conditions that lead to uremia and malnutrition. Moreover, treatment of renal disease may demand severe dietary restrictions or induce nutrient losses. Dietary management of this condition, therefore, must provide protein, energy, and other essential nutrients in amounts adequate to avoid deficiencies but sufficiently restricted to avoid stressing the diminished excretory capacity of the diseased kidney. The goals of nutritional therapy for both acute and chronic renal failure are to

maintain optimal nutritional status, to minimize the toxic effects of excess urea in blood, to prevent loss of lean body mass, to promote patient well-being, to retard the progression of renal failure, and to postpone initiation of dialysis (Burton and Hirschman 1983; Abel 1983). In children, an additional goal is to maintain growth rates as close to normal as possible (Holliday 1983).

These goals are accomplished by the methods listed below.

Restricting Fluid Intake. Energy, protein, and other essential nutrients are provided in as small a fluid volume as is possible to maintain water balance.

Restricting Protein. Nitrogen balance must be maintained without any unnecessary accumulation of urea or other toxic nitrogenous waste products. The degree of protein restriction depends on the severity of renal damage as assessed by the use of GFR determinations. To enhance incorporation of amino acids into body protein and to reduce protein breakdown in more severely ill persons, dietary protein or supplements of high biologic value (containing a high proportion of essential amino acids) are often recommended (Burton and Hirschman 1983).

Increasing Energy Intake. The higher the energy intake, the less dietary protein is required to maintain nitrogen balance. Increasing the carbohydrate and fat content of the diet provides calories that do not stress the compromised excretory capacity of the kidney. This energy is protein-sparing; it improves nitrogen balance and prevents catabolism of body proteins. Patients with acute renal failure, however, are often unable to tolerate high carbohydrate loads and may require insulin administration (Abel 1983).

Regulating Phosphate, Calcium, and Magnesium Intake. Intake of certain nutrients must be monitored carefully to ensure that they do not accumulate in blood and cause problems. Phosphate restriction is necessary to prevent the metabolic bone disease that often accompanies renal failure; phosphate levels can also be regulated with phosphate-binding agents that cause dietary phosphate to be excreted rather than absorbed. Calcium may be administered as a supplement as needed. Excessive magnesium levels are not usually present unless magnesium-containing antacids are used; avoiding them or using magnesium-binding agents prevents toxic accumulation of this substance.

Supplementing Vitamins and Trace Elements. Supplemental water-soluble vitamins and trace elements are usually provided to compensate for inadequate intake and losses in dialysis.

Using Enteral and Parenteral Methods of Nutritional Support. Intravenous administration of nutrients and energy may be necessary for patients with acute renal failure who are unable to take food by mouth (Abel 1983). Administration of supplemental nutrients by mouth or tube has also proved helpful in certain cases.

Providing Appropriate Counseling and Support. Diets for renal patients are based on contradictory principles (meet nutritional needs but restrict protein and phosphorus), are especially restrictive, and require careful monitoring of the patient's nutritional status. Thus, trained nutrition professionals are usually essential for dietary management. Long-term nutrition counseling of patient and family is especially necessary for children with renal disease to promote growth without increasing the kidneys' excretory load (Holliday 1983).

Key Scientific Issues

- Role of Protein in Renal Disease
- Role of Phosphate in Renal Disease
- Role of Lipids in Renal Disease

Role of Protein in Renal Disease

Chronic Renal Failure

Renal function begins to decline in normal humans after about the fourth decade of life (Rowe et al. 1976), and it has been postulated that high-protein diets may contribute to this decline. Typical protein intake among Americans is considerably higher than the Recommended Dietary Allowance (RDA) for dietary protein (NRC 1980), and in healthy young men and women, a high protein intake has been noted to increase renal blood flow and the GFR (Pullman et al. 1954; Wiseman et al. 1987). There are also similarities between the type of scarring that occurs in normal aging human kidneys and the kidneys of rats fed high-protein diets. In adults who have had a congenital absence, failure of development, or surgical removal of one kidney during childhood, an abnormally high incidence of spontaneous

glomerular scarring occurs in the remaining kidney (Kiprov, Colvin, and McCluskey 1982). Although the precise cause is not known, one theory is that increased glomerular capillary blood flow and pressure associated with high-protein diets may contribute to progressive renal injury in certain individuals.

In rats, a high-protein diet stimulates an increase in glomerular filtration rate, capillary blood flow, capillary blood pressure gradients, and enlargement of individual nephrons, whereas a low-protein diet will blunt or prevent these responses (Hostetter et al. 1981). Normal rats fed high-protein diets throughout life have a higher incidence of renal disease in old age (Striker et al. 1969; Lalich, Faith, and Harding 1970; Everitt, Porter, and Wyndham 1982; Zucchelli et al. 1983). When fed a high-protein diet, rats with renal injury develop progressive renal failure. When such animals are fed a low-protein diet, the progression of renal failure is retarded or arrested (Blatherwick and Medlar 1937; Farr and Smadel 1939). One current hypothesis is that a high-protein intake causes filtration and excretion of protein and, thus, causes progressive injury to the glomerulus, including its basement membrane (filtering wall), by increasing both glomerular capillary blood flow and intracapillary blood pressure (Hostetter et al. 1981; Brenner, Meyer, and Hostetter 1982). This hypothesis further holds that a low-protein diet retards or stops progressive renal damage by preventing these high pressures and flow rates.

Traditionally, dietary protein restriction has been used to minimize the toxicity that occurs in renal failure (Kopple et al. 1968). Many of the waste products that accumulate in kidney failure are products of amino acid and protein metabolism. Current evidence suggests that some of these waste products cause toxic symptoms.

Recent studies in rats and humans have demonstrated that dietary control can retard the rate of progression of renal failure in a variety of renal diseases (Mitch et al. 1984). In rats, several models of renal insufficiency have been studied, including surgical removal of renal tissue, ligation of the arteries to the kidney, and experimental glomerulonephritis (Ibels et al. 1978; Karlinsky et al. 1980; Haut et al. 1980; Laouari et al. 1983; Kenner et al. 1985). In these animals, diets low in protein or phosphorus retarded or prevented progression of renal failure.

In humans with renal insufficiency, virtually all recent studies indicate that a diet low in protein or phosphorus retards the progression of renal failure (Maschio et al. 1982; Alvestrand, Ahlberg, and Bergstrom 1983; Barsotti et al. 1983; Barsotti et al. 1984; Gretz, Korb, and Strauch 1983; Mitch et al.

1984; Rosman et al. 1984). Each of these studies, however, has limitations inherent in experimental design related to the retrospective nature of many of the studies, an insufficient number of patients studied, the lack of control groups, poor documentation of patients' actual intake, and the paucity or absence of data that indicate whether these restrictive diets induce malnutrition. Adequate controls are especially important because not all persons with renal insufficiency progress to advanced renal failure, and the rate of progression can vary markedly from individual to individual.

In assessing protein restriction in renal failure management, some investigators have used a modified low-protein diet supplemented with the nine essential amino acids or with mixtures of some essential amino acids and ketoacid or hydroxyacid analogs of other essential amino acids (Walser 1975; Alvestrand, Ahlberg, and Bergstrom 1983; Barsotti et al. 1983; Gretz, Korb, and Strauch 1983; Mitch et al. 1984). The ketoacid or hydroxyacid analog is structurally identical to its corresponding essential amino acid, except that the amino group attached to the second (alpha) carbon of the amino acid is replaced with a keto group or hydroxy group, respectively (Figure 9-1).

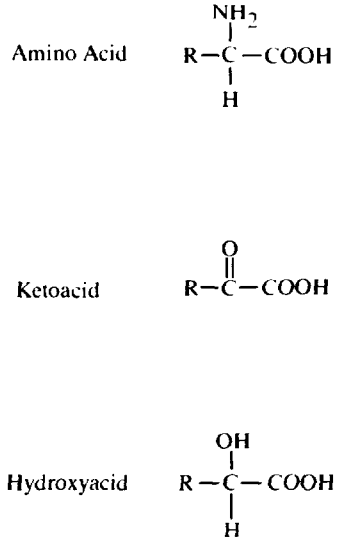

Figure 9-1. The comparative structures of amino acids, ketoacids, and hydroxyacids. The R symbol refers to the side chain of these chemicals, which is different for each individual compound.

Acute Renal Failure

Several studies in rats also indicate that a high amino acid intake by infusion may predispose to acute renal failure caused by loss of blood flow to the kidney (Zager and Venkatachalam 1983; Zager et al. 1983). The amino acid intake that predisposes to acute renal failure, when expressed per kilogram body weight, is not substantially greater than the quantity that might be consumed by humans. The reason for this effect is not known.

For unexplained reasons, acute renal failure causes a metabolic reorganization that promotes breakdown of muscle proteins and reduces the ability of the body to utilize amino acids to prevent wasting and to rebuild tissues (Clark and Mitch 1983). Although some studies in rats or humans support the benefits of nutritional therapy to prevent loss of body weight and protein mass in acute renal failure (Wilmore and Dudrick 1969; Toback 1977), most studies have not confirmed these observations. At the present time, no nutritional regimen prevents protein wasting in severely ill patients with this condition (Leonard, Luke, and Siegel 1975; Oken et al. 1980; Feinstein et al. 1981; Feinstein et al. 1983).

Merely increasing the protein intake does not stop acute wasting in many patients with acute renal failure (Feinstein et al. 1983). Giving large amounts of amino acids engenders formation of more urea with little or no evidence for increased accrual of body protein (Frohlich et al. 1974; Feinstein et al. 1981; Feinstein et al. 1983). Moreover, if greater quantities of nutrients are infused intravenously, an enhanced accumulation of water, minerals, and metabolic waste products may increase uremic poisoning or promote the need for more dialysis treatments. The inadequacies of current treatment methods for acute renal failure emphasize the importance of developing effective methods to prevent this condition.

Role of Phosphate in Renal Disease

Because the phosphate content of the diet is usually proportional to the protein content, it has been difficult to separate the effects of these nutrients on the progression of renal disease. Nevertheless, as mentioned above, diets low in phosphorus have been shown to retard the progression of renal failure in laboratory rats and in humans. One possible explanation is that a low phosphorus intake prevents the deposition of calcium phosphate in kidney tissue, which may cause further renal damage (Ibels et al. 1981; Alfrey and Tomford 1982). Whether low-phosphate diets prevent the onset of renal damage in humans has yet to be determined.

Role of Lipids in Renal Disease

Whether lipids and their metabolic products affect the development of progressive renal injury is still under investigation. Arachidonic acid is a fatty acid found in meat, fish, and certain plant foods; it is synthesized in the liver from linoleic acid and metabolized in the kidney into a family of eicosanoid compounds that include prostaglandins, thromboxanes, prostacyclins, leukotrienes (Dunn 1983). Prostaglandins affect blood flow and blood pressure inside the glomerulus, platelet aggregation, and the inflammatory process. Certain eicosanoids increase glomerular blood flow and pressure inside the glomerulus and may impair platelet clotting, while others have the opposite effect. In renal failure, there is an increased elaboration of certain eicosanoids in the kidney (Suzuki et al. 1980; Barcelli, Weiss, and Pollak 1982) that may delay further deterioration of kidney function (Klahr, Buerkert, and Purkerson 1983; Dunn 1983). The administration of prostaglandins also appears to affect the progression of chronic renal disease in animals (Zurier et al. 1977; Kelley, Winkelstein, and Izui 1979; McLeish et al. 1980).

Thus, reduced progression of renal injury and maintenance of a more normal GFR have been demonstrated in experiments in which rats and mice with impaired renal function were given fatty acid precursors of prostaglandins (Barcelli, Weiss, and Pollak 1982), injections of certain prostaglandins (Zurier et al. 1977; Kelley, Winkelstein, and Izui 1979), drugs that inhibit synthesis of prostaglandins that cause platelet clotting (Purkerson et al. 1985), or anticoagulants that inhibit platelet clotting (Purkerson et al. 1982).

These studies have been used to raise the hypothesis that renal disease may stimulate the glomerulus to synthesize eicosanoids that cause platelet clotting, inflammation, and replication of cells in the glomerulus, which, in turn, promote further renal injury (Purkerson et al. 1985). At the same time, inhibiting the synthesis of certain other eicosanoids in the glomerulus may protect the diseased kidney from continuing injury and from progressive loss of function. Because some eicosanoids appear to promote renal injury while others protect the diseased kidney from further damage, the dietary significance of these observations is as yet uncertain.

Implications for Public Health Policy

Dietary Guidance

General Public

Nutrients of particular interest in the occurrence of renal disease are protein, phosphate, and certain fatty acids. Although there is evidence in animals and humans that protein restriction can retard the progression of end-stage renal disease, there is no evidence that current protein intakes by the American population adversely affect the prevalence of renal disease.

Dietary phosphate restrictions have been noted to retard the progression of renal disease, but there is not sufficient evidence to indicate a role in the prevention of this condition. Nor may any implications be drawn for the general public on the relationship of dietary fatty acids intake to renal disease. Suggestions that certain lipids may increase the progression of renal disease have yielded conflicting research results.

Special Populations

Protein restriction is a therapeutic measure prescribed for patients with advanced renal disease, and end-stage renal disease patients on dialysis must follow a protein-, potassium-, and phosphate-restricted maintenance diet. A qualified health professional should provide information to such patients on using these diets appropriately.

Nutrition Programs and Services

Food Labels

Evidence related to the role of dietary factors in renal disease currently holds no special implications for change in policy related to food labeling.

Food Services

Evidence related to the role of dietary factors in renal disease currently holds no special implications for policy changes in food service programs.

Special Populations

Patients with renal disease should receive counseling and assistance in developing diets low in protein and low in phosphate. Those with renal stones should receive advice on diets that reduce excretion of stone-promoting factors (purines and excessive calcium) and should receive recommendations for a high daily fluid intake in excess of two liters.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in renal disease should include investigations into:

- The ability of low-protein diets to retard the decline of renal function in normal aging.
- The mechanisms by which dietary protein affects renal function.
- The relationship of the role of dietary protein to that of phosphate in its effect on kidney function.
- The mechanisms by which other nutrients such as fatty acids or amino acids might affect renal function.
- The use of various diets—such as those low in protein or phosphate—to retard the rate of progression of renal failure.
- The relative merits of specialized formula diets, pharmacologic therapy, and traditional low-protein diets in treating progressive renal failure.
- The causes of wasting, malnutrition, and other nutritional disorders that occur in renal failure.
- The treatment—with calories, amino acids, or drugs—of wasting, malnutrition, and other nutritional disorders that occur in renal failure.
- The interplay of dietary factors (such as calcium, vitamin D, phosphate, protein, and oxalate) in the etiology of renal stones.
- The effect of omega-3 fatty acids in preventing the immune inflammatory response in chronic renal disease.
- The regulatory mechanisms in the utilization and metabolism of keto-acids in humans.
- The impact of reduced protein/amino acid intake on the quantitative dynamic status of protein and specific amino acid metabolism in organs and the entire body.
- Lipid metabolism as affected by reduced protein and amino acid intake.
- The role of lipids in the progression of chronic renal disease: lipid turnover by renal cells, effect on tubular growth and function, relationship of hyperlipidemia to renal injury, and effect of drugs in the treatment of hyperlipidemia.
- Control of renal growth and impact of nutrition on renal mass.

- Mechanisms that produce toxicity of uremia and consequences of uremic symptoms.
- Effect of protein restriction, as opposed to total calorie restriction, on renal injury.

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Chapter 10

Gastrointestinal Diseases

Now good digestions wait on appetite, and
health on both.
William Shakespeare
Macbeth, III.iv. (1605–1606)

Introduction

The gastrointestinal system extracts nutrient- and energy-yielding molecules from plant and animal foods and digests them to smaller subunits that can be absorbed. Here also, indigestible food wastes are prepared for excretion. The full complement of essential nutrients is required for normal gastrointestinal function, as for any other bodily system, and malnutrition can adversely affect nutrient digestion and absorption. Similarly, infectious and other diseases that impair gastrointestinal function can impair nutritional status. These interrelationships are important in infant malnutrition as well as in the adult conditions reviewed in this chapter.

Historical Perspective

The history of digestive physiology is remarkable both for the early understanding of its importance to nutrition and health and for the imaginative research experiments that elucidated its function. This early history was reviewed by McCollum (1957).

Hippocrates (460–370 B.C.) believed that although there were many different kinds of foods, there was only one aliment. As early as the second century A.D., Galen (130–200) studied digestion in swine and concluded that the function of the stomach was to convert food into particles small enough to be absorbed.

In the 18th century, de Reaumer (1683–1757) investigated digestion in birds. He inserted food into metal tubes closed at the ends by screens and placed

the tubes in the stomach of a predatory bird. When the bird regurgitated the tubes, he was able to observe the dissolution of bones and the partial dissolution of meat in a fluid that tasted salty and bitter. Later, he performed similar experiments in dogs. Similar studies were conducted by Stevens in 1777 using as a subject a man who had earned his living for the past 20 years by swallowing stones. Stevens placed foods in perforated silver containers, and the man swallowed them. By the time the containers were recovered in stool, all foods except seeds were observed to be completely dissolved.

Perhaps the best known human digestive experiments were conducted by Beaumont (1785–1853) on a patient, Alexis St. Martin, who had a permanent opening from his stomach to the outside of his body (a fistula) as a result of a gunshot wound. Beaumont had easy access to and from St. Martin's stomach through the fistula and was able to observe gastric action on many types of foods.

Modern digestive physiology began in the 20th century with the identification of digestive enzymes. Although the basic principles of digestive physiology have been known for decades, the complex neuroendocrine interactions between the brain, digestive tract, and other tissues that control and regulate gastrointestinal function are as yet incompletely understood and are the subject of much current investigation (Nicholl, Polak, and Bloom 1985).

Significance for Public Health

Data from several national surveys provide evidence that these gastrointestinal conditions are extremely prevalent and cause considerable impairment of health and functional ability in the American population. In 1984, the incidence of digestive diseases and conditions that required medical attention or restricted normal activities was 7.6 per 100 persons per year. The incidence rate was highest for infants, children, and young adults (10.3 to 11.9 per 100) and lowest for adults ages 45 to 64 (4.7 per 100). Gastrointestinal conditions were responsible for an average of 32 days per 100 persons per year of limited activity among people of all ages, but among adults over age 65, the rate of restricted activity was 63 days per 100 persons per year (NCHS 1986).

Also in 1984, diseases of the digestive system accounted for a total of over 4 million hospitalizations at an average length of stay of 6.3 days. For patients under age 15, the leading gastrointestinal causes of hospitalization were

appendicitis, noninfectious gastroenteritis, and colitis. For patients ages 15 to 44, gastroenteritis and colitis were the leading causes. For adults ages 45 to 64, ulcers and gallstones predominated, and for adults over age 65, cancer, diverticula, and gallstones were the most important causes (NCHS 1987b). The total direct medical cost for gastrointestinal diseases in the United States is estimated at $17 billion per year (Klurfeld 1987).

Mouth, pancreas, colon, and rectal cancers were responsible for about 20 percent of all cancer deaths in 1986. There were 245,000 new cases of cancers of the mouth and digestive tract, and these diseases caused 125,000 deaths that year. Cancers of the colon and rectum are the second leading cause of new cancer cases in men and the third leading cause in women (see chapter on cancer). In 1986, 60,000 Americans died of colon and rectal cancers (Silverberg and Lubera 1987).

The interaction between infectious diarrheal diseases and malnutrition is the primary cause of infant and child mortality and morbidity worldwide (see chapter on infections and immunity), accounting for about 1.5 billion diarrheal episodes annually (Chen and Scrimshaw 1983). In the United States, these conditions are relatively rare but still were estimated to be responsible for about 5 percent of all infant deaths in 1985 (Wegman 1986).

Because most persons with diverticular disease are asymptomatic, the true prevalence of this condition is unknown. Diverticular disease is common in industrialized countries but extremely rare among rural populations in developing countries. Its frequency ranges from about 5 to 40 percent of subjects in Westernized nations (Painter 1985). Among Americans surveyed, 8.4 out of every 1,000 persons reported having diverticula (NCHS 1986). Frequency increases with age, and up to 70 percent of people from age 40 to 70 may be affected (Taylor and Duthie 1976). In 1980, diverticulosis caused 200,000 hospitalizations, incurring health care costs that exceeded $300 million dollars (Almy and Howell 1980). For hospitalizations recorded in 1984, the average hospital stay for such disorders was 8 days (NCHS 1987b).

Data from the National Hospital Discharge Survey, conducted by the National Center for Health Statistics, indicate that gallstones were responsible for 488,000 operations annually in the United States; the average hospital stay for this condition was 7.6 days in 1984 (NCHS 1987b). Nearly 3,000 Americans died of complications of gallbladder disease in 1986 (NCHS 1987a).

The estimated incidence of inflammatory bowel diseases increased from 1.9 cases per 100,000 population in the period 1935 to 1954 to 6.6 cases per 100,000 in 1965 to 1975. Projections based on incidence rates suggested that 20,000 to 25,000 new cases of this condition were admitted to hospitals in the United States in 1980 (Kirsner and Shorter 1982). The National Center for Health Statistics reported that 9.6 of every 1,000 Americans surveyed stated that they had enteritis or colitis (NCHS 1986).

Chronic liver disease and cirrhosis are the ninth leading cause of total deaths and the seventh cause of disease in the United States. They caused the death of more than 26,000 Americans in 1986 (NCHS 1987a). These conditions are discussed in more detail in the chapter on alcohol.

Scientific Background: The Digestive System

The primary functions of the digestive system are to ingest, digest, absorb, transport, and excrete food components. It accomplishes these tasks by means of the various digestive organs of the body and the enzymes listed in Table 10-1, as well as by response to the numerous regulatory neurochemical and hormonal substances produced by the brain, organs of the digestive system, and other tissues that are summarized in Table 10-2. This complex system extracts essential vitamins and minerals from diverse plant and animal foods and breaks down the carbohydrate, protein, and fat molecules in these foods to common subunits that can be absorbed. Once absorbed, these subunits are used as building blocks for the molecules that make up body tissues or for energy production. The structure and function of the digestive system, its response to disease, and the relationship between gastrointestinal function and nutritional status have been reviewed extensively (Floch 1981; Green and Greene 1984; LSRO 1987; Martin, Mayes, and Rodwell 1985; Trowell, Burkitt, and Heaton 1985).

The cellular lining of the digestive tract has a very large surface area and is readily exposed to potential mechanical, thermal, and microbial damage. Its anatomic location, gastric acidity, and elements of the immune system protect it from damage (Cole and Kagnoff 1985; Kagnoff 1983). This topic is reviewed in the chapter on infections and immunity.

Mouth

The physical and chemical breakdown of food begins in the mouth with the physical action of chewing and the enzymatic action of saliva. The parotid and submaxillary salivary glands produce fluids and enzymes that convert smaller carbohydrates and proteins to sugars and amino acids. Fats, however, are not generally altered in the mouth. Secretion of salivary fluid

Table 10-1
Summary of Digestive Processes

Source of Secretion and Stimulus for Secretion	Enzyme	Method of Activation and Optimal Conditions for Activity	Substrate	End Products or Action
Salivary glands: Secrete saliva in reflex response to presence of food in oral cavity.	Salivary amylase	Chloride ion necessary. pH 6.6–6.8.	Starch Glycogen	Maltose plus 1:6 glucosides (oligosaccharides) plus maltotriose.
Lingual glands	Lingual lipase	pH range 2.0–7.5; optimal, 4.0–4.5.	Short-chain primary ester link at *sn*-3	Fatty acids plus 1,2-diacylglycerols.
Stomach glands: Chief cells and parietal cells secrete gastric juice in response to reflex stimulation and action of gastrin.	Pepsin A (fundus) Pepsin B (pylorus)	Pepsinogen converted to active pepsin by HCl. pH 1.0–2.0.	Protein	Peptides.
	Rennin	Calcium necessary for activity. pH 4.0.	Casein of milk	Coagulates milk.
Pancreas: Presence of acid chyme from the stomach activates duodenum to produce (1) secretin, which hormonally stimulates flow of pancreatic juice; (2) cholecystokinin, which stimulates the production of enzymes.	Trypsin	Trypsinogen converted to active trypsin by enterokinase of intestine at pH 5.2–6.0. Autocatalytic at pH 7.9.	Protein Peptides	Polypeptides. Dipeptides.
	Chymotrypsin	Secreted as chymotrypsinogen and converted to active form by trypsin. pH 8.0.	Protein Peptides	Same as trypsin. More coagulating power for milk.
	Elastase	Secreted as proelastase and converted to active form by trypsin.	Protein Peptides	Polypeptides. Dipeptides.

Table 10-1 (continued)

Source of Secretion and Stimulus for Secretion	Enzyme	Method of Activation and Optimal Conditions for Activity	Substrate	End Products or Action
Pancreas (continued)	Carboxypeptidase	Secreted as procarboxypeptidase, activated by trypsin.	Polypeptides at the free carboxyl end of the chain	Lower peptides. Free amino acids.
	Pancreatic amylase	pH 7.1.	Starch Glycogen	Maltose plus 1:6 glucosides (oligosaccharides) plus maltotriose.
	Lipase	Activated by bile salts, phospholipids, colipase. pH 8.0.	Primary ester linkages of triacylglycerol	Fatty acids, monoacylglycerols, diacylglycerols, glycerol.
	Ribonuclease		Ribonucleic acid	Nucleotides.
	Deoxyribonuclease		Deoxyribonucleic acids	Nucleotides.
	Cholesteryl ester hydrolase	Activated by bile salts.	Cholesteryl esters	Free cholesterol plus fatty acids.
	Phospholipase A_2	Secreted as proenzyme, activated by trypsin and Ca^{2+}.	Phospholipids	Fatty acids, lysophospholipids.

Liver and gallbladder: Cholecystokinin, a hormone from the intestinal mucosa—and possibly also gastrin and secretin—stimulate the gallbladder and secretion of bile by the liver.	(Bile salts and alkali)		Fats—also neutralize acid chyme	Fatty acid-bile salt conjugates and finely emulsified neutral fat-bile salt micelles and liposomes.
Small intestine: Secretions of Brunner's glands of the duodenum and glands of Lieberkühn.	Aminopeptidase		Polypeptides at the free amino end of the chain	Lower peptides. Free amino acids.
	Dipeptidases		Dipeptides	Amino acids.
	Sucrase	pH 5.0–7.0.	Sucrose	Fructose, glucose.
	Maltase	pH 5.8–6.2.	Maltose	Glucose.
	Lactase	pH 5.4–6.0.	Lactose	Glucose, galactose.
	Trehalase		Trehalose	Glucose.
	Phosphatase	pH 8.6.	Organic phosphates	Free phosphate.
	Isomaltase or 1:6 glucosidase		1:6 glucosides	Glucose.
	Polynucleotidase		Nucleic acid	Nucleotides.
	Nucleosidases (nucleoside phosphorylases)		Purine or pyrimidine nucleosides	Purine or pyrimidine bases, pentose phosphate.

Source: Murray, R.K.; Granner, D.K.; Mayes, P.A.; and Rodwell, V.W. 1988. *Harper's Biochemistry,* pp. 584–85. 21st ed. San Mateo, CA: Appleton & Lange. Copyright Appleton & Lange 1988, reprinted with permission.

Table 10-2
Gastrointestinal Hormones

Hormone	Localization	Major Action
Gastrin	Gastrin antrum, duodenum	Gastric acid and pepsin secretion
Cholecystokinin (CCK)	Duodenum, jejunum	Pancreatic amylase secretion
Secretin	Duodenum, jejunum	Pancreatic bicarbonate secretion
Gastric inhibitory peptide	Small bowel	Enhances glucose-mediated insulin release. Inhibits gastric acid secretion
Vasoactive intestinal polypeptide	Pancreas	Smooth muscle relaxation; stimulates pancreatic bicarbonate secretion
Motilin	Small bowel	Initiates interdigestive intestinal motility
Somatostatin	Stomach, duodenum, pancreas	Numerous inhibitory effects
Pancreatic polypeptide	Pancreas	Inhibits pancreatic bicarbonate and protein secretion
Enkephalins	Stomach, duodenum, gallbladder	Opiate-like actions
Substance P	Entire gastrointestinal tract	Uncertain
Bombesin-like immunoreactivity	Stomach, duodenum	Stimulates release of gastrin and CCK
Enteroglucagon	Pancreas, small intestine	Unknown

Source: Adapted from Martin, Mayes, and Rodwell 1985.

depends on neuroendocrine regulation and is affected by the sight, smell, taste, and thought of food. The role of salivary secretions is discussed further in the chapter on dental diseases.

Esophagus

Swallowed food enters the esophagus and travels through it to the stomach. At the esophagogastric junction, the lower esophageal sphincter muscle

normally prevents gastric fluids from flowing into the body of the esophagus. Neurohormonal mechanisms control the pressure of this sphincter and, as discussed below, may be affected by digestion of certain foods in the small intestine (Pope 1983).

Stomach

In the stomach, food is broken down into increasingly smaller particles and compounds by mechanical, chemical, and enzymatic means. The acidic gastric secretions contain the enzyme pepsin, which converts proteins into short chains of amino acids, and gastric lipases, which, along with lingual lipase, initiate triglyceride digestion. The movement of the stomach empties liquids into the duodenum continuously while food solids are reduced to the consistency of paste. The selective rates of discharge of substances into the duodenum may be related to their caloric density (Brener, Hendrix, and McHugh 1983), to effects of neuropeptides (Morley 1982), or other hormones that control gastrointestinal function.

Small Intestine

Most digestion and absorption take place in the small intestine, as do modulation of fluid balance, orderly advancement of food residues into the colon, reabsorption of bile salts, and absorption of vitamin B_{12}. The specialized absorbing cells, enterocytes, are distinguished by numerous microvilli that greatly increase the absorptive surface area. This surface epithelium contains enzymes that split carbohydrates and small peptides. These cells also convey nutrients to the circulatory and lymphatic systems, which distribute them to the rest of the body. Digestion is primarily accomplished by enzymes secreted by the pancreas and delivered to the small intestine: amylase, which converts starch to sugar; lipase, which splits triglycerides into fatty acids and monoglycerides; and trypsin and chymotrypsin, which split proteins into amino acids and small peptides. Other substances such as secretin, which is produced by the cells of the duodenum, and pancreatic polypeptide help to control the level of intestinal acidity.

The absorption of sugars, peptides, amino acids, and fatty acids proceeds in the upper part of the small intestine (jejunum), whereas bile salts and vitamin B_{12} are absorbed in the distal portion or the ileum. By the time food residues pass the ileum, most usable food molecules have been digested and absorbed, so that only small amounts of carbohydrates (Levine and Levitt 1981), other macronutrients, and fiber are delivered to the colon.

Liver and Biliary Tract

The liver, the largest body organ, synthesizes proteins, oxidizes fat, regulates the release of glucose from glycogen, and detoxifies drugs, hormones, and other potentially deleterious substances. It also converts cholesterol into bile acids and secretes hepatic bile, which is concentrated in the gallbladder before delivery into the duodenum.

Pancreas

The pancreas has both exocrine and endocrine functions that influence digestion and nutrient metabolism. It secretes hormones such as glucagon and insulin into the blood, and digestive enzymes, principally amylase, lipase, and proteases, into the digestive tract.

Colon

The principal functions of the large intestine are to concentrate, store, and excrete food wastes. The colon contains large numbers of bacteria, which produce enzymes that act on the remaining food residues, fiber, and cells and mucus sloughed from the upper intestinal tract. The products of this bacterial digestion and fermentation include short-chain fatty acids (e.g., propionic, butyric); gases such as carbon dioxide, methane, and hydrogen; and other volatile substances (Cummings 1983). The ascending colon has a thinner muscle wall, a greater luminal volume, and a much larger population of bacteria than does the more muscular descending colon, which slows the movement of feces until they are partially dehydrated, concentrated, and ready to be expelled through the anus.

Key Scientific Issues

- Effects of Dietary Factors on Gastrointestinal Function
- Role of Dietary Factors in Intestinal Disorders
- Role of Dietary Factors in Gallbladder Disease
- Role of Dietary Factors in Other Digestive Disorders

Effects of Dietary Factors on Gastrointestinal Function

The diet must provide sufficient nutrients and energy to synthesize the rapidly renewing cells that line the gastrointestinal tract, the enzymes that digest and transport nutrients across the intestinal wall, and the regulatory neuropeptides and other hormones that control these processes. Digestive function can be seriously disrupted by inadequate nutrition as well as by

infections, toxic substances, and chronic disease. The composition of the diet can influence the rate of reproduction of bacteria in the intestine and, thus, can affect nutrient absorption. Dietary components affect the morphology and synthesis of the cells that line the digestive tract as well as fecal composition and elimination.

Malnutrition

Nutritional inadequacies can cause abnormalities of the mucous membranes of the mouth, tongue, and digestive tract. Frequent consequences of starvation and protein-energy malnutrition are an inability to absorb or digest food molecules and decreased pancreatic function (Kerndt et al. 1982). As discussed in the chapter on infections and immunity, cellular immune functions are depressed in malnutrition and starvation. Because the cells that line the digestive tract are renewed every few days, nutrient deficiencies can be reflected in ulceration, hemorrhage, or loss of resistance to micro-organisms that are usually not pathogenic.

Atrophy of the gastric and intestinal mucosa is an especially serious consequence of malnutrition. The microvilli flatten and lose much of their absorptive surface and no longer produce adequate digestive or absorptive enzymes. Food passes undigested and unabsorbed into the colon, where bacterial action induces gas production and the influx of water, inducing diarrhea and further damage to the digestive tract. These effects are most severe in young children and cause a characteristic cycle of malnutrition, infectious disease, malabsorption, and diarrhea that is common throughout the developing world (Chandra 1983; Hamilton 1985; see chapter on infections and immunity). They also occur among patients with chronic diseases that interfere with adequate nutrition, anorexia nervosa, impaired immunologic responses to certain food substances (Floch 1981), or severe microbial infections of the gastrointestinal tract (DuPont 1984).

Once the microvilli are reduced, recovery of gastrointestinal function occurs only slowly, if at all. Because food intake induces diarrhea, enteral and parenteral feeding methods that bypass the digestive tract must be employed along with immediate efforts to prevent dehydration, edema, vitamin and mineral deficiencies, and excessive accumulation of body fat (Roediger 1986).

In various conditions in which the bowel mucosa are compromised by disease, macromolecules that are normally excluded may be absorbed. These, especially protein molecules, may alter systemic immune functions (see chapter on infections and immunity).

Effects of Fiber

Most studies of the relationship of diet to gastrointestinal function have focused on the role of dietary fiber. Physiologic responses to dietary fiber occur within the entire length of the gastrointestinal tract. Dietary fibers from different plant sources have diverse chemical constituents; some are soluble and some are insoluble. The major constituents of dietary fiber are cellulose, hemicelluloses, pectins, mucilages, gums, algal polysaccharides, and lignin. Fibers from different foods have different effects on water-holding capacity, viscosity, ion-exchange capacity, binding of minerals and organic compounds, bacterial fermentation, and transit time. Food processing can alter these effects. In general, dietary fibers from many sources increase the flow of saliva, improve feelings of satiety, delay digestion and absorption, bind intestinal bile acids, increase the mass of intestinal bacteria, decrease the time stools take to pass through the bowel, and increase stool weights and frequency of elimination (Trowell, Burkitt, and Heaton 1985). Although animal studies demonstrate that fiber intake increases the length of the intestine and causes greater proliferation of mucosal cells, these effects cannot be readily distinguished from those of other dietary factors, and their applicability to humans is uncertain (LSRO 1987).

Some potential adverse effects have also been observed very infrequently with diets high in fiber, including intestinal obstruction (primarily due to gel-forming fiber); interference with absorption of calcium, magnesium, zinc, manganese, and iron; inflammation of the bowel mucosa (with certain gums); and colonic volvulus (Klurfeld 1987).

Role of Dietary Factors in Intestinal Disorders

Diseases of the gastrointestinal tract affect food consumption, digestion, absorption, and excretion. Although one might expect dietary factors to be important in preventing and treating such conditions, research in this area has not been extensive, and present understanding is limited. The dietary factors most frequently associated with gastrointestinal illnesses are alcohol (liver disease and cancer); inadequate fiber (constipation, hemorrhoids, diverticular disease, and possibly some types of cancer); fat (gallbladder disease and possibly some types of cancer); and substances such as gluten in wheat (celiac disease in genetically predisposed individuals).

Cancer

The effects of dietary risk factors such as alcohol, fat, and food mutagens and carcinogens on the causation of cancers of the gastrointestinal tract,

and the effects of substances such as fiber or vitamin A in their prevention, are reviewed in the chapter on cancer.

Celiac Disease

This genetic-immunologic disorder, also known as nontropical sprue or gluten-induced enteropathy, results from an immunologic reaction to the gluten fraction of proteins from wheat, rye, or oats (Chandra and Sahni 1981). Its symptoms may be silent and its prevalence is uncertain, but it is thought to affect about 1 in 2,500 persons in the United States (Gluten Intolerance Group 1982). When patients with this disorder ingest gluten, the cells that line the small intestine undergo atrophy, causing malnutrition, stunting of growth, and anemia. Although strict removal of gluten from the diet alleviates symptoms and restores the integrity of the intestinal mucosa, some immunologic abnormalities may persist. Neither the fundamental defect nor the genetic basis of celiac disease is understood (Cole and Kagnoff 1985).

Constipation

The National Center for Health Statistics has reported that more than 20 of every 1,000 persons surveyed state that they suffer from frequent constipation (NCHS 1986). Although constipation, defined as three or fewer bowel movements per week, can be caused by diabetes, hypothyroidism, uremia, neurogenic bowel disorders, abnormalities in the structure of the colon, rectum, or anus, and by various medications, most constipation cannot be attributed to an underlying disease. Instead, dietary intake patterns are widely presumed to cause this condition, in particular, inadequate consumption of fiber and, especially in the older person, insufficient fluid intake. The effect may vary with coarseness of bran or degree of cooking (Klurfeld 1987), but numerous studies have demonstrated that increased intake of wheat bran and other sources of insoluble fiber prevents constipation and relieves its symptoms (LSRO 1987).

Diverticular Disease

Diverticulosis occurs when diverticula, abnormal outpocketings of the intestinal wall, form in the colon and cause pain in the left lower abdomen without fever. Although diverticula may occur over extensive areas of the colon, they do not usually produce demonstrable muscle thickening, changes in intraluminal pressures, or other noticeable symptoms (Fleischner, Ming, and Henken 1964; Weinreich and Andersen 1976). A closely related disease, diverticulitis, which occurs when the outpocketings become infected, causes constipation and diarrhea, flatulence, abdominal pain, fever, and mucus and blood in the stools (Almy and Howell 1980).

Some experts believe that diverticula occur as a result of increased colonic intraluminal pressure needed to eliminate small, hard stools that form as a result of low-fiber diets (Burkitt, Walker, and Painter 1974). The idea that diverticular disease might result from inadequate intake of dietary fiber is supported by animal studies (Cello 1981); by measurements in humans of intestinal transit times, bowel motility, stool weights, and intraluminal pressures (Burkitt, Walker, and Painter 1974; Painter 1985); and by international comparisons of fiber intake and disease prevalence rates (Mendeloff 1986). Numerous dietary intervention trials have reported beneficial effects of bran and other fiber sources on pain, constipation, and other symptoms as well as on intraluminal pressures (Painter 1985; LSRO 1987). Despite concerns that these studies have not always employed adequate control groups, and despite the needs for further research to define the role of other nutrients such as fat (Manousos et al. 1985) and to identify the most effective sources and types of fiber, fiber supplements are now often used successfully in clinical management of uncomplicated diverticular disease (LSRO 1987).

Inflammatory Bowel Disease

Nonspecific inflammatory bowel disease includes two diseases of the digestive tract: (1) ulcerative colitis, characterized by rectal bleeding, diarrhea, abdominal cramping and pain, loss of appetite, and weight loss, and (2) Crohn's disease, a chronic inflammation anywhere throughout the length of the digestive tract that may induce similar symptoms along with fistulas and narrowing of the bowel (Kirsner and Shorter 1982). Their etiology and pathogenesis is unknown. Patients with these conditions can become severely malnourished. Active cases are usually treated with low-residue diets and caloric supplements (Harries et al. 1983), elemental enteral formulas (Neidich, Schussel, and Sharp 1985), or total parenteral nutrition with complete bowel rest (Ostro, Greenberg, and Jeejeebhoy 1985).

Potential food allergens, such as carrageenan thickeners and cow milk, and low-fiber diets have been suggested as possible dietary factors aggravating these diseases, but evidence to support such inferences is limited (Kirsner and Shorter 1982). Studies of the relationship of low-fiber diets to etiology or treatment of Crohn's disease (Jones et al. 1985) have yielded equivocal results, and the role of diet in inflammatory bowel disease is uncertain at this time (LSRO 1987).

Irritable Bowel Syndrome

This condition of pain, abdominal distension, and alteration in bowel habits is thought to be due to an inappropriate reaction of the intestinal wall to stress (Eastwood and Passmore 1983), motility disturbances, diet (Harvey 1985), or food hypersensitivity reactions (Bentley, Pearson, and Rix 1983). Dietary fiber has been used to treat irritable bowel syndrome with demonstrable improvements in constipation (Fielding 1985; Harvey 1985), but its effects on other symptoms have been equivocal (LSRO 1987).

Lactose Intolerance

An insufficiency of lactase, the enzyme responsible for breakdown of lactose (milk sugar) in the small intestine, can cause lactose intolerance, characterized by abdominal discomfort, pain, and diarrhea as a result of bacterial action on undigested lactose in the colon (Newcomer and McGill 1984). Lactose intolerance is not an inevitable consequence of lactase deficiency. Many lactase-deficient individuals can consume modest amounts of lactose-containing foods with little difficulty. Modification of milk and milk products by addition of lactase, or the use of fermented products such as cheese or yogurt, permits consumption of milk products by such individuals with minimal symptoms (Kolars et al. 1984; Barillas and Solomons 1987).

Genetic absence of lactase beyond the age of 5 or 6 occurs among remarkably high proportions of Asians (85 to 95 percent), Africans (50 to 99 percent), American Indians (85 to 95 percent), and American blacks (70 to 75 percent), as well as among a significant percentage of healthy Caucasians (Gray 1983). Acquired deficiencies can occur as a result of malnutrition (Kerndt et al. 1982) or disease. Reports that lactase activity is lost with aging have not been confirmed (Rosenberg and Bowman 1984).

Role of Dietary Factors in Gallbladder Disease

Cholesterol, precipitated from supersaturated bile, is the principal component of most gallstones in patients from industrialized countries. Dietary and diet-related risk factors for this condition include diabetes, obesity (Diehl et al. 1987), and excess intake of calories and dietary fat (Heaton 1985). Many of these are also risk factors for coronary heart disease.

Low-fiber diets are associated with gallstone formation. In primates, the action of fiber and other substances that bind cholesterol in the intestine is

thought to stimulate the liver to increase production of bile acids, thereby increasing cholesterol solubility (Strasberg, Petrunka, and Ilson 1976). Although cellulose, hemicellulose, lignin, and other insoluble fiber components have little effect on blood cholesterol levels, soluble components such as pectin and guar appear to reduce cholesterol levels by 10 to 15 percent (LSRO 1987). Dietary fiber has also been shown to increase the pool of bile acids in laboratory animals (Usuga et al. 1976).

In humans, large doses of wheat bran have been reported to increase bile cholesterol solubility (Pomare et al. 1976). One study has indicated that a fiber-rich diet decreases the cholesterol saturation index of bile significantly (Thornton et al. 1983). Human epidemiologic investigations, however, have not been able to distinguish associations of gallstone formation with varying levels of fiber from associations with other dietary factors such as sugar, alcohol, or other macronutrients (Smith and Gee 1979; Scragg, McMichael, and Baghurst 1984).

Role of Dietary Factors in Other Disorders of the Digestive System

Cirrhosis

The only digestive system disorder besides cancers in the 10 leading causes of death for Americans is cirrhosis (with other chronic liver diseases), and its most powerful dietary correlate is alcohol consumption. This issue is addressed in the chapter on alcohol.

Appendicitis

Studies based on epidemiologic comparisons between industrialized nations and less developed regions have associated low-fiber diets with increased prevalence of appendicitis (Segal 1985; Walker and Burkitt 1985). However, Western trends in fiber intake are not consistent with the decline in appendicitis rates during the past few decades, and not all studies have shown that patients with appendicitis consume less fiber than control subjects (Cove-Smith and Langman 1975). Nondietary factors may be more important (Barker et al. 1986). Nevertheless, reports that children 7 to 18 years of age whose fiber intake is in the upper 50th percentile have a 50 percent lower risk of appendicitis (Brender et al. 1985) warrant further investigation.

Reflux Esophagitis

This disorder, an inflammation of the lower esophagus (heartburn) caused by the backflow of stomach acids, can occur when the lower esophageal sphincter does not contract properly. Alcohol, dietary fat, and both regular

and decaffeinated coffee (Cohen 1980; Feldman et al. 1981) have been demonstrated to reduce sphincter pressure and to increase reflux. Spices and tomato and orange juices also may affect some persons.

Ulcers

Gastric and duodenal ulcers are local erosions of the mucosa that result from excessive production of gastric acid and pepsin or from decreased mucosal resistance to these substances. They may result from defects in control of secretion and motility or in synthesis of prostaglandins that either inhibit gastric acid secretion or promote secretion of bicarbonate (Johannson and Bergstrom 1982). The role of nutritional factors in the etiology of ulcers is uncertain. Speculation that refined foods reduce the buffering capacity of stomach secretions (Cleave 1975) has not been confirmed, nor is evidence sufficient to define a causal relationship for linoleic acid, prostaglandins, or peppers in peptic ulcers. The geographic distribution of duodenal ulcers is not consistently associated with fiber consumption (Tovey 1985), nor have clinical studies reported consistent effects of fiber on treatment (LSRO 1987). The observation that increased dietary fiber intake reduces rates of recurrence (Rydning et al. 1982) requires further confirmation.

The bland milk-and-cream-based Sippy diet, used in former years, is no longer recommended as treatment; it has not been demonstrated to improve symptoms better than any other method, is atherogenic, and is deficient in essential vitamins and minerals (Zucker and Clayman 1983). Today, ulcer patients typically are encouraged to consume a varied and balanced diet, taken slowly in four or five small meals a day, but limited in alcohol, coffee, and other substances that lead to discomfort and pain. Patients should avoid late evening snacking that stimulates nocturnal acid secretion (Floch 1981). Patients are also advised to avoid cigarette smoking, which accentuates symptoms and retards healing, and aspirin, which irritates the gastrointestinal mucosa and can cause mucosal hemorrhages. It should be noted that there are many current, very effective pharmacologic therapies for the management of ulcer disease.

Implications for Public Health Policy

Dietary Guidance

General Public

Dietary fat, fiber, and alcohol are significant factors associated with gastrointestinal diseases, although the great variety of these conditions makes

generalizations difficult. Because diets that contain a large proportion of calories from fat may be low in fiber, it is often difficult to separate the effects of these substances on gastrointestinal disease. Thus, current evidence on whether dietary fiber helps prevent diverticulosis is not conclusive. Similarly, whether dietary fiber helps prevent inflammatory or irritable bowel disease is uncertain. Nevertheless, evidence that dietary fiber helps treat and prevent constipation and manage chronic diverticular disease suggests the prudence of consuming diets higher in fiber and lower in fat.

The strong cause-and-effect association between excessive alcohol consumption and the development of chronic liver disease and cirrhosis (as reviewed in the chapter on alcohol) emphasizes that persons who consume alcoholic beverages should do so in moderation. Epidemiologic associations between diet and some types of gastrointestinal cancer (as reviewed in the chapter on cancer) suggest—but do not yet prove—that consuming less fat and alcohol and more fiber would help reduce the risk for these cancers.

Evidence on the role of dietary factors in the development of gastric or duodenal ulcers or reflux esophagitis is insufficient to make recommendations at this time.

Special Populations

Higher intakes of dietary fiber can prevent or relieve symptoms of constipation and chronic diverticular disease. Qualified health professionals should inform persons with these conditions about foods with relatively high fiber contents. Individuals with celiac disease should be provided with information on foods free of wheat gluten. Those with inflammatory bowel disease, irritable bowel syndrome, lactose intolerance, gallbladder disease, heartburn, and ulcers should be provided with guidance on diets appropriate to their conditions.

Nutrition Programs and Services

Food Labels

Evidence related to the role of dietary factors in gastrointestinal disease suggests that food manufacturers should include on package labels information about nutritional content of the food, especially for fat and carbohydrate components (and including fiber components to the extent permitted by analytical methods).

Food Services

Evidence related to the role of dietary factors in gastrointestinal diseases suggests that food services should include provisions for adequate intake of high-fiber and low-fat foods.

Food Products

Evidence related to the role of dietary factors in gastrointestinal diseases suggests that the public would benefit from additional products that are low in fat and calories and higher in fiber.

Special Populations

Persons with gastrointestinal diseases should receive counseling and assistance in developing appropriate diets for their particular condition. Qualified health professionals should provide appropriate training and enteral or parenteral nutritional support to persons with conditions that prevent food ingestion, cause malabsorption, or impair bowel function.

Research and Surveillance

Research and surveillance issues of special priority related to dietary factors affecting gastrointestinal function and diseases of the gastrointestinal tract should include investigations into:

- The prevalence of gastrointestinal diseases among the population.
- The influence of dietary factors such as specific dietary fibers, fat, and calories on development and function of the digestive tract.
- The influence of dietary factors on the development and release of enzymes and hormones that affect gastrointestinal function.
- The role of intestinal flora on nutrient bioavailability.
- The most effective nutrient-related interventions to improve the recovery of intestinal function following episodes of malnutrition or disease.
- The mechanisms by which dietary fiber may work in the prevention and treatment of bowel cancer, appendicitis, diverticular disease, gallbladder disease, and other gastrointestinal conditions.
- The identification of specific dietary factors that might influence the causation, prevention, and treatment of celiac disease, inflammatory and irritable bowel syndromes, ulcers, and other gastrointestinal disorders.
- The most effective means to achieve dietary counseling to help alleviate gastrointestinal disorders.

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Chapter 11

Infections and Immunity

There are sure to be two prescriptions
diametrically opposite. Stuff a cold and
starve a cold are but two ways.
Henry David Thoreau
(1817–1862)
A Week on the Concord and Merrimack Rivers, "Wednesday"

Introduction

Interactions among nutrition, infections, and immune disorders have important implications for individual, public, and economic health in this Nation and around the world. In the past decade, substantial advances in scientific knowledge have occurred in the study of malnutrition, the determinants of infection, and the components and functions of the immune system. Nevertheless, many details of this complex three-way interaction remain unclear. This chapter reviews the physiologic and immunologic mechanisms that protect people against illness, nutrition's role in the proper function of these mechanisms, malnutrition's negative effects on immune function, infectious illnesses and their detrimental effects on an individual's reserves, food allergies that cause adverse reactions, and the problems of food-associated illnesses and other diseases.

Historical Perspective

Famine and pestilence have been closely associated throughout recorded history. Ancient scriptures in India noted the apparent relation of diet and the ability to resist disease (Chandra 1983). Episodes of plagues, for example, have been recorded throughout history, although the influence of malnutrition on these outbreaks is not certain. During wars, dysentery, typhus, and smallpox were leading causes of death; malaria, diarrheal diseases, typhoid, measles, and pneumonia also caused many deaths. Poor nutrition and contaminated food invariably accompanied episodes of infectious disease. Although the impact of malnutrition on such infections is difficult to determine, malnutrition may predispose to or alter the severity of infection, and most infections aggravate malnutrition (Beisel et al. 1977; Alexander and Stinnett 1983).

Modern public health concepts concerning sanitation, water purification, good nutrition, and immunization have helped eliminate many infectious diseases in the United States. By the early 1900's, the importance of adequate nutrition and vitamins was recognized. For many years before specific antimicrobial therapy became available, a combination of bedrest and wholesome foods was commonly used with varying effectiveness to treat subacute and chronic infections such as tuberculosis. The introduction of antibiotics in the 1940's led to the control of many infectious illnesses, especially those caused by bacteria.

Vaccines have now made possible the control or elimination of many infectious diseases. For example, live-virus vaccines against measles, mumps, and rubella, first available in the 1960's, have dramatically improved the control of these diseases. Other once commonplace infections, such as cholera, typhoid fever, tetanus, rabies, poliomyelitis, diphtheria, and pertussis, have been virtually eliminated in the United States or drastically reduced by immunization programs and improved environmental and social conditions (Braude 1985). Smallpox was the first communicable disease to be eradicated worldwide, with the last known indigenous case occurring in October 1977 in Somalia (Chin 1980). Nonetheless, nutritional status can affect the immune response stimulated by vaccination; hence, especially in developing countries, nutritional and vaccination programs are essential components of infectious disease control strategies.

Food-borne microbial illness is a significant issue in infections. Since the 1906 enactment of the Wiley Act, the first pure food and drug law, much legislation has been passed to protect the food supply from infectious micro-organisms. Federal and State governments conduct or promote many activities to prevent food-borne diseases from threatening the Nation's health: they establish safety standards, inspect food establishments serving the public, train food handlers and food sanitarians, certify milk and shellfish shipped interstate, inspect meat and poultry, monitor outbreaks of disease, and act to eliminate the sources of food-borne microbial illness (Hartman, Porter, and Withnell 1981). To minimize or eliminate micro-organisms from the commercial food supply, the food industry uses a variety of processing methods and preservatives. Occasionally, a serious breach of safety in a commercial plant or process has resulted in a serious outbreak of food poisoning.

Today, and in the past, many infections occur with greater severity and some infections occur more frequently in malnourished persons than in well-nourished people. Yet, as will be discussed, many aspects of the relationships of malnutrition to immune responses and to susceptibility to

infection are still poorly understood. Although malnutrition due to prolonged food deprivation may increase the risk for infection, malnutrition is more likely to be a result than a cause of an infectious or other serious disease. During the prolonged starvation suffered by inhabitants of the Jewish ghetto in Warsaw during World War II, for example, almost 500 deaths were attributed solely to simple starvation, but many more deaths occurred because of malnutrition in combination with tuberculosis, typhus, or other infectious diseases. Not surprisingly, most of the population showed clinical evidence of poor immune function (Winick 1979).

Even now, despite many medical advances, the combined effects of infection and malnutrition constitute the most common cause of death among children throughout the developing world (Chen 1983), and they remain as major problems among premature and low birth weight infants—and among severely ill hospitalized patients—in the United States (Chandra 1983; Keusch 1984).

The history of food allergies and intolerances is less well known. Hippocrates (460–370 B.C.) and Galen (131–210 A.D.) reported a relationship between consumption of specific foods and allergic digestive and skin symptoms, specifically describing reactions to ingestion of cow and goat milks, respectively. Systematic observations of food allergies began to appear in the 20th century, and recently, the literature in this field has grown rapidly (AAAI 1984). Diet may also cause disease by transmitting infectious microorganisms or toxic substances that enter or are contained within the natural foods.

Significance for Public Health

Tremendous progress has been made in infectious disease control during the past century, yet, except for smallpox, infectious diseases remain a serious public health problem. In 1982, for example, over 25,500 tuberculosis cases were reported, along with hundreds of thousands of salmonellosis and hepatitis cases and millions of cases of sexually transmitted diseases, hospital-acquired infections, influenza, and other acute respiratory illnesses (CDC 1983). In the past decade, new varieties of infectious disease (e.g., legionnaires' disease, toxic shock syndrome, AIDS, viral diarrheas) have emerged, often with fearsome consequences. The ultimate conquest of infectious diseases, therefore, is far from over.

In the developing world, where food and water supplies are often contaminated with micro-organisms, food-borne diseases take their highest toll. In 1980, more than 1 billion cases of diarrheal diseases were estimated to

occur in children under age 5 (Chen 1983). Contaminated food and water were largely responsible for the high rates of infant and childhood mortality recorded among developing populations.

Despite high standards of sanitation in the United States, the incidence and costs of food-associated disease are considerable (although assessments of the magnitude of the problem vary widely due to difficulties with data collection and case reporting). In the United States in 1982, only 656 outbreaks of food-borne disease were reported to the Centers for Disease Control (CDC 1983). However, published estimates range from 24 to 81 million cases per year of gastrointestinal illness due to contaminated food or person-to-person spread (Archer and Kvenberg 1985). In cases in which the causes were confirmed, bacterial pathogens accounted for approximately two-thirds of the outbreaks and chemical agents for about one-fifth. Parasitic and viral outbreaks occur more infrequently in the United States. Although an outbreak is defined as an incident in which two or more persons experience a similar illness after eating a common food or in which epidemiologic analysis implicates food as a source of illness, a single case of botulism or chemical poisoning also constitutes an outbreak (CDC 1985). The discrepancies in estimates are due to limitations in the available data. The economic costs of food-associated illness have been estimated to range from $1 billion to $10 billion annually for direct medical costs, lost wages, and reduced industrial productivity (Todd 1984). A more recent analysis has placed the economic costs as high as $23 billion, excluding costs to industry (Archer and Kvenberg 1985).

Because gastrointestinal, skin, and respiratory symptoms of food allergies and intolerances resemble those caused by many other conditions, the true incidence of these food-related problems has been difficult to establish. Unexplained symptoms are often attributed to food allergies when no other reason can be found or when the symptoms improve after the offending food is removed from the diet. The percent of food allergy cases confirmed in double-blind food challenges is usually quite low. Estimates of the incidence of cow milk allergy have ranged from 0.3 to 7.5 percent, with higher rates reported for infants than for adults. Rates as high as 25 percent have been reported in individuals who had eczema as infants or asthma in childhood. The percentage of the population that reacts adversely to foods or food components is unknown (AAAI 1984).

Scientific Background

Effects of Malnutrition

Simply defined, malnutrition means poor nutrition, but malnutrition may take many forms, including excesses as well as deficiencies of body nutrients. Both deficits and excesses may be generalized, involving multiple nutrients, or they may be limited to one, or only a few, of the many nutrients the body needs to maintain normal health and body composition. Most forms of malnutrition appear to make the human body more susceptible to infectious diseases. Obesity has been linked with increased susceptibility to infection only rarely. Malnutrition is a far more common association (Edelman 1981).

Many forms of malnutrition also have detrimental effects on immune system function (Suskind 1977; Stinnett 1983). These adverse influences of malnutrition depend, to a large degree, on the severity of the nutritional deficiency (Scrimshaw and Wray 1980). Most reported examples of the interaction between malnutrition and infection deal with severe generalized malnutrition, which is also called cachexia. Dry (nonedematous) cachexia has also been termed marasmus, whereas wet (edematous) cachexia is known as kwashiorkor. The terms protein-calorie or protein-energy malnutrition are widely used in medical literature to denote generalized undernutrition, but these terms fail to indicate that most clinical forms of generalized malnutrition involves multiple nutrient deficiencies as well as protein and other sources of metabolizable energy. In contrast to severe generalized malnutrition, far less is known about the effect of single nutrient deficiency (e.g., vitamins, minerals, trace elements, amino acids, and unsaturated fatty acids) on the immune system function and other host defensive mechanisms (Beisel et al. 1981; Beisel 1982a; Chandra 1988).

Effects of Infectious Disease

Infectious agents include a wide variety of micro-organisms such as bacteria, viruses, rickettsia, fungi, and parasites. When an infectious agent invades a host, the results can range from no disease to an acute or chronic illness. Whether a clinically apparent infection develops depends on the virulence (ability to cause serious illness) and dose of the invading micro-organism, the route by which the micro-organism enters the body, and the

host's ability to resist infection. This ability is influenced by age, sex, heredity, previously acquired immunity, the presence or absence of other disease processes, and overall nutritional status. Depending on its severity, generalized or single nutrient malnutrition can adversely affect the structure and function of various body cells and tissues. These deficiencies can secondarily impair the adequacy of many non-specific host defense mechanisms (Suskind 1977). The weakening of immunologic and nonspecific defenses can lead, in turn, to a more severe illness (Scrimshaw et al. 1986). Infectious diseases and immune functions are intimately linked to each other as well as to nutritional status, and each of these variables are interactive (Beisel 1982b, 1984; Chandra 1983). Although each species of virulent bacteria, virus, parasite, or other disease-causing micro-organism produces a different, but characteristic, illness in humans, the nutritional consequences of most acute infectious diseases are quite similar. These consequences occur as a result of fever, loss of appetite, vomiting and diarrhea, and other symptoms of generalized infection. The overall increase in body metabolic rates and the reprioritization of many biochemical pathways during acute infections combine to increase the body's requirements for nutrients as well as simultaneously to increase body losses of nutrients (Beisel 1985). These nutritional costs of infection occur at a time when food intake is reduced by anorexia. Thus, the magnitude of nutrient depletion often depends more on the severity and duration of illness than on the species of infecting organism.

Most infections stimulate protective immune responses; however, some responses are harmful. Examples are kidney inflammation (Bright's disease) or rheumatic fever after some streptococcal infections and heart or thyroid inflammation after certain viral infections. Abnormal function of the immune system increases the chance for infections that lead to malnutrition. As will be discussed later, malnutrition depresses the immune system and makes infected people more susceptible to still other infections (Scrimshaw, Taylor, and Gordon 1968). Malnutrition, depressed immunity, and infection thus interact in a cyclical downhill spiral that can eventually lead to death (Mata 1975; Keusch 1984).

Nonspecific Host Defense Mechanisms

Nonspecific defenses include both active and passive components. Passive mechanisms (such as normal microbial flora, skin and mucous membranes, and body surface secretions) help prevent micro-organisms from entering body tissues. For example, surface secretions and coughing cleanse the lungs and prevent microbial entry, as does the production of mucus in the intestine and normal intestinal motion. Many of these passive components are impaired by inflammation and in severely malnourished patients.

The more active forms of nonspecific host defenses include the ability of body cells to kill micro-organisms or to release substances that aid in eliminating them. These defenses are also impaired during malnutrition (Beisel 1985; Kauffman, Jones, and Kluger 1986). For example, whenever an infection begins, acute-phase responses are triggered by the release of interleukin-1 (IL-1) and other substances from body cells (Kluger, Oppenheim, and Powanda 1985; Dinarello 1988; Movat et al. 1987). IL-1 is a hormone-like mediator produced by activated blood monocytes and tissue macrophages. In addition to its ability to stimulate the immune system through its action on lymphocytes, IL-1 initiates numerous metabolic and physiologic changes that make up the nonspecific but active host defense mechanisms known as acute-phase responses. IL-1 acts on the brain (Breder, Dinarello, and Saper 1988) and on the liver, islet of Langerhans cells in the pancreas, bone marrow, contractile cells of skeletal muscle, circulating blood granulocytes, vascular endothelium, intestinal mucosa, and adipocytes of fat depots (Beisel 1985; Dinarello 1988). Another defense mechanism is the complement system, which includes about 20 proteins that circulate in inactive forms in the blood. When an infection occurs, these proteins are activated to produce inflammatory responses, membrane lysis, and other effects that cause bacterial death (Claman 1987). These nonspecific defense responses are also impaired by malnutrition, as will be discussed later in this chapter.

Cellular and Humoral Immunity

The immune system protects the body against infection by producing specific substances in response to foreign materials called antigens. Immunity to specific antigens occurs through the cooperative interactions of two subsets of blood cells, T lymphocytes and B lymphocytes, that give rise to cell-mediated (cellular) and antibody-mediated (humoral) immunity, respectively (Claman 1987).

Cell-mediated immunity is provided largely by thymus-dependent T lymphocytes. There are several subtypes of T lymphocytes, each with specific functions. Helper and suppressor T lymphocytes regulate the quantities of antibodies produced, while killer T lymphocytes, which respond selectively to foreign material, can search and destroy internally infected, transplanted, or malignant body cells. Each T lymphocyte class responds to different types of infection or to different forms of malnutrition (Beisel 1982a, 1984). Mature lymphocytes in blood can be classified by their function and by unique marker molecules on their surfaces.

Humoral immunity is provided by antibodies, which are specific immunoglobulin (Ig) proteins produced by B lymphocytes in response to specific

antigens. Antibodies of various classes, such as IgM, IgG, or IgA, are of major importance in preventing or terminating infections of many different types, and they also neutralize toxins of bacterial origin, such as those produced by diphtheria or tetanus bacilli (Braude 1985). This protection can be long term. Exposure to a specific antigen, either through an infection or vaccination, stimulates the immune system to produce antibodies.

Preformed, concentrated antibodies against specific antigens and contained in serum (e.g., antiserum or antitoxin) can be administered therapeutically or prophylactically to provide direct immediate short-term passive immune protection. For example, antitoxin is used to treat botulinism, and hyperimmune globulin is given to help prevent hepatitis. In addition to these protective functions, harmful immune responses sometimes can occur as a consequence of circulating antibodies, as in allergies or autoimmune diseases.

Methodological Issues

Despite recent advances in immunologic methodology that permit identification of pathogens and various subsets of lymphocytes, clinical assessment of immune function is still quite difficult and uncertain, especially under field conditions. Immunologic responses to antigens may take months to develop. Skin testing for immediate and delayed reactions to antigens is not specific enough to accurately assess infection or immunologic function in all situations (Miller 1978). Adequate methods to evaluate the immunologic status of body surface secretions, especially within the gastrointestinal tract, have not yet been developed. Although the functional capabilities of various types of immune system cells can now be evaluated in specialized laboratories, these studies require exacting techniques to transport the blood sample, to isolate the cells, and to maintain them in culture throughout the testing. As a result of these difficulties, few reliable data have been obtained in human subjects on the influence of individual essential nutrients on specific immune system functions or on the mechanisms of interaction between nutrition and immunity (Chandra 1981; Solomons and Keusch 1981). In addition, as with other studies in diet and health, the use of animal models for the study of infection and malnutrition presents problems. Animal species differ from each other and from humans in their nutritional requirements, rates of growth, and susceptibility to infections (Chandra 1983). The amounts of protein in a diet, for example, and the duration of feeding, the age, and the species of animal studied can all influence immune responses (Jose and Good 1973).

Key Scientific Issues

- Effects of Malnutrition on the Immune System
- Effects of Infection on Nutritional Status
- Role of Diet-Immune System Relationships in Food-Associated Illnesses

Effects of Malnutrition on the Immune System

Role of Generalized Malnutrition

Throughout the world, generalized malnutrition is a common cause of acquired, correctable immune system dysfunction (Chandra 1983; Suskind 1977; Stinnett 1983). Deficits in both calories and protein tend to be closely linked during generalized malnutrition, and it has not been possible to separate their effects on the immune system. Infectious diseases are extremely prevalent in children with either the marasmus or kwashiorkor forms of generalized malnutrition (Brown et al. 1981). The impact of malnutrition on infectious illnesses is not clearly evident when the malnutrition is mild.

Generalized malnutrition increases both the likelihood of contracting an infectious disease and the severity of infections such as tuberculosis, whooping cough, herpes, bacterial and viral diarrheas, as well as systemic parasitic infections. Severe malnutrition suppresses a person's ability to generate fever, inflammatory responses, or leukocytic reactions (Garre, Boles, and Yovinov 1987). In persons with severe, prolonged diseases, generalized malnutrition increases susceptibility to all infections, but especially those caused by opportunistic organisms that do not usually cause disease in healthy individuals (Baron 1986).

Malnutrition's effects on infection may be synergistic, antagonistic, or show no apparent interaction. In synergistic interactions, infections are made worse by malnutrition, whereas antagonistic interactions occur when an infection is milder than would be expected in a malnourished host. Although most bacterial infections become more severe with malnutrition, nutrient deficiencies have attenuated some viral infections (Scrimshaw, Taylor, and Gordon 1968). The generalized weakening of host defensive mechanisms, including those of the immune system, can explain synergistic interactions. Antagonism occurs because host cells and invading

micro-organisms compete for available nutrients and because host-immune reactions that normally produce disease symptoms are suppressed. Viruses, for example, must use metabolic processes of the host cell to multiply, and nutritionally deprived cells may not contain the nutrients needed for viral proliferation (Beisel 1982b). Parasites such as malaria may also be less able to multiply when the patient is malnourished (Murray and Murray 1977; Solomons and Keusch 1981). Tuberculosis may be acutely exacerbated by feeding starving people; the body's inflammatory reaction to the tuberculous bacillus, which was suppressed by starvation, may flourish after feeding and cause symptoms, particularly if the patient has not received antituberculosis drugs (Murray and Murray 1977).

Malnutrition due to starvation produces different effects on metabolism and body composition than those due to illness or injury, and this difference profoundly affects susceptibility to infection (Beisel 1987). During uncomplicated starvation, extensive metabolic changes serve to conserve body protein stores. Metabolic rate is reduced, nitrogen is conserved, and the use of body fat as a source of energy is increased. Because protein is saved, immune system competence and resistance to infection persist until starvation is greatly advanced (Kerndt et al. 1982).

In contrast, the extreme body wasting (cachexia) caused by acute illness or injury is associated with rapid protein breakdown and a concomitant weakening of resistance mechanisms. Metabolic rate and loss of body nitrogen increase, and large quantities of gluconeogenic amino acids are metabolized to produce glucose; branched chain amino acids are oxidized in muscle cells to produce energy; and the metabolic destruction of tryptophan and phenylalanine is accelerated (Beisel 1985). Such diversions of free amino acids reduce their availability for the synthesis of new proteins. The adequacy of immune functions and other host defense mechanisms ultimately depends on the ability of body cells to synthesize a variety of new proteins. But protein synthesis is impaired when the supply of free amino acids is inadequate or when an imbalance exists among the essential free amino acids. Thus, when overwhelming disease or trauma causes severe generalized malnutrition, the resulting deficits of body protein and free amino acids can be linked directly to a depression in host resistance (Beisel 1985). In short, the metabolic consequences of fever and loss of appetite lead to poor nutritional status, deficits in immune system competence, and an increased susceptibility to infectious disease within a relatively short time period (Beisel 1984).

Severe malnutrition due to any cause will impair cell-mediated immunity and may affect immunity mediated by antibodies circulating in the blood and secreted by mucosal surfaces (Suskind 1977; Chandra 1983; Stinnett 1983; Gershwin, Beach, and Hurley 1985; Watson 1984). Patients with severe generalized malnutrition consistently exhibit atrophy and other defects of the lymphoid tissues of the immune system. The total number of lymphocytes is reduced, with the greatest losses occurring among T lymphocytes (Suskind 1977). These abnormalities lead to poor T cell function, diminished ability to reject grafted tissue, and a reduction in secretion of lymphokines and other anti-infective substances.

Even with severe malnutrition, however, total antibody production remains normal and may even be accelerated if infection is present (Chandra 1983). The capacity to produce or to secrete the immunoglobulin IgA into the fluids that cover mucosal surfaces of the body is diminished, however, and specific antibody responses to new vaccines or other new antigens are clearly depressed despite maintenance of nonspecific blood immunoglobulin levels.

When infections occur in malnourished patients, concentrations of individual components of the complement system tend to decline rather than to show a typical infection-induced increase (Suskind 1977; Keusch and Farthing 1986). Complement system deficiencies depress immune system function (Watson 1984) and increase the risk of bacterial infections (Chandra 1983).

With severe generalized malnutrition, the production and mobilization of phagocytes (the cells of the immune system responsible for ingesting microbes or other cells and foreign materials) are often reduced in number. Phagocytic cell function is also impaired, including their responses to stimuli, their participation in inflammatory processes, and their ability to ingest and kill invading micro-organisms (Beisel 1984; Keusch 1984; Garre, Boles, and Yovinov 1987).

Severe generalized malnutrition impairs tissue integrity and causes damage to epithelial surfaces, loss of respiratory tract cilia, and reduction of mucosal secretions. The bacteria in the intestine may be altered, and the normally sterile upper small bowel may become colonized. The stomach's secretion of hydrochloric acid is reduced (Kerndt et al. 1982). All of these defects in the nonspecific defense mechanisms can increase the risk for infection by pathogenic micro-organisms. Dietary replenishment to correct the identified deficiencies can resolve these problems.

Role of Specific Dietary Factors in Immunity

Certain nutrients described in the following sections are particularly important to immune system function.

Protein. Proteins in food provide the body with essential and nonessential amino acids as well as contribute 4 kcal/g to the body's overall energy needs. An adequate intake of animal protein, or certain mixtures of vegetable proteins in the diet, will yield the balance of free amino acids necessary to allow for an optimal synthesis of new body proteins, including those that maintain immune functions. If dietary protein intake is excessive, the unneeded amino acids are broken down (deaminated), and their carbon skeletons are either diverted into energy generation or stored as fat. On the other hand, a prolonged deficit in protein intake will contribute to generalized undernutrition.

There is a normal continuous turnover of proteins in the body, with both the catabolism and anabolism of individual body proteins taking place concurrently. Anabolic protein synthesis predominates during periods of active body growth and during convalescence from illness if protein intake is adequate. Both the anabolic and catabolic processes are accelerated during acute infectious illnesses, but catabolic activity predominates. The role of protein and amino acid metabolism in body defensive reactions will be described in subsequent portions of this chapter.

Carbohydrate. Dietary carbohydrate serves chiefly as a source of metabolic energy for the body. Like excessive dietary protein, excessive carbohydrate in the diet will be diverted into fatty acid molecules and deposited in body fat depots. During infection, most of the extra energy needed to produce hypermetabolism and fever comes from the oxidation of glucose. Various hormonal and metabolic stimuli accelerate the manufacture of new glucose (chiefly within the liver) during infection. If the body is unable to sustain the gluconeogenic process, severe hypoglycemia may occur as a terminal complication of infection. This problem is most likely to develop during neonatal sepsis, gram-negative septicemia, or severe hepatitis.

Fats. Dietary fats contribute about 9 kcal/g to body energy needs as their principal metabolic function. In addition, a small quantity of essential unsaturated fatty acids in the diet is required for maintaining the integrity of the exterior surface membrane of body cells and for mounting primary and secondary antibody responses (Chandra 1981). However, a dietary excess of polyunsaturated fatty acids, such as linoleic acid, can suppress cell-mediated immune functions in mice (Mertin and Hunt 1967). The greatest

immune suppression in experimental animals seems to occur when the excess polyunsaturated fatty acids have the highest numbers of unsaturated carbon:carbon bonds per molecule (Beisel 1982a).

Fatty acid-derived mediators of inflammation are important in allergic and other inflammatory diseases. For example, asthma patients were put on diets enriched with high- and low-dose eicosapentaenoic acid (EPA) for 8 weeks (Payan et al. 1986). When leukocytes from study patients were examined, it was found that those taken from patients on the high-dose regimen had inhibition both of white cell migration to sites of inflammation (chemotaxis) and the generation by white cells of potent chemical mediators (leukotrienes) of the inflammatory component of chronic asthma when compared with those on the low-dose regimen. However, the clinical role of EPA is still open to question because EPA at either dose did not affect the clinical course of asthma.

There is little doubt that excess quantities of host lipids, occasioned by high-fat, high-energy diets or by lipid infusions, can initiate changes in immune function. However, solid evidence directly linking obesity, high-fat diets and hyperlipidemia with the outcome of human infection is meager (Edelman 1981). The incidence of only one category of infections, postoperative wound infections, is clearly increased in obese patients, and the mechanisms of this effect may be other than nutritional. Moreover, there are no convincing data in humans on the interaction of obesity, body lipids, and autoimmune diseases (Edelman 1981).

Vitamins and Minerals. As discussed throughout this report, deficiency diseases such as scurvy (from vitamin C deficiency), pellagra (niacin deficiency), beriberi (thiamin deficiency), and anemia (iron deficiency) are often associated with decreased resistance to infection. Of special recent interest, for example, are the findings that adequate vitamin A protects against complications of measles (Anonymous 1987) and is associated with overall improvements in mortality rates (Sommer et al. 1986). Subclinical deficiencies of vitamins and minerals may also affect host defense mechanisms (Beisel et al. 1981; Beisel 1982a; Good, Hanson, and Edelman 1982). The lack of information about threshold values at which a nutritional deficit might impair the immune system, however, makes research in this area difficult.

Deficiencies of zinc, pyridoxine, iron, folate, vitamin B_{12}, choline, or methionine have been associated with reduced function of T cells (Good, Hanson, and Edelman 1982; Chandra 1985). Zinc is required for adequate

function of T lymphocytes and cell-mediated immunity in several animal species (Fraker, Caruso, and Kierszenbaum 1982; Beisel 1982a). In humans, persons with acrodermatitis enteropathica, an inherited inability to absorb zinc, have severe immune system failure, widespread infections of skin and mucosa, and early death. When instituted early enough, correction of body zinc deficits in these patients has been followed by functional recovery of the immune system, elimination of infections, and a return to good health (Allen, Kay, and McClain 1981; Castillo-Duran et al. 1987). When volunteers ingested excessive zinc, however, the phagocytic functions of neutrophils and the response of lymphocytes to mitogens were impaired (Chandra 1984).

Deficiencies of ascorbic acid, iron, vitamin B_{12}, folate, and zinc all impair neutrophil function, although in different ways (Good, Hanson, and Edelman 1982). Although deficiency of vitamin C blocks the mobility of neutrophils, clinical trials have failed thus far to demonstrate that massive daily doses of vitamin C either prevent or cure the common cold or that it improves immune system functions beyond normal (Beisel 1982a; Gershwin, Beach, and Hurley 1985).

As discussed in the chapter on anemia, iron deficiency has been associated with increased incidence of certain infections (Chandra 1981), perhaps because it impairs the function of peroxidase enzymes and leads to deficits in the production of free oxygen radicals and hydrogen peroxide that can kill ingested bacteria (Beisel 1982a; Stinnett 1983).

Age-Related Issues

Infants. As discussed in the chapter on maternal and child nutrition, prematurity and low birth weight increase the risk for infectious disease, other complications, and consequent mortality. The fetus receives immunoglobulins from the mother by selective transfer across the placenta, but infants born to undernourished mothers typically have abnormally low antibody concentrations in plasma once autonomous antibody production begins. In developing countries where standards of sanitation are poor and children are exposed to multiple infections, children may in fact demonstrate a precocious rise in antibody concentrations compared with adult values (Chandra 1983). Nevertheless, the infant's immune system can be easily overwhelmed by gastrointestinal infections. Such infections prevent intake, absorption, and utilization of food energy and nutrients and initiate the debilitating cycle of infection, diarrheal disease, malnutrition, and, often, death.

Breastfeeding provides an infant both with nutrients and some degree of immunity against infections (Chandra 1979; Welsh and May 1979). Even under conditions of poor sanitation and poverty, breastfeeding protects an infant and fosters normal growth (Mata 1975). Once an infection is established, breastfeeding provides additional protection against its severity (see, for example, Victora et al. 1987). Such protection has been observed in studies in the United States (Duffy et al. 1986), although its overall clinical significance in industrialized societies is uncertain (Leventhal et al. 1986; Bauchner, Leventhal, and Shapiro 1986). In bottle-fed infants, unsanitary conditions, use of contaminated water in preparing bottles, and the lack of maternal antibodies all contribute to infections, especially diarrheal illnesses (see chapter on maternal and child nutrition).

Older Persons. The extensive anatomical and physiologic changes that characterize aging are reviewed in the chapter on aging. One change is a gradual senescence of some—although not all—components of the immune system. Studies in experimental animals and in humans reveal a gradual atrophy of the thymus gland along with decreases in the numbers of T lymphocyte helper/inducer cells and in cell-mediated immune functions (Katz 1982). Such changes are similar to those observed in malnutrition. As discussed in the chapter on aging, distinguishing such age-related physiologic changes from those due to malnutrition in older persons has not yet been possible. Progressive impairment of cellular immunity with age might cause the older population to have more infections than younger people of equivalent nutritional and health status, and if malnutrition is responsible for depressed immune functions, improved diet should restore such functions and improve disease resistance. Research has not yet resolved these issues, and the relationships among malnutrition, infections, and changes in immune system functions in elderly persons have yet to be clarified (Thompson, Robbins, and Cooper 1987).

Effects of Infection on Nutritional Status

As noted earlier, severe infections can compromise nutritional status through a variety of mechanisms: hypermetabolism, appetite depression and reduced food intake, decreased intestinal absorption of nutrients, altered nutrient metabolism, increased nutrient excretion, and internal diversion of nutrients (Beisel 1984). Additional nutritional losses occur with vomiting, diarrhea, sweating in fever, or loss of sputum in pneumonias. Liver damage caused by hepatitis can disrupt nutrient metabolism. Antimicrobial drugs may affect nutrient digestion and absorption or alter intestinal flora (Braude 1985). Many of these losses can be overcome by improved feeding methods (Siegel 1987).

Hypermetabolism

Acute-Phase Responses. Acute-phase responses during acute infectious illnesses are of major nutritional importance because they involve many body functions and because they speed up the consumption of nutrients in the body and deplete nutritional stores (Beisel 1985). They result in general symptoms and signs of illness, including fever, loss of appetite, increase in numbers of white blood cells, heightened body metabolism, muscle pains and breakdown of skeletal muscle protein, use of some free amino acids from this breakdown for generating energy rather than for synthesizing new protein, altered metabolism of sugars and fats, redistribution of trace minerals, and stimulation of the immune system. The nutrient costs of these acute-phase responses depend on the severity and duration of the infectious process, the prior nutritional status of the patient, and the effectiveness of therapeutic interventions (NRC 1976; Beisel et al. 1977).

Acute-phase responses to infection are initiated by a common mechanism—the release of IL-1 and other hormone-like mediators from cells. The nutritional consequences of this release are similar regardless of the infecting organism. These include an increase in secretion of insulin and glucagon from pancreatic islets and alterations in the metabolism of carbohydrate, fat, and protein (Kluger, Oppenheim, and Powanda 1985; Dinarello 1985; Movat et al. 1987) that increase use and loss of body nutrients (Keusch 1984).

In some infections, especially those caused by gram-negative bacteria, body macrophages are stimulated by lipopolysaccharide toxins to release another hormone-like mediator. This mediator was initially termed cachectin, although it has proved to be tumor necrosis factor (TNF). Because TNF inhibits the membrane-bound enzyme lipoprotein lipase, it contributes to the accumulation of triglycerides in the plasma during gram-negative sepsis as well as to other alterations in body lipid metabolism. TNF also plays a role in the development of hypotensive shock during sepsis. Experimental evidence shows that TNF and IL-1 act synergistically, thereby amplifying the loss of body nutrients that lead to cachexia (Tracey et al. 1988).

Fever. Fever causes metabolic rates to increase about 7 percent for each increase of 1° F. This hypermetabolism affects all cells of the body. In addition, phagocytic cells increase their rate of oxygen consumption whenever they take up bacteria or other particles. Because this extra energy comes largely from amino acid metabolism (Siegel 1987; Bell et al. 1983), the body stores of muscle protein amino acids and nitrogen are rapidly depleted (Beisel 1985). Loss of nutrients may also occur through sweating

associated with fever. Controlling the infection minimizes fever and reduces losses of body nutrients.

Loss of Appetite. Severe loss of appetite is a common symptom during most infectious diseases and often leads to an almost total cessation in food consumption. Based on studies in laboratory animals, the effects of IL-1 and other monokines on the appetite centers in the brain may cause this anorexia (Kluger, Oppenheim, and Powanda 1985; Dinarello 1988).

Reduced Absorption. Vomiting, diarrhea, altered bowel motility, and infection-induced decreases in synthesis of intestinal enzymes further reduce the absorption of nutrients from the intestinal tract. Antibiotics and other medications also modify intestinal absorption and motility, as discussed in the chapter on drug-nutrient interactions.

Altered Metabolism

Protein. Some proteins break down (catabolize) and others are formed during acute-phase reactions, but the catabolic aspects predominate and lead to clinically evident losses of muscle mass and body nitrogen (Rennie and Harrison 1984). IL-1 induces the release of amino acids from contractile proteins (Kluger, Oppenheim, and Powanda 1985) and the preferential oxidation of branched-chain amino acids (leucine, isoleucine, valine) to provide metabolic energy in muscle. Alanine, synthesized in muscle from glucose and components of the branched-chain amino acids, is then taken up by the liver and used to manufacture glucose.

Despite the accelerated input into plasma of free amino acids from muscle, concentrations of most free amino acids are lowered because of increased use of body cells and reduced dietary intake due to loss of appetite. These free plasma amino acids are used to manufacture the new body cells and proteins needed for defense against infection. As described previously, the liver takes up large amounts of free plasma amino acids during infection and uses them to synthesize glucose and to make compounds that contribute to nonspecific host defenses (Powanda and Canonico 1981).

Excess nitrogen derived from these processes is metabolized to urea and excreted in urine, thereby accounting for most of the nitrogen lost during infection. Infection-induced nitrogen losses can be quite extensive. For example, malaria, which was once used as a form of therapy for neurosyphilis (Howard, Bigham, and Mason 1946), has caused extensive losses of body nitrogen and advanced cachexia in as little as 30 days. Even brief, self-limited viral infections and brief fevers induced by bacterial infections

can cause sizable losses of nitrogen (Beisel et al. 1977); although protein-nitrogen losses of mild or promptly treated infections do not lead to cachexia, they suggest that large losses of body protein can occur in even a week-long infection accompanied by fever. The magnitude of body protein catabolized can be quantitated roughly by the excesses of total nitrogen in the urine. The breakdown of contractile protein in skeletal muscle can be estimated by the amount of 3-methyl-histidine excreted in urine (Beisel 1985).

Although the catabolism of body proteins is a predominant feature of the acute-phase response, the anabolism of certain proteins is also stimulated. Proteins needed for the reproduction of white blood cells and immunoglobulins account for some of this anabolic activity. The liver is stimulated to synthesize a large number of proteins for intracellular use (e.g., enzymes and metallothionines) as well as a variety of proteins that enter the plasma. These include components of the complement system, the kinin system, and the coagulation system. Also synthesized within the liver are a group of plasma glycoproteins termed acute-phase reactants. In humans, these include haptoglobin, C-reactive protein, ceruloplasmin, alpha-antitrypsin, and orosomucoid, all of which appear to play some protective role during infection (Beisel 1985).

Lipids. During infections, hormonal influences on the liver lead to the synthesis of excessive amounts of free fatty acids (Powanda and Canonico 1981) and a reduction in the conversion of free fatty acids to ketones, a process that normally occurs during periods of reduced food intake. These phenomena lead to increased production of triglycerides, the accumulation of fat droplets within liver cells, and an increase in triglyceride concentrations in blood. These changes are especially pronounced in infections caused by endotoxin-containing bacteria, apparently because of the release of the monokine TNF, which inhibits lipoprotein lipases on cell walls (Beisel 1985). In addition, IL-1 is thought to activate phospholipase enzymes in cell walls that stimulate the production of arachidonic acid, which, in turn, is converted into prostaglandins or leukotrienes within body cells (Kluger, Oppenheim, and Powanda 1985).

Vitamins. Tissue and plasma concentrations of most vitamins have been reported to decline during infections, perhaps because of increased metabolism or excretion. The concentration of vitamin C, for example, declines in neutrophils and in the adrenal cortex during active steroid production, which may occur during the stress of illness. The accelerated metabolism or loss of vitamins during infections may precipitate recognizable deficiency states (Scrimshaw et al. 1968; Beisel 1985).

Minerals. During infection, all of the principal intracellular elements are lost from the body, roughly in proportion to the losses of nitrogen (Beisel 1985). Blood mineral concentrations decline slightly and may be severely reduced under certain circumstances. Calcium (in conjunction with calmodulin) is intimately involved in many altered molecular responses of body cells during febrile infections, but calcium is not generally lost from the body unless an infection causes muscle paralysis or requires prolonged bed rest. These mineral losses are readily replaced by supplying adequate intake during convalescence (Beisel 1985).

Responses induced by IL-1 also cause the redistribution of iron, zinc, and copper within the body. Both iron and zinc leave the plasma and are held in a storage form for as long as the infection persists. Zinc is held in hepatic cells by newly produced binding proteins (metallothionines), and iron is stored as ferritin or hemosiderin. In contrast, copper leaves the liver and accumulates in blood as a component of ceruloplasmin. This redistribution appears useful for host defenses against infection, although specific functions have not been established (Beisel 1982a).

Electrolyte metabolism is altered in most systemic infections by the renal retention of sodium and chloride and, therefore, of extracellular water. In some infections, especially those that localize in the brain, an inappropriate secretion of antidiuretic hormone causes more intense retention of body water and dilution of the electrolytes in body fluids (Beisel 1985). Conversely, significant quantities of sodium, chloride, and other nutrients may be lost through the sweating associated with fever and infection, and any infection that causes diarrhea will induce fecal losses of sodium, chloride, potassium, and bicarbonate, as well as water. Cholera, for example, induces extensive water and electrolyte losses from the gastrointestinal tract, and cholera deaths are from dehydration rather than from the infection itself. Such losses are especially dangerous in already malnourished infants and children (Beisel 1985).

AIDS: A New Example of Complex Infection-Nutrition-Immunity Interactions

AIDS (acquired immunodeficiency syndrome), caused by the human immunodeficiency virus (HIV), is a disease with multiple pathologies, most of which are the consequence of a profound immunodeficiency. The CD4-bearing T lymphocytes appear to be the primary population of target cells that are lost in HIV-infected patients. This loss includes the majority of helper T cells that help killer T cells and B cells function properly. Therefore, killer cell function is reduced, which leads to a loss of recognition and

elimination of body cells infected with other micro-organisms. Reduced B cell function disables the body's ability to make new antibodies for the neutralization or elimination of micro-organisms located in extracellular body fluids. In addition, there is a profound loss of the lymphokine mediators normally produced by helper T cells. This loss reduces the activation of macrophages and the maturation and effectiveness of natural killer cells that help combat infections and cancer (Weissman 1988).

Weight loss and deteriorating nutritional status are critical features of the AIDS disease process (Anonymous 1985; Kotler, Wang, and Pierson 1985). Anorexia, nausea and vomiting, fever, and diarrhea are common features of advanced AIDS, as are malabsorption of fats, carbohydrates, and protein and some intestinal injury and dysfunction (Garcia, Collins, and Mansell 1987; Kotler 1987). The underlying causes of these gastrointestinal symptoms include infections by viral, parasitic, or bacterial pathogens as well as disseminated Kaposi's sarcoma. Even before recognition of AIDS, several research groups reported unique and multiple enteric pathogens in homosexual men (Quinn et al. 1983; Baker and Peppercorn 1982). These infections are strongly associated with depressed appetite, decreased food intake, and severe wasting typical of illness-induced malnourished states (Kotler, Wang, and Pierson 1985; O'Sullivan, Linke, and Dalton 1985).

As noted earlier, such severe malnutrition is associated with impaired function of specific components of the immune system and a generalized reduction in the energy resources needed to support cell growth and proliferation. The similarity of immune abnormalities resulting from malnutrition and those seen in AIDS has led to suggestions that malnutrition might predispose to AIDS or that nutritional therapy might improve immune status and prevent AIDS (Jain and Chandra 1984) or improve its prognosis (Kotler 1987). Little evidence, however, supports either of these suggestions. Although the most severely malnourished AIDS patients are at highest risk, severe malnutrition is more likely to be a result of AIDS-related intestinal injury than a cause of this condition. As in other conditions, correction of malnutrition would be expected to improve response to therapy and to decrease susceptibility to opportunistic infections, but complications of intravenous nutritional support—electrolyte imbalances, excessive concentrations of blood sugar and fat, and infections of the intravenous access routes—have made it difficult to test these hypotheses in AIDS patients (Kotler 1987). Although some preliminary studies have observed improved weight maintenance in AIDS patients receiving nutritional support (Domaldo and Natividad 1986), others indicate that weight gain is due to water retention rather than to repletion of body cell mass

(Kotler, Wang, and Pierson 1985; Kotler 1987). To date, suggestions that AIDS-specific immune dysfunctions can be either arrested or reversed by nutritional therapy are not supported by clinical or biochemical evidence (Kotler 1987).

Nutritional Rehabilitation

The early convalescent period following a serious infection is an important time to restore normal metabolic processes and replenish energy reserves. Frequently, this period is accompanied by a marked hunger. An appropriate refeeding program can replace nutrient losses rapidly and stimulate the recovery of normal host defensive and immunologic functions. However, nutritional support for severely wasted patients with infections is often difficult (Siegel 1987; Bell et al. 1983) because of nutrient imbalances and other complications (Baron 1986) and because of insufficient knowledge of the actions, or side effects, of nutrients administered parenterally (Siegel 1987). Other problems are caused by severe weaknesses of the respiratory musculature in wasted patients (Bell et al. 1983), who may be unable to get rid of the large quantities of carbon dioxide produced when extra energy sources are provided to the body. Further research is needed to develop more effective methods to overcome malnutrition induced by severe infectious diseases.

Role of Diet-Immune System Relationships in Food-Associated Illnesses

Adverse reactions to food involve both immunologic and nonimmunologic mechanisms. Immunologic reactions are known commonly as food allergies. Nonimmunologic intolerances include those that are biochemical (food toxicities, poisonings, and digestive disorders) or psychologic. Foods may also transmit micro-organisms that cause infectious illnesses. The numerous causes of food-associated illness are listed in Table 11-1.

Immunologic Mechanisms (Allergies)

Although the immune system usually protects the body against foreign substances, antigen-specific immune responses can sometimes produce adverse, even fatal, effects. Food is the largest antigenic challenge confronting the human immune system (Sampson, Buckley, and Metcalfe 1987). Food allergies are examples of the negative consequences of immune function on the gastrointestinal tract, skin, lungs, and other organ systems. Symptoms can include acute abdominal pain, swelling, nausea, vomiting, rashes, vascular collapse, chronic itching, headache, tension, and fatigue. Eczema, asthma, and rhinitis are more common in children than in adults (Metcalfe 1985).

Table 11-1
Causes of Food-Associated Illness

Food-borne Infections Due to:	Food Origin Toxemias Due to:	Food Allergies Due to:	Nonallergic Food Intolerances	
			Due to Natural Products:	Due to Chemicals:
Bacteria	Botulinum toxins	Milk	Lactose	Sulfites
Salmonella	Staphylococcal		Sucrose	Nitrites
Shigella	Enterotoxins	Eggs	Galactose	Nitrates
Campylobacter	*Escherichia coli*		Gluten	Monosodium
Escherichia coli	Enterotoxins	Wheat	Borad beans	glutamate
Vibrio parahemolyticus	Verocytotoxins		(favism)	Tartrazine dyes
Listeria monocytogenes	Clostridial	Peanuts	Laythyrus peas	Benzoic acid
Yersinia	Perfringen toxins		(laythyrism)	Organophosphates
	Difficile toxins	Soybean	Caffeine	Oxalates
Parasites	*Bacillus cereus*	products	Theobromine	Heavy metals
Trichinella	Enterotoxins		Histamine	Mercury
Toxoplasma		Nuts	Tyramine	Lead
Amoeba	Mushroom toxins		Tryptamine	Arsenic
Giardia		Fish	Serotonin	Copper

Isosporia (Coccidia)
Cryptosporidia

Viruses
- Hepatitis A virus
- Norwalk agent
- Other Norwalk-like viruses
- Rotaviruses
- Adenoviruses[a]
- Astroviruses[a]
- Echoviruses
- Snow Mountain agent
- Cockle agent
- Coxsackie B viruses
- Caliciviruses[a]

Fungal toxins
- Ergot, mycotoxins Trichothecenes
- Aflatoxins

Puffer fish
- Tetrodotoxin

Ciguatoxins
Scrombroid fish toxin
- Shellfish saxitoxin

Shellfish

Other foods

Phenylethylamine
Solamine

Aspartame
Butylated-hydroxytoluene
hydroxyanisole

[a]Viruses that cause gastroenteritis and may be food borne.

To distinguish a true allergic reaction from an intolerance due to a biochemical or psychologic disturbance, the specific food causing the reaction must be clearly identified, a proper diagnostic procedure followed, and the cessation of symptoms documented when the offensive food is eliminated. A scientifically rigorous diagnosis requires additional diagnostic tools such as the Radioallerogosorbant Test (RAST), the Enzyme Linked Immunosorbant Assay (ELISA), and skin testing (although all of these are of limited value), elimination diets, and double-blind food challenges (Sampson, Buckley, and Metcalfe 1987). The efficacy of cytotoxic testing, provocative subcutaneous testing, and provocative sublingual tests of food extracts to diagnose food hypersensitivity are unproved, and use should be limited to well-constructed diagnostic trials. At present, no single diagnostic test appears to be definitive in the diagnosis of food allergy (AAAI 1984).

Allergic reactions are caused by an adverse interaction between a protein antigen and an IgE immunoglobulin antibody. The IgE antibody first binds to the surface of a mast cell, a cell that is capable of releasing histamines and other factors. This binding prepares the mast cell for subsequent binding of a food antigen, which, in turn, triggers the cell to release histamine and other vasoactive mediators that produce the signs and symptoms of food allergies (AAAI 1984). This type of allergic hypersensitivity occurs within minutes to hours and, in rare instances, can be life threatening. The molecules of several antigens in foods capable of triggering mast cell reactions have been isolated and their structures identified (Moroz and Yang 1980; Metcalfe 1985).

The most common foods to which people are allergic are egg, milk, wheat, peanut, soybean, chicken, fish, shellfish, and nuts (Atkins 1983). Responses to such foods are not always consistent, however, because they depend on the amount and form of the food consumed and the presence of other foods in the diet or of medications. Thus, foods that have not caused reactions in the past may induce allergic responses when other mitigating factors are present (Atkins 1983).

Estimates of the incidence of food allergies in infants range from 0.3 percent to 20 percent. Because allergies tend to be outgrown, the incidence decreases to less than 3 percent in adults (Butkus and Mahan 1986; Bock and Martin 1983). Because only about one-fourth of histories of adverse food reactions can be confirmed by diagnostic tests (May 1980; AAAI 1984), these estimates may be too high (IFT 1986).

Enteric pathogens are thought to alter the permeability of the intestinal mucosa, permitting entry of normally excluded, immunogenic macromolecules, although conclusive evidence is lacking. Uptake of intact egg protein (ovalbumin) in humans and animals with gastroenteritis has been demonstrated (Keljo et al. 1987; Walker 1981; Gruskay and Cooke 1955). If operative, the effect of such uptake may result in induction of allergy, autoimmunity (particularly immune complex-mediated disease), and other disorders (Walker 1981).

Nonimmunologic Mechanisms

The causes of nonimmunologic adverse reactions to foods include food toxicities, food poisonings, and pharmacologic or metabolic reactions. Such intolerances occur more frequently than true food allergies and are related to dose as well as to the concurrent presence of medications, other diseases, or genetic errors of metabolism.

One example is sulfite-induced asthmas. Sulfur dioxide and sulfiting agents are widely used to retard deterioration of perishable produce, to condition dough, to prevent microbial growth, and to provide antioxidant action. The average intakes of sulfite and sulfite derivatives are estimated to be 6 mg per capita per day but are higher for wine and beer drinkers and for individuals consuming larger amounts of sulfite-treated foods. These amounts may exceed current estimates of safe levels of intake (IFT 1986). Approximately 1 to 8 percent of people with asthma are sensitive to ingestion of sulfite, and those using steroid control agents are affected more frequently. Adverse reactions vary with the individual's sensitivity threshold, the type of sulfiting agent, and the type of food in which it is consumed (Bush, Taylor, and Busse 1986). The FDA has proposed that sulfite be declared on labels when levels exceed 10 ppm as total sulfite dioxide and that its "Generally Recognized As Safe" (GRAS) status be rescinded, but no final rules have been issued.

Other examples include asthma induced by tartrazine, a yellow dye used to color medicines, soft drinks, and foods; a syndrome caused by monosodium glutamate (see chapter on neurologic disorders); and symptoms caused by preservatives such as benzoic acid and sulfiting agents (Butkus and Mahan 1986). Nonimmunologic reactions also include lactose intolerance (an intestinal deficiency of the digestive enzyme lactase) and celiac sprue, the inability to metabolize gluten (see chapter on gastrointestinal diseases). In addition, toxic contaminants such as bacteria, insect parts,

and molds; vasoactive amines (e.g., histamine) found in tomatoes, avocados, cheeses, pineapples, and wines; and caffeine may cause symptoms in sensitive individuals. Other gastrointestinal diseases, such as reflux peptic esophagitis, peptic ulcers, gallbladder disease, and mesenteric vascular insufficiency are associated with acute symptoms after eating. Persons suffering adverse reactions may mistakenly attribute the cause to a food allergy rather than to their underlying illness (AAAI 1984). Finally, psychologic mechanisms can provoke physical and mental symptoms of food sensitivity that do not appear to be mediated by the immune system. In individuals with psychologically induced allergic symptoms, no physiologic or biochemical nonimmunologic mechanisms can be identified (May 1984) and true immunologic mechanisms are rarely found (Johansson 1984).

Prevention and Treatment

Individuals with food intolerances should exclude the offending foods from their diet either completely or partially. Those with potentially life-threatening sensitivities should carry an epinephrine-containing syringe (Atkins 1983) and wear a bracelet identifying the problem. Desensitization shots, oral desensitization, and use of bee pollen are not effective treatments for food allergies (Butkus and Mahan 1986).

The likelihood of an infant developing an IgE-mediated reaction is estimated at 58 percent when both parents are affected, 38 percent when one parent is affected, and 12.5 percent when neither parent is affected (Butkus and Mahan 1986). Special precautions should be taken in feeding infants at high risk, especially during the first year (Glaser 1966). Some research suggests that the incidence of food allergies is decreased if breastfeeding is continued for 3 to 6 months (Hamburger et al. 1983; Saarinen and Kajosaari 1980; Chandra 1979). Other research, however, disputes this suggestion (Kovar et al. 1984). Because some food antigens are transferred through the breast milk to the infant, mothers should avoid foods to which the infant is sensitive. Likewise, formula-fed infants sensitive to cow milk or to soybean-based formulas should be given formulas prepared from casein hydrolysate (Butkus and Mahan 1986). Delaying the introduction of solid foods, especially those most likely to induce allergies, may prevent or minimize the development of food allergies (Chandra 1979; Hamburger et al. 1983). As a general rule, new foods should be introduced into the infant diet one at a time to permit observations of allergic reactions (see chapter on maternal and child nutrition).

Food-borne Microbial Diseases

Ingestion of water or foods that are contaminated with chemicals, pathogenic micro-organisms, or the toxins they elaborate can lead to illness. Food-borne pathogens commonly cause diarrhea, vomiting, abdominal cramps, or other gastrointestinal symptoms. Less commonly, they affect the liver or nervous system. Symptoms range from minor discomfort to severe disease and even death. Their causes are listed in Table 11-1. In 1982, the factors most common to food-borne disease outbreaks, in order of frequency, were (1) improper food handling, (2) food from an unsafe source, (3) inadequate cooking, (4) poor personal hygiene, and (5) contaminated equipment (CDC 1985). Appropriate public health procedures related to food handling and storage can usually prevent these problems.

The preferred treatment for most forms of food-borne illnesses is fluid and electrolyte replacement for dehydration caused by diarrhea (Rohde et al. 1983). Antimicrobial drugs may be useful in some instances; in rare cases, such as botulism poisoning, an antitoxin should be administered. However, because most food-borne illnesses are self-limiting and antibiotics may disturb normal bacterial flora and prolong the illness, antibiotic therapy is not routinely used (Altman 1985). Food-borne infections that trigger an acute-phase response will be accompanied by nutritional losses comparable to those seen in other infections.

The major microbial causes of food-borne illness are bacteria, viruses, and parasites. Chemical contamination of foods occasionally causes illness. Bacterial food poisoning, the most common type, is caused by ingestion of water or food that contains living organisms or toxins they produce or enterotoxins produced in the intestine after their ingestion. These diseases are most common in the developing world where the water supply is inadequately treated and food easily becomes contaminated.

As mentioned earlier, food-borne illnesses affect large numbers of people in the United States. For example, more than 40,000 cases of salmonellosis (excluding typhoid fever) were reported to CDC in 1982 (CDC 1983), although only about 2,000 of them were confirmed. Among these cases, eight deaths were reported (CDC 1985). More than 18,000 cases of shigellosis were reported in the United States in 1982; although the true incidence is thought to be considerably higher (CDC 1983), only 116 of the reported cases were confirmed (CDC 1985). At least one outbreak of gastrointestinal disease has been traced to *Campylobacter fetus* contami-

nation of raw milk (Klein et al. 1986), but some investigators believe that the incidence of campylobacter-induced illness is greater than the total combined cases of salmonellosis and shigellosis (Blaser 1983; Skirrow 1977; Archer and Kvenberg 1985). *Clostridium perfringens* was confirmed as the etiologic agent in nearly 2,000 cases of food-borne illness in 1982 (CDC 1985). *Clostridium botulinum* causes an average of 15 outbreaks of food-borne botulism annually in the United States, with 21 outbreaks involving 30 people and 8 deaths reported for 1982 (CDC 1985). An estimated 20,000 cases of *Yersinia* infection occur annually in the United States, causing acute abdominal symptoms (Kvenberg and Archer 1987). Although more than 23,000 cases of hepatitis A were reported to the CDC in 1982 (CDC 1983), only 325 cases were confirmed (CDC 1985). Hepatitis A is transmitted almost exclusively by the fecal-oral route through food and water contaminated by food handlers. In 1982, approximately 5,000 cases of food-borne Norwalk gastroenteritis were reported to the CDC (CDC 1985). These derived from two large outbreaks, one related to eating bakery items with contaminated icing and the other associated with eating contaminated coleslaw. Other outbreaks have involved shellfish and drinking water.

Implications for Public Health Policy

Dietary Guidance

General Public

Adequate nutrient and energy intake is critical to the maintenance of optimal immune function. However, evidence related to the role of specific dietary factors such as fatty acids, vitamin C, or zinc is insufficient to recommend changes in dietary guidance policy for the general public. Evidence related to the role of microbial and chemical contamination of food and water in human health suggests that the general public should receive information on appropriate food handling and storage methods to prevent outbreaks of food-borne disease.

Although the overall public health significance of breastfeeding in the United States is uncertain, studies in developing countries have shown the importance of breastfeeding in preventing diarrheal diseases and in reducing their severity. The immune protection conferred by breastfeeding also helps reduce the severity of certain infectious diseases among infants. Breastfeeding should continue to be recommended to pregnant women and to new mothers as the optimal method of infant feeding.

Although the relationship between malnutrition and changes in immune function observed with aging is not well understood, it is clear that adequate intake of nutrients is basic to the adequate immune protection in older Americans.

Special Populations

Infections produce well-documented adverse effects on nutritional status, and nutritional rehabilitation restores immune function and reduces the severity of infectious disease complications. Thus, the nutritional status of persons with infectious illnesses should be assessed regularly, and appropriate nutritional support measures should be instituted whenever necessary. Qualified health professionals should advise persons with food allergies and intolerances on the diagnosis of these conditions and on diets that exclude foods and food substances that induce symptoms.

Nutrition Programs and Services

Food Labels

Evidence related to diet-immune function interactions reinforces the need for food manufacturers to include explicit and complete ingredient statements to protect individuals who may have severe adverse reactions to foods.

Food Services

Current evidence about the role of dietary factors in the maintenance of optimal immune function has no special implications for change in policy related to food service programs. Evidence related to the spread of infections suggests that food service personnel should receive adequate training in sanitary food handling and storage procedures.

Food Products

Evidence related to diet-immune function interactions suggests that food product manufacturers should take special precautions to use good manufacturing practices to avoid contamination with ingredients that may produce severe reactions and to reduce microbial and chemical contamination during production and storage. Manufacturers should continue to develop new products that are free of substances likely to induce allergic symptoms in susceptible individuals.

Special Populations

Patients with infectious diseases should be treated as rapidly and effectively as possible to minimize the depletion of body nutrients. Convalescing patients should be counseled and assisted in the development of diets that provide adequate intake of nutrients to regain an appropriate nutritional status. Patients with food intolerances should be counseled and assisted in the development of diets that omit foods and food factors that induce symptoms.

Research and Surveillance

Research and surveillance issues of special priority related to interactions between diet, infection, and immunity should include investigations into:

- The mechanisms by which generalized malnutrition depresses the function of specific components of the immune system.
- The effects of deficient or excess intake of single nutrients such as vitamin A, zinc, iron, or dietary fat on specific elements of the immune system and on immune function.
- The mechanisms by which deficient or excess intake of single nutrients might depress or improve immune system function.
- The factors in breast milk that protect infants from infectious disease.
- The role of breast milk in transmitting allergens, infectious agents, or toxicants such as drugs.
- The role of nutrition in maintaining adequate immune function in older persons.
- The mechanisms by which infectious diseases alter nutrient metabolism and impair nutritional status.
- The most effective means of restoring nutritional status to malnourished individuals recovering from infectious illnesses.
- The identification of natural food products and chemical additives that induce adverse physiologic responses and the mechanisms by which they do so.
- The basic biochemistry of food antigens and biologically active components.
- The effects of processing and digestion of food substances with conversion to or inactivation of allergenic fractions.
- The value of therapeutic procedures designed to induce tolerance to food antigens.

- The prevalence of food-borne infections and intolerances and immunologic reactions to food in the population.
- The identification of behavioral determinants of unsanitary food handling and storage procedures and the development of effective educational methods to prevent transmission of food-borne illnesses.
- The effect of nutritional status on susceptibility to infectious diseases, including HIV infection, and on the complications of AIDS.

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Chapter 12

Anemia

She was very anaemic. Her thin lips were pale, and her skin was delicate, of a faint green colour, without a touch of red even in the cheeks.
W. Somerset Maugham
Of Human Bondage, 1915

Introduction

Anemia occurs when the concentration of the pigment hemoglobin in red blood cells falls below normal. Hemoglobin is essential for delivering oxygen from the lungs to the body's tissues, and anemia impairs the capacity of the blood to supply the tissues with oxygen for the production of cellular energy in the form of adenosine triphosphate. Severe deficits in the delivery and use of oxygen increase fatigability, decrease work capacity, impair brain function, and lessen ability to maintain body temperature (Bothwell et al. 1979; Dallman, Siimes, and Stekel 1980; Finch 1982; Dallman 1986).

Historical Perspective

Chlorosis, the green sickness or "virgin's disease," was a condition associated with anemia that afflicted young women in Europe and North America from about 1500 to 1900 (see quotation). Chlorotic women appeared pale and suffered weakness, lassitude, breathlessness, and menstrual disorders. This condition was attributed to lovesickness, ovarian insufficiency, or the pressure from a tight corset on the spleen. Treatment consisted of bloodletting and the administration of iron tonics and pills, especially in the 19th century after it was established that the disease involved iron deficiency (Loudon 1980). Today, with improved nutrition and better health care, chlorosis is no longer observed. However, iron deficiency is still prevalent (Crosby 1987).

The credit for introducing iron into therapeutic use is usually given to the 18th-century English physician Sydenham, who observed improvements

in his anemic patients when he prescribed a "steel tonic" prepared by steeping iron filings in Rhine wine (McCollum 1957).

Iron was one of the first substances identified as essential in the human diet. The physiologic function of iron in hemoglobin and its role in anemia was determined over a 200-year period, from the 1680's, when Boyle first analyzed the chemical composition of blood, to the 1860's, when iron was first recognized as an essential nutrient for animals.

Although chlorosis disappeared during the first part of the 20th century, a relatively rare but more deadly nutritional anemia continued to puzzle clinicians and scientists until the 1920's. In 1849, Addison first described pernicious anemia, so called because no cure could be discovered. Not until 1926 was it learned that extracts of liver—now known to contain vitamin B_{12}—could cure the disease (Herbert 1984). A few years later, Wills discovered that an impure extract of liver could reverse a macrocytic anemia found in Hindu women in Bombay, particularly in those who were pregnant. Scientists now know that this extract contained folic acid and that requirements for this vitamin increase during pregnancy.

The first public health efforts in the United States to prevent iron deficiency occurred during World War II when the Food and Drug Administration developed regulations for the fortification of cereal and grain products, including flour (Food and Nutrition Board 1974; Yetley and Glinsmann 1983). Infant cereals were first fortified with iron after about 1950, and infant formulas began to be fortified with iron in the late 1950's (Marsh, Long, and Stierwolt 1959). As a result of this and other public health measures reviewed in this chapter, rates of iron deficiency have declined rapidly.

Significance for Public Health

Anemia has genetic, environmental, and nutritional causes. For example, the most frequent causes of anemia among older persons are infection and chronic disease. Iron deficiency, however, is the most common cause of anemia among young women and children and is the major focus of this discussion. When used precisely, the terms anemia, iron deficiency, and iron deficiency anemia all have distinct meanings. Anemia signifies a blood hemoglobin concentration that is two standard deviations below the mean for normal individuals of the same age and sex. Although iron deficiency is generally the most common cause of anemia, there are many other nutritional, genetic, and environmental causes as well. In this chapter, iron deficiency refers to a lack of iron that not only results in loss of iron stores,

but that also would be expected to impair iron-dependent physiologic functions. The term "impaired iron status" has a similar connotation (LSRO 1984b) and is applied to individuals in whom two or more laboratory tests of iron metabolism are abnormal. Iron deficiency anemia refers to anemia that results from iron deficiency or impaired iron status. Iron-dependent physiologic functions can become impaired before anemia develops. These issues are discussed in greater detail below.

Iron deficiency has received much attention over the years in the United States, although its overall prevalence is low. The best recent estimates of impaired iron status are derived from the second National Health and Nutrition Examination Survey (NHANES II), conducted by the National Center for Health Statistics between 1976 and 1980 (LSRO 1984b; Dallman, Yip, and Johnson 1984).

Iron-dependent physiologic functions can be impaired before anemia becomes apparent (see below). To estimate the prevalence of impaired iron status, with or without concurrent anemia, survey results were analyzed by averaging the results of three methods that detect iron deficiency at varying stages of development of anemia. The prevalence of impaired iron status revealed by these methods is given by age and gender in Table 12-1. These methods found the highest prevalences of iron deficiency among children ages 1 to 2 (9.3 percent), women ages 15 to 19 (7.2 percent), and women ages 20 to 44 (6.3 percent). The lowest prevalence, less than 1 percent, was in men between the ages of 15 and 64.

Because iron deficiency anemia represents a late stage of impaired iron status, rates of clinical anemia would be expected to be even lower than these figures. Both anemia and iron deficiency were less common in NHANES II than was anticipated from the limited data of earlier surveys (Dallman, Yip, and Johnson 1984). Furthermore, the anemia surveillance data collected primarily on low-income children by the Centers for Disease Control show a gradual decline in overall prevalence of anemia (as assessed by stringent laboratory criteria), from 7.8 percent in 1975 to 2.9 percent in 1985 (Anonymous 1986; Stockman 1987; Yip, Binkin, et al. 1987). Prevalences among middle-income children were even lower (Yip, Walsh, et al. 1987). The paucity of moderate or severe anemia in recent analyses may indicate that iron deficiency is becoming less common in the United States.

Among infants and younger children in the United States, increased breastfeeding, greater use of iron-fortified infant formula and cereals, and decreased consumption of cow milk during infancy have also improved iron

Table 12-1
Estimates for Percent Prevalence of Impaired Iron Status: Average of Estimates Using Three Methods[a]: NHANES II, 1976–80

Age (years)	Males and Females	Males	Females
	Average percent prevalence (range)		
1–2	9.3 (9.2–9.4)		
3–4	4.3 (3.6–5.5)		
5–10	3.9 (3.2–4.5)		
11–14		4.1 (3.5–12.1)	2.8 (2.7–6.1)
15–19		0.6 (0.1–0.9)	7.2 (2.5–14.2)
20–44		0.7 (0.6–0.8)	6.3 (4.0–9.6)
45–64		2.0 (1.9–2.0)	4.4 (3.8–4.8)
65–74		2.8 (1.8–3.6)	3.2 (2.7–3.7)

[a]Three methods:
1. Prevalence of two or three abnormal laboratory values using serum ferritin, transferrin saturation, and erythrocyte protoporphyrin.
2. Prevalence of two or three abnormal laboratory values using mean red cell volume, transferrin saturation, and erythrocyte protoporphyrin.
3. Relative prevalence of anemia derived from the rise in median hemoglobin after exclusion of persons with abnormal laboratory values.

Source: Life Sciences Research Office. 1984. *Assessment of the iron nutritional status of the U.S. population based on the data collected in the second National Health and Nutrition Examination Survey, 1976–1980,* ed. S.M. Pilch and F.R. Senti, p. 65, Bethesda, MD: Federation of American Societies for Experimental Biology.

status. Some of these changes may have resulted from public health programs aimed at prevention of iron deficiency.

Although iron deficiency anemia can occur in all socioeconomic groups, it has historically been most common among the poor (LSRO 1984b; DHHS/USDA 1986) and is still the case today (Yip, Binkin, et al. 1987; Yip, Walsh, et al. 1987). This observation provides a basis for the particular attention to iron nutrition in Federal programs such as the School Lunch Program and the Special Supplemental Food Program for Women, Infants, and Children (WIC). The WIC program provides iron-fortified formulas and cereals and periodic health screenings and has been associated with improved iron status in its participants independent of socioeconomic status (Yip, Binkin, et al. 1987).

Studies in Sweden have shown a decline in anemia rates among women, from 30 percent in 1965 to 7 percent only 10 years later (Hallberg et al. 1979). This decline was attributed to a relatively high level of fortification

of food with iron, and the increased use of iron tablets, increased consumption of ascorbic acid, and the effects of oral contraceptive use. Extrapolation of these results to women in the United States, however, must be made with caution because both the severity of anemia and levels of fortification differ in the two countries.

Variations in diagnostic criteria according to age and sex present an additional difficulty in interpreting data on prevalence rates of anemia. Screening programs often use hemoglobin status as an initial criterion for diagnosis. Hemoglobin levels, however, differ with age and gender and must be compared with appropriate standards. They may also differ with race. Data from NHANES indicate that hemoglobin levels are somewhat lower among black than among white Americans (LSRO 1984b), and some studies have suggested that such differences remain even after diet, gender, and socioeconomic factors are taken into account. However, other studies found that the small differences of mean hemoglobin values between blacks and whites may be attributable to a subset of blacks who have mild hereditary anemia such as thalassemia traits (Yip, Schwartz, and Deinard 1984; Castro et al. 1985). Whether these observations mean that the hemoglobin levels of blacks and whites should be compared with different standards is as yet uncertain.

Scientific Background

Causes of Anemia

There are three main causes of anemia: (1) reduced production of red blood cells and hemoglobin; (2) hemolysis, or increased destruction of red blood cells; and (3) loss of blood from the circulation, as in internal or external bleeding. Because the synthesis of blood cells requires many cellular and metabolic steps, a deficiency of any nutrient essential to hemoglobin production produces adverse effects on these processes. Good nutrition is fundamental to adequate red cell production. Nutritional anemia may be due to a dietary deficiency of iron, folate, vitamin B_{12}, protein, vitamin E, vitamin A, vitamin B_6, riboflavin, vitamin C, zinc, or copper. Because the most common nutritional cause of anemia in the United States and in other developed countries is iron deficiency (LSRO 1984b; Dallman, Yip, and Johnson 1984), it is the principal focus of this discussion. Deficiencies of folate (LSRO 1984a), vitamin B_{12}, and other nutrients are far less significant causes. Other causes of anemia include the inherited or acquired inability to use nutrients required for hemoglobin production, chronic inflammatory or infectious diseases, and lead poisoning. Normal levels of hemoglobin also vary according to genetic factors such as race. Thus,

diagnosis of anemia must distinguish nutritional from other potential causes and must relate hemoglobin levels to appropriate standards.

Nutritional anemia should be distinguished from deficiencies *per se* of iron, folate, or vitamin B_{12}, because an individual may have manifest any one of these deficiencies without being anemic. Iron deficiency, for example, in its early stages is typically present without anemia. The term "iron deficiency anemia" signifies that the iron deficiency has become severe enough to depress the hemoglobin concentration below the normal range. Although this chapter focuses on nutritional anemia, there are many additional health consequences of nutritional deficiencies that occur concomitantly with anemia but are not caused by the anemia itself. For example, iron is not only required for hemoglobin biosynthesis but is also an essential component of many enzymes required for the production of energy in cells throughout the body. In iron deficiency, the impairment of these and other iron-dependent processes may account for disorders in immune function and behavior that are not directly attributable to the anemia. Similarly, the impaired nerve function of vitamin B_{12} deficiency occurs independently of anemia. Thus, anemia is just one possible consequence of these nutritional deficiencies.

Role of Iron in the Body

The total amount of iron in the body is slightly less than the weight of a 5-cent coin, about 4 g for adult males (Bothwell et al. 1979). Most of this iron is used to transport and use oxygen in the production of cellular energy. The distribution of iron in the bodies of men, women, and infants is given in Table 12-2. An average of about 58 percent of the body's iron for men and 73 percent for women is contained in hemoglobin, and 11 percent for men and 14 percent for women is present in myoglobin (which stores oxygen and makes it available to the muscle when it is needed during contraction). A smaller but critically important amount of iron, about 3 percent, is present in iron-containing enzymes such as the cytochromes, which are required for the production of cell energy.

In addition to these essential iron compounds that fulfill physiologic functions, two proteins, ferritin and hemosiderin, serve as a storage reserve. These storage compounds account for an average of 25 percent of body iron in men and 10 percent in women and are located primarily in the liver, spleen, and bone marrow. There, they serve as alternate sources of iron to produce essential compounds when dietary supplies are insufficient. The vulnerability of an individual to iron deficiency depends on the abundance of these iron reserves. In some individuals, however, these reserves can accumulate to toxic levels, most often as a result of a genetically deter-

Table 12-2
Total Body Iron and Storage Iron

	Men	Women	Infants (age 1 year)
Total iron, g	4.0	2.7	0.45
Hemoglobin iron, %	58	73	78
Myoglobin iron, %	11	14	6
Enzyme iron, %	3	3	5
Storage iron, %	25	10	11

Source: Bothwell et al. 1979.

mined failure to reduce iron absorption when stores are adequate. This and other causes of iron overload suggest a need for prevention of excessive iron intake in certain individuals.

Almost all compounds containing iron in the body are continuously broken down and resynthesized (Bothwell et al. 1979). The iron released by the degradation of hemoglobin and other iron-containing proteins is efficiently conserved and reused to replace these compounds. An important consequence of this metabolism is that very little iron is lost from the body on a daily basis, except when bleeding occurs. In adult men, normal iron losses in the feces, sweat, and sloughed cells amount to about 0.9 mg/day, equivalent to less than one-tenth of 1 percent of iron stores. This amount is readily absorbed from the diet. Women in their childbearing years require an average of 1.3 mg/day to make up for the additional iron that is lost in menstrual blood (Bothwell et al. 1979). In children, a proportionately more generous amount of iron is required for growth (Dallman, Siimes, and Stekel 1980). Consequently, premenopausal women and children are more likely to develop iron deficiency than are men.

Iron Absorption

The bioavailability of iron—that is, the amount absorbed from food—is determined both by the nature of the diet and by regulatory mechanisms in the intestinal mucosa that reflect the body's physiologic need for iron. Two types of iron are present in food: heme iron, which is found principally in animal products, and nonheme iron, found mainly in plant products.

Nonheme Iron. Most of the iron in the diet, usually more than 80 percent, is present as nonheme iron and consists primarily of iron salts. The composition of a meal determines nonheme iron solubility in the upper part of the small intestine, which, in turn, determines the absorption of the iron

(Hallberg 1981; Charlton and Bothwell 1983). Consequently, the amount of iron finally absorbed is influenced by other constituents of the diet that either enhance absorption by increasing iron solubility or inhibit absorption by decreasing solubility in the intestine. For example, nonheme iron absorption from a representative meal containing enhancers such as meat, fish, or chicken is about four times greater than when foods containing inhibitors (e.g., milk, cheese, or eggs) are substituted (Cook and Monsen 1976).

Iron absorption tends to be poor from meals in which whole grain cereals and legumes predominate, but the addition of even relatively small amounts of meat or foods containing vitamin C (ascorbic acid) substantially increases the absorption of iron from the entire meal. Compared with water, orange juice or foods containing vitamin C increase absorption of nonheme iron from a meal. Tea and coffee, on the other hand, decrease absorption of nonheme iron when compared with water (Hallberg 1981; Rossander, Hallberg, and Bjorn-Rasmussen 1979).

Breast milk is relatively low in iron, but its iron is relatively well absorbed (Saarinen, Siimes, and Dallman 1977) in comparison with iron in cow milk or unfortified cow milk formula. This increased iron absorption may explain why breastfed infants are less vulnerable to iron deficiency than infants fed unfortified cow milk formula.

The absorption of iron from infant foods varies with the form of iron, its concentration, the total iron content and composition of the meal, and, presumably, the iron status of the child. For example, one study found that only about 4 percent of the iron was absorbed from a cow milk formula that was fortified with about 12 mg of iron per liter in the form of ferrous sulfate and with ascorbic acid (Rios et al. 1975; Saarinen and Siimes 1977). Even at this low percentage of absorption, the amount of iron in fortified formula meets the Recommended Dietary Allowances for this age group. Other investigators have reported higher rates of absorption, especially from formulas supplemented with both iron and ascorbic acid (Stekel et al. 1986).

Heme Iron. Heme iron comes from the hemoglobin and myoglobin in meat, poultry, and fish. Although heme iron accounts for a smaller proportion of iron in the diet than nonheme iron, its role is important; the body absorbs a much greater percentage of heme iron, and its absorption is less affected by other dietary constituents than absorption of nonheme iron (Hallberg 1981).

When both forms of iron in the diet are considered, men absorb an average of about 6 percent of total dietary iron and women absorb 13 percent in their childbearing years (Charlton and Bothwell 1983). The higher absorption in women is related to their lower iron stores and helps to compensate for iron losses of menstruation.

Intestinal Regulation. The regulation of iron entry into the body takes place in the mucosal cell of the small intestine (Charlton and Bothwell 1983), and transferrin may act as an iron carrier (Huebers and Finch 1987). If iron stores are low, as is true for most women and children, transferrin in the intestinal mucosa readily takes up iron and increases the proportion absorbed from the diet. The saturation of transferrin is decreased in iron deficiency. Conversely, the high iron stores typical of men and older women reduce the percentage of iron absorbed, thereby offering some protection against iron overload (which is discussed later in this chapter).

Key Scientific Issues

- Role of Iron in Anemia
- Role of Folate and Vitamin B_{12} in Anemia

Role of Iron in Anemia

Because iron is one of the earth's most abundant elements, it may seem surprising that iron deficiency should ever become a nutritional problem. One explanation is that the most common forms of iron in food are relatively insoluble and cannot be absorbed from the intestine. Other factors predisposing to iron deficiency are related to evolving changes in the diet, not only during past millennia, but also within the last century (Eaton and Konner 1985). As noted above, iron is best absorbed from diets that are rich in meat, poultry, fish, and ascorbic acid and is poorly absorbed from diets consisting primarily of whole grain cereals and legumes (Hallberg 1981; Charlton and Bothwell 1983). Even though whole grain foods contain substantial amounts of iron, the form of iron cannot be as readily dissolved and absorbed. Thus, in some cases, the iron content of whole grain cereals and legumes may not wholly compensate for their decreased absorption. This problem may be one reason that iron deficiency anemia remains much more common in developing countries than in the United States where cereal grain products are commonly fortified with iron (Florentino and Guirriec 1984).

Stages of Iron Depletion

Iron depletion occurs in three stages (Cook and Finch 1979). The first involves a decrease in iron stores (as measured by a decrease in serum ferritin) without loss of essential function. This stage is not associated with adverse physiologic consequences, but it does represent a condition of vulnerability. In the United States, women of childbearing age, for example, may characteristically have very low iron stores, but in only a very small number is there a progression to anemia (LSRO 1984b). The risk of developing anemia is minimized by the body's ability to increase iron absorption as iron stores diminish.

The second stage is characterized by biochemical changes that reflect the lack of sufficient iron for normal production of hemoglobin and other essential iron compounds, as indicated by a fall in transferrin saturation levels and an increase in erythrocyte protoporphyrin. Because the hemoglobin concentration has not yet fallen below levels considered anemic, this stage is regarded as iron deficiency without anemia.

The third stage is frank iron deficiency anemia, which occurs when hemoglobin production has been sufficiently depressed to result in a hemoglobin concentration (and mean corpuscular volume) below the normal reference range for individuals of the same age and sex. In this chapter, the term iron deficiency refers to the second and third stages.

Causes of Iron Deficiency

The major causes of iron deficiency are insufficient assimilation of iron from the diet, dilution of body iron by rapid growth, and blood loss (Bothwell et al. 1979; Dallman, Siimes, and Stekel 1980). Because the manifestations of iron deficiency are rarely obvious, most cases are detected by laboratory tests done at a routine examination. The groups at highest risk for iron deficiency are infants, children, adolescents, and women, especially pregnant women, between the ages of menarche and menopause (LSRO 1984b).

Age-Related Factors in Susceptibility

Infants. The prevalence of iron deficiency among infants is highest between about 4 months, when neonatal iron stores accumulated during fetal life are first likely to become depleted, and 3 years of age (Dallman, Siimes, and Stekel 1980). During this period, total iron in the body should more than double to accommodate a rapid rate of growth and an increase in red cell mass. Excessive consumption of cow milk, which is a poor source of iron and commonly associated with occult intestinal blood loss in early infancy,

is a frequent cause of iron deficiency in young infants (Fomon et al. 1981). In premature infants and in twins, iron deficiency anemia may develop as early as 3 months after birth because their neonatal iron stores are smaller and weight gain is proportionately greater than in full-term or single infants. In older children, iron deficiency results from inadequate dietary intake and is associated with poverty (DHHS/USDA 1986).

Adolescents. Iron deficiency is common during adolescence (LSRO 1984b; Dallman, Yip, and Johnson 1984). Boys gain an average of 10 kg, or 22 lb, during the peak year of their growth spurt, usually between 12 and 15 years of age. At about the same age as the growth spurt, and in relation to sexual maturation, the concentration of hemoglobin increases between 0.5 and 1.0 g/dl/year towards values that are characteristic of adult men. The double burden of increased red cell mass and increased hemoglobin concentration requires an increase of about 25 percent in total body iron during the year of peak growth. Adolescent girls also need more iron. Their average weight gain during the peak years of the growth spurt—9 kg, or 20 lb, usually between 10 and 12 years of age—is almost as great as in boys. Although the concentration of hemoglobin changes very little during this period, the onset of menstruation imposes additional iron needs.

Women of Childbearing Ages. The major factors that predispose to iron deficiency anemia in this group are menorrhagia (excessive loss of blood during menstruation) and pregnancy (Bothwell et al. 1979). Heavy blood loss occurs in about 20 percent of women (Hallberg et al. 1966). The use of intrauterine devices increases the prevalence of menorrhagia to about 30 to 50 percent of women, depending on the type used (Israel, Shaw, and Martin 1974). Oral contraceptives, on the other hand, decrease menstrual blood loss by about half and are rarely associated with menorrhagia (Hefnawi, Askalani, and Zaki 1974).

Many women with menorrhagia are usually unaware that they have greater-than-normal menstrual blood loss (Hallberg et al. 1966). For this reason, blood tests at routine health examinations can sometimes detect anemia in women, even when the history of menstrual blood loss is unimpressive.

Iron deficiency anemia may develop during pregnancy (Svanberg et al. 1975) because of the increased requirements for iron to supply the expanding blood volume of the mother as well as the rapidly growing fetus and placenta. True anemia, however, must be distinguished from low hemoglobin values that normally occur as a result of blood volume expansion and must be diagnosed with the use of appropriate standards. Healthy women who are not pregnant have about 2.6 g of total body iron, but only about 0.3

g of this amount is storage iron. The total iron requirement during the entire course of pregnancy averages 1 g and, therefore, exceeds the amount of storage iron in most women. However, an increase in efficiency of dietary iron absorption compensates in part for the limited iron stores. Most of the additional iron is needed for growth of the fetus and placenta during the last half of pregnancy (Bothwell et al. 1979).

Even with the normal adaptive increase in iron absorption that takes place during pregnancy, iron stores may become depleted. For this reason, clinicians commonly recommend an iron supplement that provides the equivalent of about 30 mg of elemental iron or more per day during the last half of pregnancy. After delivery, the iron requirement of the mother is temporarily reduced below normal as the expanded mass of red cells decreases to baseline levels.

Mild iron deficiency in the pregnant woman generally has no detectable effect on hemoglobin concentration in the newborn. However, the severe iron deficiency anemia seen in pregnant women in some developing countries can cause decreased placental weight and birth weight as well as anemia in the newborn (Singla et al. 1978).

Men and Postmenopausal Women. Normally, iron stores increase throughout adult life in men and after menopause in women (Cook, Finch, and Smith 1976), so overt nutritional iron deficiency rarely develops in these groups. Among older persons, anemia is more commonly associated with chronic diseases, inflammation, and infections than with iron deficiency. However, factors that can predispose these groups to iron deficiency anemia include frequent blood donations (three or more times a year) and blood losses due to chronic aspirin ingestion, bleeding ulcers, and colorectal cancers.

Frequent aspirin consumption impairs blood coagulation and leads to blood loss from the intestine, usually in minute amounts that can be detected only by sensitive tests. For example, one study found that 300 mg of aspirin taken three times a day for a week increased intestinal blood loss to 5 ml/day (which averages several times normal menstrual losses) from a normal average of 0.5 ml/day (Pierson et al. 1961).

When there is no known basis for iron deficiency anemia, lesions such as a peptic ulcer or carcinoma may cause chronic and inapparent blood loss from the intestine. Parasitic infestation, particularly with hookworm, commonly causes inapparent intestinal blood loss in some developing countries, but is relatively rare in the United States.

Consequences of Iron Deficiency

The manifestations of iron deficiency can be subtle and depend on the relative severity of functional impairment caused by reduced levels of the "essential" iron compounds (Dallman 1982). These manifestations are related to the effects of iron deficiency on other tissues, to the resultant anemia, or to a combination of the two (Dallman 1986). One difficulty in interpreting studies in this area is that the effects of impaired iron status may differ among iron-deficient individuals who are—or are not—anemic.

Work Performance. Studies in humans as well as in rats show that iron deficiency causes a substantial reduction in work capacity, particularly when the concentration of hemoglobin falls below 10 g/dl, which is 2 to 4 g/dl below the lower limit of normal for adults. Some studies in humans indicate that even mild anemia can decrease performance in brief, hard exercise (Viteri and Torun 1974). To determine the practical significance of these findings for productivity, manual laborers in developing countries who were suffering from iron deficiency anemia were studied. For example, among men on a rubber plantation in Indonesia (Basta et al. 1979) and women on a tea plantation in Sri Lanka (Edgerton et al. 1979), the productivity of iron-deficient individuals was significantly less than that of workers with a normal hemoglobin concentration. After iron supplementation, the performance of the iron-deficient subjects improved, with the greatest improvement occurring in those who had the lowest initial hemoglobin concentrations.

In these studies, it has not been possible to distinguish the extent to which this impaired work performance is due to anemia *per se* or to the tissue abnormalities accompanying iron deficiency. Experiments with rats have shown that dietary iron deficiency also results in a marked impairment in the oxidative production of cellular energy in skeletal muscle (Finch et al. 1976; McLane et al. 1981; Davies et al. 1984). The major consequence of this muscle impairment is a lessened capacity for prolonged exercise or physical endurance, whereas anemia primarily restricts the performance of brief, strenuous exercise (McLane et al. 1981; Davies et al. 1984).

Body Temperature Regulation. An impaired capacity to maintain body temperature in a cold environment is another characteristic of iron deficiency anemia. This abnormality is related to decreased secretion of thyroid-stimulating hormone and thyroid hormone (Beard et al. 1984) and to the anemia itself; studies of the iron-deficient rat show that a transfusion of red blood cells corrects the abnormality. Furthermore, normally fed rats

develop impaired heat production when they are made anemic by an exchange transfusion that replaces red blood cells with plasma that lacks hemoglobin.

Behavior and Intellectual Performance. Increasing evidence suggests that changes in behavior and impaired development and intellectual performance may result from iron deficiency (Lozoff and Brittenham 1986; Pollitt 1985). Most studies have evaluated infants between 6 months and 2 years of age using the Bayley Scale of Infant Development, a test to evaluate sensory development, fine and gross motor skills, and language development in this group. By this standard, infants who are even mildly iron deficient have a statistically significant decrease in responsiveness, activity, and attentiveness and have increased body tension, fearfulness, and tendency to fatigue (Lozoff et al. 1982b). The long-term significance of these observations has not been determined. Of particular interest is the observation that these deficits are most profound in the oldest infants (19 to 24 months), in whom iron deficiency may have been present for the longest period (Lozoff et al. 1982a). Another important finding is that even infants with very mild iron deficiency anemia, or simply with early evidence of impaired hemoglobin production, do not score as well as infants with no laboratory evidence of iron deficiency or evidence merely of depleted iron stores (Lozoff et al. 1982b; Oski et al. 1983; Walter, Kovalskys, and Stekel 1983). Although the results of these studies are not as conclusive, the behavioral abnormalities are significant because the brain's rapid rate of growth and differentiation during infancy might make it particularly vulnerable to nutrient deficiencies. Because the same adverse environmental factors that lead to iron deficiency could also be responsible for behavioral deficits, these studies are difficult to interpret. This complexity may help to explain why some children display a rapid improvement in the Bayley score after iron treatment (Oski et al. 1983), whereas others do not (Lozoff et al. 1982a, 1982b).

Resistance to Infections. Decreased resistance to infection is characteristic of iron deficiency in both humans and experimental animals (Beisel 1982; Vyas and Chandra 1984; Dallman 1986). Iron-deficient children have abnormalities in lymphocytes and neutrophils, two types of white blood cells that help defend against infections (see chapter on infections and immunity). Although infections are associated with decreases in measures of iron status, these decreases may not be related to deficient iron intake.

Despite numerous studies that show an impaired resistance to infection under laboratory conditions, no conclusive evidence demonstrates that iron deficiency itself causes an increased rate of infections in free-living

individuals. Iron deficiency anemia and infections are both common among poor populations, but a cause-and-effect relationship, although plausible, has not been established (Strauss 1978). These issues are discussed further in the chapter on infections and immunity.

Lead Poisoning. Iron deficiency substantially increases the risk of lead poisoning, particularly in young children. Iron-deficient individuals absorb increased amounts of lead (Watson et al. 1986), and elevated blood lead concentrations have been observed among some children with laboratory evidence of iron deficiency (Yip and Dallman 1984).

Prevention of Iron Deficiency

Iron deficiency can be prevented by increasing dietary iron intake, improving the bioavailability of iron in the diet, or decreasing body losses of iron. Dietary iron intakes can be improved by increasing the consumption of iron-rich foods, administering iron supplements to specific target populations, and fortifying certain food products with iron. Parental awareness of appropriate diet is especially important for infants, whose diet is relatively simple. Typically, an infant's diet is discussed during routine health maintenance visits.

Fortification of cereal and grain products is a relatively inexpensive and effective means of increasing iron intake (International Nutritional Anemia Consultative Group 1982; Clydesdale and Wiemer 1985). These foods usually reach the population as a whole in adequate amounts to make a difference without the need for individual counseling. Nevertheless, several aspects of fortification are controversial. Because some iron compounds are poorly absorbed (Cook and Reusser 1983; Yetley and Glinsmann 1983; Hurrell 1984), it is difficult to document that eating fortified foods helps prevent iron deficiency, especially because baseline data are unavailable. Readily absorbed forms of iron react with foods and sometimes decrease shelf life. One compound that may strike a reasonable compromise between shelf life and bioavailability is finely powdered metallic iron, although some studies find that this form, too, is poorly absorbed (Elwood et al. 1968; Hallberg, Brune, and Rossander 1986).

Continuation of breastfeeding for 6 months or more confers substantial protection against development of iron deficiency in full-term infants (AAP Committee on Nutrition 1985). Iron-fortified infant formula, which was introduced about two decades ago in the United States, has gradually supplanted most unfortified formulas and fresh cow milk as infant food during the first year of life (Martinez and Nalezienski 1979). In a large

survey conducted in 1984, 77 percent of 5- to 6-month-old infants in the United States who were receiving cow milk formula were consuming the iron-fortified form (Martinez 1985). Today, iron deficiency in otherwise healthy infants is almost entirely restricted to those on a diet of fresh cow milk (Sadowitz and Oski 1983) or unfortified cow milk formula (Saarinen 1978).

Vitamin C (Ascorbic Acid) Fortification. The absorption of iron from fortified cereals can be increased twofold to threefold if the cereals are also fortified with about 5 mg of vitamin C per mg of iron (International Nutritional Anemia Consultative Group 1982; Cook and Bothwell 1984). Some of the effectiveness of iron-fortified infant formulas in preventing iron deficiency has been attributed to their fortification with this vitamin (Stekel 1984).

Iron Supplements. Supplementation has the disadvantage of requiring extra effort and expense compared with fortified foods. People do not always remember to take medications consistently and regularly. Supplements are less available to the poor and other groups most likely to be iron deficient. Supplementation is, however, a reasonable approach to prevention of iron deficiency in breastfed premature infants, in pregnant women, and in targeted high-risk population groups. In these situations, a large amount of dietary iron is provided over a short period of time. Its usefulness for a given individual requires evaluation by a qualified health professional. Iron supplement use and recommendations to increase dietary iron intake are usually not necessary for the general population. Among Americans as a whole, poor iron status is relatively rare (LSRO 1984b) and iron supplements are not associated with improved iron status (Looker et al. 1987). An additional concern is that increased iron intake can harm individuals who are susceptible to iron overload (LSRO 1984b).

Federal Food Programs. Because iron deficiency is more common among the poor than among persons above the poverty line (DHHS/USDA 1986), iron status should improve as a result of Federal food programs that serve socioeconomically disadvantaged groups. In one study, infants and children who had not received aid from the WIC program in 1973–74 were far more frequently anemic than a similar population in 1977 who were enrolled in the WIC program since birth (Miller, Swaney, and Deinard 1985). Although differences unrelated to iron intake probably existed between the two groups, which might account for differences in iron status, the foods provided by the WIC program included several sources of iron or enhan-

cers of iron absorption: formula fortified with 12 mg of iron per liter for infants up to 12 months of age, and iron-fortified infant cereal and ascorbic acid-fortified fruit juice for infants between 6 and 12 months of age.

Potentially Adverse Consequences. Under ordinary circumstances, a modest excess of dietary iron (over requirements) does not have adverse consequences. On the other hand, increased iron intake might be harmful for some individuals. A much discussed example is the hereditary condition hemochromatosis, in which abnormal amounts of tissue iron accumulate over the years as a result of a genetic defect in absorption, eventually damaging the liver, heart, pancreas, and adrenal glands (Bothwell et al. 1979). A subset of homozygous individuals with hemochromatosis usually develops symptoms by middle age. Heterozygous carriers of the hemochromatosis gene may be at slightly increased risk for iron overload (Brown 1981), but the clinical significance of this risk is uncertain. Although there is no direct evidence that current levels of iron fortification are harmful, concerns have been raised that any increased level of iron in the food supply may harm individuals susceptible to iron overload. Individuals who require repeated blood transfusions for relatively rare conditions, such as thalassemia, may also accumulate excess iron, which is then deposited in soft tissues. Fortification iron adds an undesirable, but relatively small, load compared with that administered by transfusion.

Excessive iron intake may affect the absorption of other trace elements. Although a high dose of iron medication impairs the absorption of zinc or copper administered at the same time (Solomons and Jacobs 1981), this interaction probably does not occur at the much smaller fortification levels. Of greater concern is the possibility of compromised zinc or copper absorption in groups who take larger amounts of iron as supplements, such as infants and pregnant women (Breskin et al. 1983; Hambidge et al. 1987).

Excessive iron administration may increase the risk of infection (Pearson and Robinson 1976; Beisel 1982). The basis for this concern is that a high degree of unsaturation in the iron-binding protein transferrin suppresses the growth of many bacteria. Conditions of iron overload are associated with very low levels of unsaturation. Although this issue may be important in clinically diagnosed iron overload, recent U.S. survey data have found a low prevalence of abnormally high transferrin saturation values in the general population (LSRO 1984b).

Role of Folate and Vitamin B_{12} in Anemia

Although deficiencies of folate or vitamin B_{12} are relatively rare among the general U.S. population, certain groups are particularly at risk for developing these nutrient deficiencies. Folate deficiency is of special concern. Its extent in the general population is virtually unknown. Low socioeconomic groups at vulnerable stages of the life cycle are at greatest risk—pregnant women (especially adolescents), infants (especially those who are small or premature), young children, and older persons (Shojania 1984). Surveys of the folate status of these groups have been too limited in sample size and methodology to permit adequate evaluation (LSRO 1986).

Folate requirements for pregnant women are greatest in the last trimester of pregnancy; however, most women's diets meet these requirements. Oral folate supplementation during this period is often recommended for high-risk groups. Premature infants, particularly those of very low birth weight, may need more folate to support their growth than is provided by infant formula or breast milk. Under a physician's guidance, this folate can be supplied as an oral supplement. Infants fed primarily unfortified goat milk are also at risk for folate deficiency because of the unusually low folate content of this food.

Other risk factors for folate deficiency include chronic disease and use of alcohol and drugs. Chronic and severe diarrhea, as in tropical sprue or celiac disease, for example, can cause folate deficiency. Folate deficiency also occurs among alcoholics (see chapter on alcohol). As discussed in the chapter on drug-nutrient interactions, individuals who use oral contraceptives and other medications may be at increased risk for folate deficiency, but the extent and public health significance of these interactions is uncertain (LSRO 1984a).

A dietary vitamin B_{12} deficiency can occur in strict vegetarians who avoid all foods derived from animals, including eggs and dairy products. Nursing infants of women consuming such diets or of women who are vitamin B_{12}-deficient are also at risk because the vitamin B_{12} content of the breast milk decreases as the mother's vitamin B_{12} stores decline (Shojania 1984). Any strict vegetarian who becomes pregnant should be advised to supplement her diet with vitamin B_{12}.

Implications for Public Health Policy

Dietary Guidance

General Public

Prevention of nutrition-related anemia depends on adequate dietary intake of iron, vitamin B_{12}, and folate as well as the full complement of other essential nutrients. Except for younger children and women of reproductive age, who are at greater risk for iron deficiency, it appears that current iron consumption levels are sufficient for most of the population.

Special Populations

Routine health care for infants and pregnant women, the groups at highest risk for anemia, should include laboratory evaluation for anemia and nutritional advice on methods to ensure adequate iron intake. Nonpregnant women in their childbearing years and adolescents are also at greater risk for iron deficiency anemia; these individuals should be monitored and should receive special counsel on preventing iron deficiency. Frequent blood donors, another high-risk group, should be advised by blood bank personnel about dietary methods to enhance iron intake and absorption. Groups who may need iron supplements, such as premature infants, pregnant women, women with excessive menstrual bleeding, frequent blood donors, strict vegetarians, and regular aspirin users, should also receive advice from health professionals on enhancing iron bioavailability from the diet. Specific education efforts directed toward these special groups, even though difficult, are needed.

Folate deficiency anemia usually occurs among women late in the course of pregnancy, among small and premature infants, and among alcoholics. These groups, especially from low-income families, should receive advice about dietary and supplemental sources of this vitamin.

Strict vegetarians who consume no foods of animal origin, especially women who are pregnant or nursing, should be advised to consume supplemental sources of vitamin B_{12}.

Nutrition Programs and Services

Food Programs

Because groups that benefit from food programs are those at highest risk for anemia, such programs should continue to be made available to high-

risk groups and should encourage consumption of foods rich in iron and folate. Evidence suggests that current levels of iron fortification are safe and adequate, and no changes should be recommended at this time.

Food Labels

Evidence related to the role of iron and folate in anemia suggests that food labels should indicate the content of these nutrients.

Special Populations

Patients with anemia should receive counseling and assistance to develop diets that have adequate amounts of bioavailable iron, folate, or vitamin B_{12} from dietary or supplemental sources.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in anemia should include investigations into:

- Screening for earlier stages of iron deficiency using tests that identify iron depletion (e.g., erythrocyte protoporphyrin).
- Elucidation of the health consequences of conditions of iron depletion prior to development of anemia.
- Validation of methodologies for identification of the extent of deficiencies of iron, folate, and vitamin B_{12} in the general population and in high-risk groups.
- Interactions between iron, folate, vitamin B_{12}, and other nutrients consumed in the diet.
- Improved methods for analysis of the folate content of food.
- Determination of iron requirements at various stages of the life cycle and under various physiologic conditions.
- Identification of appropriate levels and types of iron in the food supply for individuals with hereditary conditions of excess iron absorption.
- Identification of the level of iron intake that confers maximum protection against major infections.
- Determination of trends in iron fortification in the U.S. food supply.
- Development of effective methods to educate the general public and high-risk groups about consuming diets adequate in iron and folate.

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Chapter 13

Neurologic Disorders

The man is, above all else, the mind of the man, and not only the mind as an organ of conscious thought but the mind as an organ of bodily nutrition. . . .
James J. Putnam
Boston Medical and Surgical Journal (1899)

Introduction

Historical Perspective

Since biblical times, brain function and certain nutritional factors have been thought to be related, but knowledge of the interaction between nutrition and neurology is still sparse. Scientific interest in the link between nutrition and brain function began in the early 19th century when Magendie proposed that the central nervous system controlled appetite (Anand 1961; Widdowson 1982). Due to the predominance of theories that hunger was purely a peripheral sensation (Cannon and Washburn 1912), it was not until the 1930's that control of feeding began to be attributed to specific regions of the brain.

Classically, nutritional deficiencies have also been related to brain function. Starvation was shown to produce a variety of overt behavioral changes as well as mental deterioration (Blanton 1919), and severe malnutrition in animals is now associated with impaired brain development and learning (Winick 1976). The absence of specific vitamins or minerals from the diet has been known for many years to produce behavioral or neurologic symptoms in animals (Funk 1911). In the early 20th century, disorders of the human nervous system were observed as consequences of deficiencies of certain vitamins, copper, and magnesium in the diet (Widdowson 1972). In most industrialized societies, however, only a few nutritional deficiency diseases, such as those associated with alcoholism (see chapter on alcohol), occur with sufficient frequency to be of substantial concern to policymakers and the public.

Because the brain appears to be protected by the blood-brain barrier from fluctuations in plasma nutrient levels caused by eating, it has been difficult to demonstrate effects of specific foods or dietary components on brain function. Furthermore, the nutrient transport and cellular uptake mechanisms as well as the factors affecting the nutrient content of the brain are not fully understood (Pardridge 1986). In laboratory animals, brain levels of certain essential constituents have been reported to vary markedly as a function of the nature and timing of food consumption (Pardridge 1977; Wurtman, Hefti, and Melamed 1981; Blusztajn and Wurtman 1983), but whether human neurotransmitter systems are affected by the intake of dietary precursors (Wurtman, Wurtman, and Growdon 1981b; Blusztajn and Wurtman 1983) is as yet uncertain.

This chapter reviews these and other nutritional aspects of neurologic phenomena, and because cerebrovascular diseases account for such a large proportion of neurologic cases and hospital admissions, it also reviews the relationship between diet and stroke.

Significance for Public Health

Stroke is the most common life-threatening neurologic disease in the United States: It ranks third after heart disease and cancer as a cause of death and is also a major cause of long-term disability (NCHS 1986). Although stroke mortality rates have declined dramatically in recent years (see chapter on high blood pressure), in part as a result of improved high blood pressure management, about 500,000 new cases still occur annually. About 2 million Americans are estimated to suffer from stroke-related disabilities at an annual cost of more than $11 billion (NINCDS 1986). The mortality rate among black Americans is almost twice that of whites. Because a significant portion of the important risk factors for stroke are under behavioral control, efforts to reduce these risks seem to be especially worthwhile.

Other neurologic conditions are also prevalent in the U.S. population. Approximately 2 million Americans suffer from epilepsy, at an estimated health care cost of $3 billion. Chronic headaches afflict 40 million people in the United States and are responsible for 8 million annual visits to a physician and 64 million days of work lost due to pain. Alzheimer's disease affects 2 to 3 million Americans, at an estimated annual health care cost of up to $50 billion (NINCDS 1986). Whether any appreciable fraction of these conditions can be prevented or ameliorated by dietary means is unknown but seems unlikely given current evidence.

Scientific Background

Nutritional Needs of the Nervous System

The brain and nervous system probably require the full complement of essential nutrients and energy to develop and to maintain their neurons and supporting cells. Although it seems reasonable to expect that a deficiency of any one of the essential nutrients or of energy would impair the development and subsequent maintenance of these structurally and functionally complex tissues, evidence to support this hypothesis has been difficult to obtain (Shoemaker and Bloom 1977; Nowak and Munro 1977).

The human brain normally metabolizes 100 to 150 g of glucose per day as fuel, but the mature nervous system is relatively insensitive to restrictions of energy and protein. During starvation, it adapts and uses ketones, derived from breakdown of body fat stores, for energy and thus spares blood glucose and conserves body protein. The documented behavioral changes that occur in starving individuals—depression, apathy, irritability, and loss of libido—do not necessarily reflect damage to the nervous system (Kerndt et al. 1982).

Most direct research on the neurologic effects of nutritional deprivation has been performed on experimental animals. In part because of species variability in the time course of neurologic development, the results of this research may not be applicable to humans.

Additional information on the effects of dietary deficiencies on human brain development and nervous system function derives from "natural experiments" of human starvation or inadequate dietary intake. With a few notable exceptions, it has been difficult to separate the effects of nutritional deficits in these situations from those of other environmental, social, and medical problems that often accompany poor nutritional status (Pollitt and Thomson 1977).

Nonetheless, severe deficiencies of vitamins, especially the B-complex group, impair nervous system function (Dreyfus 1988; Lipton, Mailman, and Nemeroff 1979). Thiamin deficiency causes beriberi neuropathy as well as a peripheral neuropathy and polyneuritis that leads to Wernicke-Korsakoff's syndrome (paralysis of the eye muscles, loss of muscular coordination, and memory loss) in long-term alcoholics (Dreyfus 1988; see chapter on alcohol). Inadequate niacin intake causes pellagra, with symptoms that include intellectual impairment and dementia, in individuals of all ages. Deficiency caused by vitamin B_{12} malabsorption in untreated pernicious

anemia or as a result of a long-term vitamin B_{12} deficient vegetarian diet can result in subacute degeneration of the spinal cord, optic nerves, cerebral white matter, and peripheral nerves (Dreyfus 1988). Severely deficient intakes of other vitamins of the B-complex group also affect neurologic function. In the early stages, these symptoms are readily overcome by increased dietary intake of the appropriate vitamin, but nerve damage in later stages appears to be irreversible (Lipton, Mailman, and Nemeroff 1979). Whether subclinical deficiencies of these vitamins affect nervous system function is as yet uncertain (Goodwin, Goodwin, and Gary 1983).

Deficiencies of other nutrients may relate to defects in nervous system function. For example, iodine deficiency during brain development causes mental retardation and neuromotor abnormalities. Chronic iron deficiency is associated with deficits in cognitive abilities (Lozoff et al. 1987). A few cases of vitamin E deficiency-induced spinal cord, cerebellar, and peripheral nerve degeneration with muscle wasting have been reported among patients with severe cholestatic liver disease or malabsorption syndromes (Muller, Lloyd, and Wolff 1983; Laplante et al. 1984; Weder et al. 1984). Levels of vitamin E are greatly reduced in the peripheral nerves of such patients (Traber et al. 1987). In most cases, neurologic damage resolves with administration of vitamin E (Sokol et al. 1985), suggesting that vitamin E deficiency may be responsible.

The effects of nutritional deficiencies on the developing nervous system are difficult to interpret. Studies in rats have almost always restricted total dietary intake rather than that of specific nutrients. These studies have indicated that nutritional deprivation at various stages of fetal and postnatal development produces its own constellation of defects. Early maternal malnutrition reduces fetal brain weight and brain protein and DNA content. Postnatal malnutrition also induces deficits in brain weight and, in addition, reduces myelination and dendrite formation and retards development of mature enzyme patterns (Shoemaker and Bloom 1977). These changes persist even after adequate nutrition is restored (Nowak and Munro 1977; Winick 1976). In experimental studies of pregnant animals, diets deficient in zinc and folate result in high rates of malformations such as neural tube defects and spina bifida in the offspring (Hurley and Shrader 1972; see chapter on maternal and child nutrition). Supplementation of these animals resulted in a significant reduction in the incidence of these congenital nervous system defects.

Studies in animals have shown that the neuropathology resulting from intrauterine starvation or postnatal malnutrition does not produce recognizable focal lesions but instead produces diffuse anatomical effects that

appear to be spread throughout the brain. Different effects occur in different brain regions depending on the rate of cell division within each region. Because changes of this type provide little information about functional connections, the significance of these changes for cognitive and behavioral function is uncertain (Nowak and Munro 1977).

The relevance of animal studies for human brain development and cognitive functioning is also uncertain. Reduced cellularity and myelination have been shown to occur in the brains of severely nutritionally deprived human infants. Malnutrition during and after pregnancy produces human infants with lower birth weights, smaller stature, and, therefore, smaller head circumferences and lower brain weights. None of these changes, however, has been demonstrated to affect higher mental processes (Dobbing 1984).

Dietary Precursors of Brain Neurotransmitters

Nervous system function is mediated through the work of various neurotransmitters such as serotonin, the catecholamines (dopamine and norepinephrine), and acetylcholine. These neurotransmitters are manufactured by the action of enzymes in the brain on the precursor amino acids tryptophan, tyrosine, and choline, respectively. Because the brain cannot make adequate quantities of the various precursors, it must rely on uptake from the bloodstream. Studies in animals have suggested that meal composition can affect plasma levels of the precursors and, therefore, synthesis of these neurotransmitters (Wurtman, Hefti, and Melamed 1981; Pardridge 1977).

Whether the various high dose dietary contributions to precursors of brain neurotransmitters affect neurologic function in animals other than the rat is uncertain (Trulson 1985). The effects of dietary precursors of neurotransmitters on animal function and behavior are also uncertain (see chapter on behavior). Also unknown is whether dietary precursors of neurotransmitters can alter normal human behavior (Spring 1986; Young 1986) or correct abnormal behavior (Growdon 1979a; Van Praag and Lemus 1986).

Clinical investigators have tested the utility of neurotransmitter precursors as treatments for diseases associated with neurotransmitter deficiencies such as Alzheimer's and Parkinson's diseases, depression, and sleep disorders (Growdon 1981; Growdon and Wurtman 1982; Growdon and Gibson 1982; Young 1986; Van Praag and Lemus 1986). There is no evidence that such conditions result from nutritional deficiencies. Thus, tryptophan, tyrosine, and choline (as such or as phosphatidylcholine) were given in

these studies in purified form independent of other food constituents. In the case of choline, doses were greater than would ordinarily be consumed in the normal diet.

Pharmacologic amounts of L-tryptophan, for example, have been administered to human subjects to induce sleep (Hartmann 1982), treat insomnia in older persons (Jenicke 1985), relieve anxiety and suppress food consumption in obese persons (Wurtman, Hefti, and Melamed 1981), suppress posthypoxic myoclonus (Growdon 1979b), and treat certain pain syndromes (Hosobuchi, Lamb, and Bascom 1980; Lieberman et al. 1982; King 1980). However, the effectiveness of tryptophan for these purposes has not been established, and its use remains controversial (DeFeudis 1987). Similarly, tyrosine, the dietary precursor of the neurotransmitters dopamine and norephinephrine, has been used to accelerate dopamine turnover in patients with Parkinson's disease (Growdon and Melamed 1982) and to treat patients with mild Parkinson's disease (Growdon 1981) or endogenous depression (Van Praag and Lemus 1986); however, these applications are also preliminary and require further confirmation.

Large doses of choline and purified phosphatidylcholine, precursors for the neurotransmitter acetylcholine, have been reported to improve the symptoms of patients with tardive dyskinesia (Growdon and Wurtman 1982) and mania (Cohen et al. 1980). These observations remain to be confirmed. Similar treatment of patients with Huntington's disease, Gilles de la Tourette's syndrome, familial ataxias, and epilepsy has produced negative or inconclusive results (Wood and Allison 1982).

Despite a single report that suggests that the administration of phosphatidylcholine for at least 6 months might retard the progression of Alzheimer's disease in a subset of older patients with this disorder (Little et al. 1985), more than a dozen additional studies have found choline to be ineffective in the treatment of this condition (Bartus et al. 1982). Evidence is also lacking for the hypothesis that Alzheimer's disease is a consequence of the breakdown of phosphatidylcholine in neuronal membranes to produce choline for acetylcholine biosynthesis (Blusztajn and Wurtman 1983).

Key Scientific Issues

- Role of Diet in Cerebrovascular Disease (Stroke)
- Role of Diet in Other Neurologic Disorders
- Role of Noncaloric Dietary Components in Neurologic Disorders

Role of Diet in Cerebrovascular Disease (Stroke)

Stroke is the sudden loss of brain function caused by one of four vascular events: thrombosis, or blood clot, in a cerebral artery; embolism, or blockage, of a cerebral artery by a circulating clot; stenosis, or narrowing, of a cerebral artery by atherosclerosis; or hemorrhage from rupture of a cerebral artery. These events deprive the brain of blood and oxygen and cause tissue death and irreversible damage to nervous tissue. The effects of the damage depend on the location and size of the tissue loss. Symptoms range from those too trivial for the victim to notice to major sensory deficits, blindness, paralysis, speech loss, coma, and death. Although some return of function is possible in tissues damaged but not destroyed, losses persisting beyond weeks are likely to be permanent.

Persons at greatest risk for stroke are those with hypertension and diabetes and those who smoke cigarettes and display impaired cardiac function due to coronary heart disease, congestive heart failure, or hypertensive heart disease. These major risk factors for stroke are in part related to nutritional, dietary, and lifestyle factors. Current evidence suggests that certain dietary substances that promote high blood pressure or diabetes may increase the likelihood of stroke. Thus, excessive dietary consumption of calories (if it results in obesity), sodium, and alcohol may increase the risk for stroke. The evidence that links dietary factors to high blood pressure and diabetes is reviewed in detail in the chapters devoted to those topics. Although there is a wealth of evidence supporting the relationship between diet, blood cholesterol levels, and atherosclerotic coronary disease (see chapter on coronary heart disease), the link to cerebrovascular disease is less clear.

Persons with hypertension are at greatly increased risk for stroke. This risk increases with elevations in blood pressure regardless of age and sex; it decreases when blood pressure is reduced. How hypertension predisposes to stroke is not fully understood, but it appears to injure cerebral artery walls. Diabetes and high blood cholesterol may also act, alone or in concert, to injure the inner wall of a cerebral artery. Through consequent platelet interaction, the injury becomes the site of plaque formation and subsequent atherosclerosis. Thus, hypertension seems to be the precursor of the hemorrhagic, the stenotic, and the embolic types of stroke.

Moderate sodium restriction (Koolen and Van Brummelen 1984; Kawasaki et al. 1978), high potassium intake (Treasure and Ploth 1983; Langford 1983; Kaplan et al. 1985), vegetarian diets (Ophir et al. 1983), calcium (Blaustein

and Hamlyn 1983; McCarron et al. 1984), weight reduction, and alcohol restriction all have been suggested as factors associated with blood pressure lowering. Of these, weight reduction and restriction of sodium have the most evidence to substantiate this association, but excessive consumption of alcohol is associated with increased rates of hypertension (Klatsky et al. 1977; MacMahon and Norton 1986; Potter and Beevers 1984). Epidemiologic evidence associates excessive drinking with increased frequency of subarachnoid hemorrhage and cerebral infarction (Hillbom and Kaste 1978, 1982), and heavy alcohol intake has been identified as an independent risk factor for stroke in humans (Gill et al. 1986).

The effect of dietary potassium on stroke has also been investigated recently. In a prospective study, individuals consuming somewhat higher levels of potassium from food sources had a reduced risk for stroke-associated mortality (Khaw and Barrett-Connor 1987). The effects of specific dietary factors on causation of stroke warrant further investigation.

Role of Diet in Other Neurologic Disorders

Headache

Headache, one of the most common complaints evaluated by neurologists, is estimated to affect 40 million Americans. Clinical investigations of the role of foods in precipitating vascular or migraine headaches remain controversial (Dreyfus 1988). The foods most frequently implicated often contain tyramines (e.g., cheese, red wines) or more rarely phenylethylamine (e.g., chocolates) (Dreyfus 1988; Egger et al. 1983). The "Chinese Restaurant Syndrome" is associated with numbness around the mouth, tingling, flushing of the face, dizziness, and headache (Kenny 1980). Use of the artificial sweetener aspartame has been found not to be associated with increased susceptibility to headache (Schiffman et al. 1987).

Current evidence suggests that dietary factors are unlikely to be responsible for most cases of headache, although toxicity of vitamin A, caused by excess intake of supplements, has been reported to cause headaches. Until conclusive evidence has established the link between certain foods and the occurrence of headaches, especially migraine, it may be prudent for such individuals to abstain whenever possible from those foods thought to provoke an attack (Dreyfus 1988).

Epilepsy

Low levels of magnesium can cause seizures, and the magnesium-deficient rat is used as a model of experimental epilepsy (Buck, Mahoney, and

Hendricks 1978). Magnesium deficiency in humans most often results from kidney disease and is not a significant cause of epilepsy in people. A wide variety of neurobehavioral symptoms common in the general population, including epilepsy, have been reported to occur in people consuming the artificial sweetener aspartame (Wurtman 1985). No well-controlled clinical studies have indicated that a causal relationship exists. Ketogenic diets (low in carbohydrate) have been used for decades to treat certain forms of intractable epilepsy. The mechanism of action of this diet is not understood (Withrow 1980), and it is tolerated poorly by some patients (Trauner 1985). Furthermore, it is nutritionally inadequate, unpalatable, and inappropriate for use in young children. Other specific nutrients such as vitamin D_3 have been suggested to have beneficial effects on seizure thresholds in rats (Siegel et al. 1984), but more information is needed before conclusions can be drawn about the role of diet in epilepsy.

Role of Noncaloric Dietary Components in Neurologic Disorders

Excessive Vitamin Intake

Vitamin A intoxication can result from the chronic use of relatively low levels (14,000 IU/day in infants and 25,000 to 50,000 IU/day in adults) of the vitamin (Farris and Erdman 1982), and toxic symptoms may appear suddenly with the onset of liver dysfunction due to other causes (Hatoff et al. 1982). Excessive intake of vitamin A causes reversible intracranial hypertension, which when not so identified has led to needless surgery; it can also occasionally result in headache, blurred vision, seizures, and encephalopathy. High doses of pyridoxine (vitamin B_6) have been used to treat conditions such as carpal tunnel syndrome; however, excessive pyridoxine in gram quantities has recently been associated with peripheral nerve deterioration, and more recent studies indicate that lesser amounts may produce toxic symptoms (Ditmars and Houin 1986; Dreyfus 1988; Schaumberg et al. 1983).

Endogenous and Exogenous Toxins

Naturally occurring food-borne toxins either consumed in the diet or produced by the body as a result of rare metabolic diseases also affect the mature nervous system; brain damage resulting from lung, liver, or kidney failure is a common example. Moreover, rare metabolic diseases or inborn errors of metabolism can cause naturally occurring food constituents to become toxic (e.g., copper in Wilson's disease, phenylalanine in phenylketonuria) (Dreyfus 1988). The seeds of certain cycad plants contain neurotoxic substances that, when ingested by experimental animals, cause symptoms similar to those of amyotrophic lateral sclerosis (ALS), parkin-

sonism, or Alzheimer's disease (Spencer et al. 1987). However, in man, the role of cycad plants and other dietary factors in ALS is still controversial (Garruto and Yase 1986). Other neurotoxins have caused acute poisonings on those rare occasions when they have contaminated foods in large quantities. These include ingestion of lead-contaminated paint, soil, or food and water (Mahaffey 1981); industrial contamination of shellfish with methyl mercury; and paralytic poisons produced by certain shellfish (Hatten et al. 1983).

Specific dietary constituents, such as heavy and trace metals, may have especially adverse effects on the nervous systems of older adults. For example, increased amounts of aluminum and calcium have been reported in brains of patients with Alzheimer's disease, and concentrations are especially high in the damaged neurons of the cortex (Linton et al. 1987), particularly in association with the senile plaques and tangles. Whether aluminum causes the cellular damage or accumulates simply because the cells are dying has not been established (see chapter on aging).

Food Additives

Numerous compounds added to foods can affect the nervous system. Some investigators have reported that very high levels of the dipeptide sweetener aspartame raise brain levels of tyrosine in rats and, as a consequence, impair synthesis of catecholamine neurotransmitters (Yokogoshi et al. 1984; Pardridge 1977), but others have not been able to identify such effects (Potts, Bloss, and Nutting 1980; Torii et al. 1986). The rat, unlike humans, rapidly converts phenylalanine (a component of aspartame) to tyrosine. Until aspartame has been tested in well-controlled human clinical studies, its effects on the nervous system remain speculative.

Drug-Nutrient Interactions

Some of the drugs used to treat neurologic diseases can lead to vitamin deficiencies by changing the metabolism of the vitamins, causing a secondary impairment of brain function (see chapter on drug-nutrient interactions). Dilantin, used to treat epilepsy, can increase folate requirements and cause vitamin K deficiency in the infants of mothers treated with this drug. In addition to the hypertensive medication effects on mineral metabolism described in the chapter on drug-nutrient interactions, hydralazine is a vitamin B_6 antagonist that can cause peripheral neuropathy. Tranquilizers such as chlorpromazine and other phenothiazines may cause hyperphagia and weight gain. Monoamine oxidase inhibitors can cause acute hypertensive crises, including excruciating headaches or fatal intracranial hemor-

rhages, when taken with foods or beverages high in tyramine. Long-term intake of Sinemet, used to treat parkinsonism, may cause niacin deficiency (Bender, Earl, and Lees 1979).

Caffeine is a pharmacologically active agent found in foods and drugs (Snyder et al. 1981) that can enter the brain because of its lipid solubility. Animal studies have suggested that foods can impair the efficacy of drugs by blocking their uptake into the brain. For example, a high-protein meal may diminish the efficacy of L-dopa (used to treat parkinsonism) or of Aldomet (used for high blood pressure) because these drugs are transported into the brain by the same carrier molecules that transport certain amino acids. The significance of these suggestions for either animal (Peter and Harper 1985) or human drug metabolism is uncertain at this time.

Implications for Public Health Policy

Dietary Guidance

General Public

Nutrients of concern in stroke are those associated with its major diet-related risk factors—hypertension, diabetes, and obesity. Evidence suggests that diets low in sodium and alcohol, as well as caloric intake and physical activity to achieve and maintain desirable body weight, should be recommended as public health measures to prevent stroke and its related conditions. Excessive drinking has been associated with stroke; hence, this practice should be avoided. Although some evidence links very large exposures of major dietary components (e.g., amino acids, choline) to nervous system disorders other than stroke, this evidence is, for the most part, preliminary and remains to be confirmed by additional clinical evidence before implications can be drawn.

Over- or underconsumption of certain vitamins and minerals can damage the nervous system as in the occurrence in alcoholics of thiamin deficiency-related Wernicke-Korsakoff's syndrome.

Special Populations

Studies in patients with major diet-related risk factors for stroke indicate that similar dietary changes can reduce the level of the risk factor and help prevent cardiovascular disease (see chapters on high blood pressure, diabetes, and obesity). Qualified health professionals should provide patients with information on the means to achieve these changes. In addition to a

focus on weight reduction and sodium restriction, this information should emphasize the importance of alcohol restriction in patients with high blood pressure and/or high glucose levels.

Suggestions that certain foods or food components might influence headache or epilepsy have yielded conflicting research results and are too preliminary to draw conclusions.

Nutrition Programs and Services

Food Labels

Evidence related to the role of dietary factors in stroke and other neurologic diseases supports the need for sodium labeling of packaged food products.

Food Services

Food service programs should emphasize diets low in sodium and calories to maintain ideal body weight and to control obesity and diabetes.

Special Populations

Patients at high risk for stroke and other neurologic conditions should be provided with counseling and assistance in the development of diets appropriate to their conditions.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in neurologic disease should include investigations into:

- The role of specific dietary factors in the etiology and prevention of stroke.
- The relationship, if any, between specific dietary factors and specific brain functions such as memory, alertness, and response time.
- The mechanisms by which food components, such as dietary precursors of neurotransmitters and certain additives and toxins, might affect nervous system function.
- The role, if any, of specific dietary factors in the etiology and prevention of Alzheimer's disease.
- The nutritional needs of the brain and nervous system in health and throughout life.

- The effects of excessive intake of nutrients and supplements (vitamins A, B_6, etc.) on nervous system function.
- The mechanism or mechanisms by which excessive alcohol intake increases the risk for stroke.
- The ability of diets low in calories, sodium, alcohol, and, perhaps, other dietary factors to prevent stroke.
- The most effective methods to educate the public about diet-related risk factors for stroke, and to assist the public in making recommended dietary changes.
- The comparative effects of dietary insufficiency on cognitive function and neurologic disease.
- The understanding of the blood-brain barrier nutrient transport processes and the mechanisms by which diet may influence brain function and health.
- The role of preexisting nutritional disease and nutritional status on the impact of neurotoxins.

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Chapter 14

Behavior

Thus it may appear, that there ought to be a great reciprocal influence between the mind and alimentary duct.
David Hartley
Observations on Man,
Vol. I, Chapter II, Section 2 (1749)

Introduction

The disciplines of nutrition and behavior are not usually considered to be closely related, but there are in fact several key areas of overlap between these fields. Behavioral factors determine the choice of foods in the diet, and any attempt to change dietary patterns must necessarily involve changes in behavior. Because eating itself is a behavior controlled by the brain, all disorders of eating inherently involve the central nervous system and may be associated with mood changes. Although considerable public attention has focused on suggestions that ingestion of certain foods or nutrients might influence behavior, it has been difficult to confirm such effects. Similarly, suggestions that some nutrients can modify specific aspects of brain function and behavior also require further confirmation. This chapter reviews relationships between nutrition and behavior. For more detailed discussion of these issues, the reader is referred to recent volumes on this topic (Miller 1981; Olson 1986; Wurtman and Wurtman 1977–86) and to the chapter on neurologic disorders in this Report.

Historical Perspective

That diet influences behavior is an ancient human belief. Primitive people attributed friendly and unfriendly feelings to plants and animals and expected these feelings to be transferred to anyone who ate such foods. Eating the heart of an aggressive animal, for example, was thought to confer strength and courage, whereas consumption of timid or weak creatures would undermine desirable attributes (Farb and Armelagos 1980).

In religious teachings, the behavior of mankind was said to change instantly when Eve ate the apple. Solomon, suffering the pangs of love, was comforted with apples (Cussler and deGive 1952). The ancient Greeks proposed that the human body is composed of four "humors"—hot, cold, wet, and dry—that control health, feelings, and behavior, and extended these categories to foods and other factors in the environment. Imbalances in these humors were thought to cause disease; physical and mental health could be restored by consuming foods in the opposite, complementary categories. Anger, for example, was considered hot and dry, and melancholy was cold and dry. These ill humors could be corrected by consuming foods that were cold and wet, or hot and wet, respectively (Farb and Armelagos 1980). Such ideas have carried forward to the present day, when many cultural groups believe in hot/cold or yin/yang approaches to food and health (Ludman and Newman 1984).

Systematic study of cultural influences on food intake began early in this century as anthropologists examined the use of food in isolated cultures and ethnic groups. These studies recognized the importance of societal influences on food selection and use, and they indicated that food intake is not an isolated, individual response to the sensory properties of food but instead depends greatly on the symbolic meanings of food in each culture (Goode, Curtis, and Theophano 1981). Even in contemporary times, foods are endowed with magical powers (Kimmens 1975) and are believed to symbolize feelings such as those of satisfaction and security (Bruch 1973).

Significance for Public Health

The reduction of behavioral risk factors for chronic disease and the development of effective means to do so are major public health goals, and improvement of the food choices and dietary practices of individuals and populations is the key to control of the conditions reviewed in this Report. Obesity, for example, is a common nutritional problem in the United States today, affecting about 34 million adults. Dietary fat and cholesterol increase the risk for a number of chronic diseases, including the Nation's leading killer, cardiovascular disease. These conditions are discussed in the respective chapters.

Other eating-related problems such as anorexia nervosa (self-starvation) or bulimia (binge/purge syndrome) are relatively uncommon. Anorexia nervosa occurs most often in females from the upper and middle social classes and usually begins between the ages of 13 and 20. Even among persons at highest risk, the prevalence is less than 1 percent. In the general population, approximately 1 in 250 suffer from anorexia nervosa in any given year

(APA 1987). Furthermore, despite a general impression to the contrary, the incidence of anorexia nervosa does not appear to be rising significantly (Williams and King 1987). Because of difficulties in its diagnosis, estimates of the incidence of bulimia vary from 2 to 19 percent among college women, the group at highest risk (Lustic 1985; Zuckerman et al. 1986), and are about 5 percent for men (Halmi, Flak, and Schwartz 1981). A recent survey of university students, however, identified only 1.3 percent of the female and 0.1 percent of the male respondents as meeting standard diagnostic criteria for this condition (Schotte and Stunkard 1987).

Pica (consumption of nonfood substances) is another eating disorder of concern. Because definitions of pica vary and individuals who practice pica are reluctant to admit it, it has been difficult to establish the prevalence of this condition. Thus, estimates of the proportion of individuals in selected groups of children, pregnant women, or other adults who practice pica have varied from 0 to 66 percent (Danford 1982), and no conclusions can as yet be drawn about its prevalence in the general population.

Other behavioral disorders commonly associated with food choices include childhood hyperactivity, antisocial behavior, and hypoglycemia. Neither the prevalence nor the nature of these conditions is reliably established.

Scientific Background: Methodological Issues

Although many research reports have concluded that food and nutrients influence behavior, most of these accounts do not meet criteria for controlled scientific research. Environmental, cultural, socioeconomic, and psychologic factors can induce symptoms such as anxiety, depression, fatigue, insomnia, or irritability, and it is difficult to demonstrate that such symptoms are caused by dietary factors unless research studies are designed to rule out other potential causes (Kanarek and Orthen-Gambill 1986).

Understanding of nutrition and behavior is also limited by unresolved questions about the applicability of much animal research to humans and by inadequacies in present knowledge of the effects of nutrients on brain function. Imprecise and inappropriate definitions and methods of measuring normal behavior also limit understanding. Such difficulties explain why research studies produce results that are often inconsistent and cause public and professional controversy.

Various authorities have emphasized the importance of methodologically rigorous research in this field and have urged investigators to design studies that include appropriate standards of measurement, adequate sample sizes, controls for confounding variables, elimination of sources of investigator and subject bias, appropriate statistical treatments, and caution in the interpretation of results (Sprague 1981; Anderson and Hrboticky 1986). These issues are especially important in establishing cause or effect as well as in establishing policies for regulation or labeling (Sobotka 1986).

Key Scientific Issues

- Behavioral Determinants of Eating Habits
- Behavioral Aspects of Eating Disorders
- Effects of Foods and Nutrients on Behavior

Behavioral Determinants of Eating Habits

Behavioral Issues in Food Selection

Although infants do not begin life with a choice of food, some of the most obvious reflexes at birth are those associated with eating. Infants learn to associate eating with security and relief from anxiety, tension, and distress. Later, children eat in conformance to cultural and familial standards. Throughout life, food symbolizes and mediates social relationships and is strongly linked to deep feelings of acceptance and comfort or deprivation (Bruch 1973). These ingrained meanings attached to the roles of food in society suggest reasons that food habits often can be changed only with difficulty.

Although the choice of certain foods as opposed to others may greatly affect nutritional status, surprisingly little is known about the factors that determine food selection beyond the fact that they include multiple environmental, cultural, genetic, social, and sensory variables that interact in complex ways (Rozin 1984). People must choose foods from those that are available, but the foods selected to be grown and sold vary greatly among different cultures. Within a given culture, individual food choices depend greatly on sociocultural systems that govern food production, distribution, and consumption (Goode, Curtis, and Theophano 1981; Harris 1985).

Individual preferences are the chief factors in food choices, but the elements that determine food preferences are poorly understood. Preferences for flavor and taste are learned, culturally determined, and dependent on

the degree of exposure (Story and Brown 1987). The one exception appears to be an innate preference for foods that are sweet. This preference is observed in early childhood and continues throughout life (Desor, Mallor, and Greene 1977). Aversions to foods are also learned and seem to occur most often when associated with gastrointestinal distress or the introduction of novel foods (Rozin 1984).

Selection of foods for nutritional or health reasons is also a learned behavior. Contrary to a commonly held opinion, infants have not been shown to have an inborn ability to select a balanced, nutritious diet (Story and Brown 1987). Recent studies indicate that the variety of foods available has an important effect on food consumption; the more the available foods are varied, the more of them people will eat (Rolls 1985).

Behavioral Aspects of Dietary Change

Behavior change—especially in dietary practices—is a key element in reducing the risk for chronic disease. Individual and public health efforts to induce beneficial changes in dietary habits are based on the assumption that people who understand the risks associated with their present practices will alter them to prevent illness. Although this assumption appears self-evident, education may not have as great an impact on food behavior as might be expected unless it can overcome counteracting barriers, including, perhaps, a general belief that some dietary practices are worth the risk (Syme 1986).

Extensive societal and behavioral forces inhibit dietary change. Eating behaviors are acquired over a lifetime; to change them requires alterations in habits that must be continued permanently—long beyond any short-term period of intervention. Dietary advice is often restrictive and viewed as depriving or unpleasant. It may also be incompatible with cultural or familial standards of appropriate food intake. Dietary changes may require increased cost, skill, time, or effort needed for food preparation (Glanz 1986).

Furthermore, environmental factors such as peer pressure, advertising of high-calorie foods and alcoholic beverages, or other cultural determinants may strongly counteract recommended changes (Syme 1986). Social and political values and economic considerations may also be obstacles (Somers and Weisfield 1986). Together, these barriers suggest that dietary advice (like much other advice) is far easier to give than to accept.

Despite these difficulties, considerable evidence supports the effectiveness of nutrition education in changing dietary intake to reduce risk factors for or symptoms of conditions such as coronary heart disease, diabetes, hypertension, and renal disease. For reasons that are poorly understood, public health efforts to reduce the incidence of obesity have been considerably less effective (Glanz 1986) and are discussed below.

Although no single method of counseling for dietary change is universally effective, the key elements of the more successful strategies have been identified repeatedly. These are (Zifferblatt and Wilbur 1977; Glanz 1986):

- To set realistic, achievable, and measurable goals.
- To tailor recommendations to individual lifestyle and dietary preferences.
- To use whatever social support systems are available to provide training in skills as well as to provide information.
- To establish good communication between educator and clients.
- To provide systematic followup, reinforcement, and monitoring.

Behavioral Aspects of Eating Disorders

Obesity

Obesity is the excessive accumulation of fat in the body. As discussed in the obesity chapter, approximately one-fourth of Americans are classified as overweight (Abraham et al. 1983). The definition, prevalence, cause, and treatment of obesity are discussed in that chapter.

At one level of understanding, the cause of obesity is quite simple: fat accumulates when more calories are consumed than are expended. It is difficult to demonstrate a positive correlation between total food consumption and the extent of obesity in specific individuals, although such relationships can be observed in population studies (Rolland-Cachera and Bellisle 1986). Human obesity is often a familial disorder; obese parents tend to produce obese offspring. While this observation does not distinguish the influences of heredity and environment, studies of twins suggest that there is a substantial genetic component to human obesity (Stunkard et al. 1986). It is also possible that some people become obese and sustain their obesity because mechanisms that normally regulate food intake are impaired (Wurtman et al. 1981; Rosenthal, Sack, James, et al. 1984). Obesity is more common among women than among men at all ages, and its prevalence increases with age but decreases among individuals of higher socioeconomic status and greater levels of physical activity.

Behavioral Determinants. Behavioral and psychiatric contributions to obesity—those factors that affect eating behavior—have been the focus of extensive investigation, based largely on the assumption that overeating is the primary cause of obesity. The evidence for this assumption is, at best, only partially correct (see chapter on obesity). Once obesity is established, food choices and caloric intake are no longer "normal," and personality differences between obese and normal-weight individuals may be due more to the results of physiologic changes, social discrimination, or dieting than to behavioral factors.

Because of these complexities, which impede scientific understanding at basic levels, numerous behavioral hypotheses have been proposed to account for the differences in weight between obese and normal-weight individuals. These hypotheses have been reviewed recently (Striegel-Moore and Rodin 1986) and are summarized in Table 14-1.

Considerable research supports many of these theories, but none has yet been demonstrated to account consistently for group differences between obese and normal-weight individuals. For most variables measured, no group differences have been found. Instead, the many tests of these hypotheses suggest that variation between individuals is greater than that between the groups; that behavioral correlates might be the result of obesity rather than its cause; and that even when a behavioral effect is identified, its relation to the etiology of obesity is uncertain (Striegel-Moore and Rodin 1986). The precise causal role of behavioral factors in obesity is still to be determined.

Table 14-1
Behavioral and Psychologic Hypotheses to Explain Obesity

Unconscious personality conflicts
Response to anxiety or depression
Neurotic personality traits
External locus of control
Preference of immediate gratification
Abnormal eating styles
Excessive food intake
External eating cues
Response to food palatability
Taste perception
Response to food variety
Restrained eating (response to dieting)
Arousal misperception

Source: Striegel-Moore and Rodin 1986.

Behavioral Associations. Of the various emotional disturbances to which obese persons are subject, three are specifically related to their obesity: disparagement of body image, psychologic complications of dieting, and binge eating (Wadden and Stunkard 1985). A fourth complication—fear of obesity—has also been reported. Binge overeating occurs in only a small percentage of obese persons and is discussed below with regard to bulimia.

Disparagement of body image affects a larger percentage of obese persons than nonobese persons who characteristically dislike their own bodies. Such feelings are closely associated with self-consciousness and impaired social functioning, and these feelings are not unexpected in view of the pervasive social biases and discrimination against the obese in this society (Brownell 1984). They are usually observed in persons who have been obese since childhood. Even among this group, however, fewer than half suffer from impaired body image.

Psychologic complications of dieting include anxiety, depression, irritability, and preoccupation with food. These disturbances may arise from the same mechanisms that occur in normal-weight persons who restrict their food intake (Stunkard and Rush 1974) and are discussed further in the chapter on obesity. Fear of obesity has been reported as a cause of self-induced dieting and subsequent weight loss, growth retardation, and delayed puberty in a small group of boys and girls ages 9 to 17 (Pugliese et al. 1983).

Behavioral Treatment. Although weight reduction ought to confer great benefits upon obese persons and be simple to accomplish, clinical experience has shown obesity to be remarkably resistant to treatment. The basis of weight reduction is deceptively simple: Establish an energy deficit by consuming fewer calories than are expended or by expending more calories than are consumed. As discussed in the obesity chapter, the most effective treatment methods involve combinations of diet, exercise, and behavior modification. Most such treatment in the United States is carried out under the direction of nonmedical groups and counselors in programs that pose minimal hazard, although they are of uncertain long-term effectiveness.

The role of behavioral strategies to enhance the effectiveness of weight loss programs has been the subject of active investigation. These strategies derive from the key assumptions and characteristics of behavior therapy: Behavior is acquired; treatment measures should be specified and outcomes evaluated; treatment should be individualized; and treatment effectiveness should be assessed (Wilson and O'Leary 1980). Behavioral weight control programs usually include group participation at weekly meetings

for periods of 2 months or longer and involve techniques of stimulus control (e.g., shop from a list, do not save leftovers), eating behavior (do nothing else while eating, chew thoroughly), reward, self-monitoring, nutrition education, physical activity, and cognitive restructuring in which patients are encouraged, for example, to set reasonable weight goals and to think about progress rather than failure (Stunkard and Berthold 1985).

Evaluations of the effectiveness of such programs have indicated that when spouses of obese patients were included during treatment, followup weight loss is greater (Brownell et al. 1978). Obese patients who participated in regular peer group meetings following the completion of formal treatment have been observed to maintain their weight loss better than those who do not participate in such meetings (Perri et al. 1984). Other behavioral studies have described factors associated with prevention of relapse following weight loss programs, such as strategies to cope with the presence of favorite foods (Marlatt and Gordon 1985).

Effects of Mood Disorders. It has been known for many years that disturbances of appetite and weight regulation are important symptoms of certain mood disorders. In pioneering work on manic-depressive disorders, for example, body weight was observed to fall early in a depressed phase, while a rise in body weight was often one of the earliest signs of recovery (Kraepelin 1921). Other patients, however, gained weight during protracted depression. In later large-scale studies of depression, eating and weight disturbances were found in 70 percent of depressed subjects (Leckman et al. 1984), and weight gain was observed in 70 percent of 263 depressed subjects during their recovery from depression (Kraines 1957). Depression can be accompanied by either gain or loss of weight, and in general, disturbances in appetite and weight regulation are accepted as central features of mood disorders (Herzog and Copeland 1985; Rosenthal, Sack, James, et al. 1984b; Slochower 1983), although it is important to distinguish such effects from those of antidepressant medications. Nevertheless, because disturbances in eating behavior may be characteristic of specific subcategories of depression, the study of eating behavior may provide an excellent source of objective information regarding the physiologic mechanisms that underlie particular psychiatric disorders.

Different patterns of appetite, eating behavior, and weight gain may reflect fundamental differences in brain biochemistry. Although there is considerable information on central neurotransmitters that may be involved in the regulation of appetite, much less is known about the neurophysiology of human mood states. Certain hypothalamic nuclei implicated in the control of feeding appear to be associated with reward or pleasure centers in the

brain (Morley and Levine 1983), and abnormal neurotransmission in these areas might produce concurrent disorders of eating habits and mood. Disturbed hypothalamic function has for some time been postulated as a fundamental defect in depression (Sachar 1976). Unfortunately, interpretation of data concerning such centers is complicated by the fact that the destructive lesions used to study them also damage other areas of the brain.

Several types of neurotransmitters are thought to play a role in appetite regulation, including the monoamines, opioid peptides, other neuropeptides, and gamma-aminobutyric acid. Disturbed regulation of these neurotransmitters has been postulated to be associated with depression, because abnormalities of both serotonin and norepinephrine metabolism, for example, seem to be present in depression (Murphy, Campbell, and Costa 1978; Jimerson 1984). Serotonin may also play a role in regulating carbohydrate intake, because ingestion of carbohydrate foods increases brain serotonin synthesis and release (Fernstrom and Wurtman 1972). Its agonist, fenfluramine, has been reported to decrease the proportion of dietary carbohydrates chosen by a group of so-called "carbohydrate cravers" (Wurtman and Wurtman 1983).

While decreased appetite and weight loss have long been recognized as prominent symptoms in endogenous depression (also known as endogenomorphic depression or melancholia), this weight loss is not usually observed in patients with nonendogenous, or neurotic, depression (Hopkinson 1981), whose symptoms instead are overeating, weight gain, and oversleeping (Davidson et al. 1982). In one study, patients observed to have an increased appetite during depression were predominantly female, neurotically rather than endogenously depressed, less severely depressed, and possibly more obese prior to the onset of depression (Paykel 1977). Although it might be beneficial for clinical and research purposes to categorize depressed patients into those who do and those who do not have increased appetite and weight gain, few investigators have evaluated these matters in depressed populations. In one attempt, decreased appetite was the symptom with the greatest value for discriminating between endogenous and nonendogenous types of depression (Feinberg and Carroll 1982), but in another, it was the severity of depression that determined whether weight was gained or lost (Weissenburger et al. 1986).

In a study of seasonal depression (with episodes during the winter but not in spring or summer), 71 percent of 125 patients experienced an appetite increase during their depressions, 17 percent a decrease, 9 percent a mixed reaction, and only 2 percent reported no appetite change (Rosenthal, Sack, Gillin, et al. 1984; Rosenthal, Sack, James, et al. 1984). Changes in weight,

as expected, paralleled appetite changes, with 72 percent reporting increased weight, 13 percent decreased weight, 3 percent a mixed picture, and 12 percent no change. These patients were predominantly women with a less severe, nonendogenous type of depression (Paykel 1977).

An association between weight change and sleeping patterns in depression has been noted (Crisp and Stonehill 1973). Depressives who lost weight differed from those who gained. The sleep duration for those losing weight was shorter, they awakened earlier, and their sleep was more disrupted. In a recent study, sleep-disrupted depression was associated with increased appetite and weight gain (Garvey, Mungas, and Tollefson 1984). In similar studies, overeating and weight gain were also associated with sleep disorders in patients with seasonal mood problems (Rosenthal, Sack, Gillin, et al. 1984).

Such patients also appear to crave carbohydrates (Rosenthal, Sack, James, et al. 1984), a symptom that has been associated with premenstrual tension, depression, and fluid retention in a survey of 300 nurses (Smith and Sauder 1969) and that has also been reported as a side effect of treatment with the antidepressant drug amitriptyline (Paykel, Mueller, and de la Vergne 1973). Studies of these and other relationships between mood and weight require further explanation and confirmation before their significance for obesity can be determined.

Anorexia Nervosa

Anorexia nervosa is a condition characterized by extreme weight loss, amenorrhea, and a constellation of psychologic problems that have been described as "the relentless pursuit of thinness" (Bruch 1979; Garfinkel and Garner 1982). The term anorexia is technically incorrect because there is no loss of appetite in this condition until advanced stages of cachexia have been reached. The American Psychiatric Association's diagnostic criteria for anorexia nervosa are listed in Table 14-2.

The most common course of the disease is a single episode with full recovery, but anorexia nervosa can also be episodic or unremitting until it causes death by starvation (APA 1987). Thus, it may become necessary to hospitalize anorectics to prevent death. Followup studies indicate that rates of overall mortality are between 15 and 21 percent, among the highest levels recorded for psychiatric disorders (Herzog and Copeland 1985).

Etiology. Most teenage girls who develop anorexia nervosa are described as having been model children (Bruch 1973). Unlike many other psychiatric disorders, anorexia nervosa tends to occur in intact families and is

Table 14-2
Diagnostic Criteria for Anorexia Nervosa and Bulimia

Anorexia Nervosa

A. Refusal to maintain body weight over a minimal normal weight for age and height, e.g., weight loss leading to maintenance of body weight 15 percent below that expected; or failure to make expected weight gain during period of growth, leading to body weight 15 percent below that expected.

B. Intense fear of gaining weight or becoming fat, even though underweight.

C. Disturbance in the way in which one's body weight, size, or shape is experienced, e.g., the person claims to "feel fat" even when emaciated, believes that one area of the body is "too fat" even when obviously underweight.

D. In females, absence of at least three consecutive menstrual cycles when otherwise expected to occur (primary or secondary amenorrhea). (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)

Bulimia

A. Recurrent episodes of binge eating (rapid consumption of a large amount of food in a discrete period of time).

B. A feeling of lack of control over eating behavior during the eating binges.

C. The person regularly engages in either self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise to prevent weight gain.

D. A minimum average of two binge eating episodes a week for at least 3 months.

E. Persistent overconcern with body shape and weight.

Source: American Psychiatric Association. 1987. *Diagnostic and statistical manual of mental disorders, third edition, revised,* pp. 67–69. Washington, DC: American Psychiatric Association. Copyright 1987, reprinted with permission.

often precipitated by seemingly minor events during adolescence. Various psychologic and physiologic hypotheses have been advanced to explain anorexia nervosa, but none is generally accepted. Most theories fall into one of four categories: (1) organic, (2) psychodynamic, (3) familial, and (4) sociocultural (Johnson, Thompson, and Schwartz 1984). The organic theories of anorexia nervosa are predominantly genetic and endocrinologic and have focused on the hypothalamic-pituitary axis (Gold et al. 1986). Support for a genetic basis of the disease is weak, but the disorder does occur with greater frequency among sisters, with a high incidence of various psychopathologies seen in relatives of such patients. Most theories of anorexia nervosa focus on psychologic trauma or unempathetic and overly domineering mothering as possible underlying causes of the disease (Johnson, Thompson, and Schwartz 1984), but these too are unproved. Sociocultural

theories suggest that the disease represents an exaggeration of the current inordinate weight consciousness of adolescent girls at a time when high-calorie foods are readily available and fewer calories are expended through exercise (Strober 1986).

Clinical Features. Typical symptoms of the disease include depression and obsessive-compulsive behaviors, although it is not clear whether these psychiatric problems precede weight loss or occur as a later result of semistarvation. Depression is often the first visible sign of anorexia nervosa, but sometimes it develops only after recovery. Abnormal hormonal patterns characteristic of starvation also occur (Mitchell 1986).

The clinical features of anorexia nervosa are personality characteristics such as rigidity or perfectionism, fear of obesity preceding the onset of the disorder, and the symptoms of starvation accompanying it. Serious body image disturbance is common, manifested by a lack of recognition of the severe emaciation and a belief that one is too fat. Individuals are usually preoccupied with food, thinking about it much of the time, preparing meals for others, and often engaging in bizarre eating rituals. Many anorectics engage in very extensive physical exercise. The disorder is also associated with a pervasive sense of personal ineffectiveness.

Anorectics have been divided into two general types, each comprising about half of the afflicted population. "Restricters," who confine their eating disorder to restriction of food intake, differ in a number of psychologic dimensions from "bulimics," who engage in eating binges and subsequent vomiting and purging (see below). Bulimic anorectics tend to be older, manifest other impulsive behaviors such as kleptomania, alcohol and drug abuse, and sexual promiscuity, and have a poorer prognosis (Garfinkel and Kaplan 1986).

Anorectics typically deny their weight-losing behaviors and the existence of any illness and avoid treatment even when they have become severely emaciated. Family members often must insist upon medical treatment. Some anorectic persons effectively hide their weight-losing behaviors even after they are forced to seek medical assistance, which makes establishment of an accurate diagnosis difficult.

Treatment. Most persons with anorexia nervosa are resistant to entering treatment because of their fear of weight gain and so are usually brought by their families under protest. No treatment method has proved unusually effective. Because starvation plays such an important role in the clinical picture of anorexia nervosa, some clinicians begin treatment with a period

in the hospital designed to restore body weight. In patients 35 to 40 percent below normal weight, the provision of enteral nutritional support may be necessary (Winston 1987). Such treatment, which removes the patient from the environment supporting the illness, may permit the use of behavioral rewards for weight gain and provides the opportunity to work on issues of control. Some medications have proved helpful in the treatment of anorexia nervosa. These include cyproheptadine (an appetite stimulant), antidepressant medication, and chlorpromazine. Family therapy is increasingly used in treatment, a course that seems reasonable in view of the disordered functioning of many of these families. In addition, cognitive-behavioral therapy is useful for inpatient and outpatient therapy (Garner 1986).

Bulimia

Bulimia is a disorder characterized by recurrent episodes of binge eating in which large amounts of food are consumed over a short period of time (Hawkins, Fremouw, and Clement 1984). These episodes are usually terminated by abdominal pain, self-induced vomiting, sleep, or the appearance of another person on the scene. Standard diagnostic criteria for this condition are given in Table 14-2.

As noted above, bulimia is present in half the patients with anorexia nervosa but in a much smaller percentage of obese patients. Recent interest in bulimia has focused on the disorder as it occurs among persons of normal weight. The severity of binge eating ranges from occasional episodes of morbid overeating at a party to the severe form of the disorder, bulimia nervosa, in which vomiting or purging follows frequent episodes of binge eating.

There are many similarities between patients with anorexia nervosa and those with bulimia. Both occur primarily in young women, although the onset of bulimia occurs in slightly older individuals; both may relate to the current preoccupation with thinness and dieting; and both usually begin with a period of dieting (Boskind-White 1986.)

First-degree relatives of bulimic patients have an increased prevalence of affective disorders, and probably of obesity as well. Thus, the symptoms of depression in the majority of bulimic patients and the presence of biologic markers of depression suggest that bulimia may represent a variant of a mood disorder (Agras and Kirkley 1986). Treatment for bulimia, still in the early stages of development, is cognitive-behavioral and pharmacologic. Behavioral treatments include modification of the behavioral program designed for obese patients and a combination of cognitive-behavioral and

insight-oriented approaches. Controlled clinical trials of these methods have produced encouraging results, although the size and number of studies are too small to permit firm conclusions about efficacy. The results of studies using antidepressant medications have similar difficulties, and conclusions are also uncertain (Wilson 1986).

Pica

Pica is the intentional and compulsive consumption of substances not commonly regarded as food. It occurs worldwide and is common among people of either sex and of all ages and races. Because pica is often associated with nutritional deficiencies or toxicities, it is of special concern among young children and pregnant women (Danford 1982).

Pica is usually classified into four categories distinguished by the substance consumed. Geophagia is the consumption of earth and clay; amylophagia is the consumption of starch and paste; and pagophagia is the eating of ice. The fourth (miscellaneous) category includes consumption of ash, chalk, antacids, paint chips, plaster, wax, and other substances (Crosby 1976).

The origin of this practice is poorly understood. One common hypothesis is that people are driven to consume these substances by nutritional deficiencies, but pica is not necessarily correlated with poor nutritional status (Grivetti 1978). Theories that it represents a method for reducing stress, preventing nausea during pregnancy, or obtaining calcium, iron, or other nutrients are equally unproven. Despite recent reports of similarities between clay and standard antidiarrheal medications (Vermeer and Ferrell 1985), geophagia has not been shown to prevent diarrheal diseases.

The nutritional hazards most frequently associated with pica are lead poisoning and iron deficiency anemia, but whether pica is a cause of these problems, their result, or both is as yet uncertain (Danford 1982).

Effects of Foods and Nutrients on Behavior

Normal Behavior

At least three types of food constituents have been evaluated in controlled studies for their possible behavioral effects on healthy people: amino acid precursors of brain neurotransmitters, other protein and carbohydrate foods, and caffeine.

Amino Acid Neurotransmitter Precursors. Certain large neutral amino acids found in substantial amounts in protein-containing foods are the

precursors of important brain neurotransmitters. These amino acids are transported across the blood-brain barrier into the brain where they could affect behavior. One of these is tryptophan, the precursor of the neurotransmitter serotonin. When pure tryptophan is administered to experimental animals, it increases brain tryptophan and serotonin levels. Tryptophan supplements have been reported to affect normal human mood, sleep, and pain sensitivity, functions believed to be regulated in part by serotonin neurons (Hartmann, Spinweber, and Ware 1976; Hartmann 1983; Lieberman et al. 1983; Seltzer et al. 1982; Young, 1986). They have also been reported to modify the appetites of certain patients (Wurtman, Hefti, and Melamed 1981). Tyrosine, the precursor of the neurotransmitters dopamine and norepinephrine, has also been reported to affect the neurotransmitter biosynthesis.

There is some evidence that certain doses of tryptophan are sedative and/or hypnotic. Investigators have demonstrated the effects of gram quantities of tryptophan on human alertness, as measured by self-report mood questionnaires, and on the period of time needed to fall asleep (Hartmann 1983). These effects are consistent with reports implicating brain serotonin neurons in the regulation of sleep. Although tryptophan does not appear to be as potent as prescription hypnotic drugs, it may have some clinical utility as a treatment for mild insomnia.

Protein and Carbohydrate Foods. In experimental animals, high-protein and high-carbohydrate meals have opposite effects on brain levels of tryptophan and its neurotransmitter product, serotonin. Meals of relatively high carbohydrate proportions tend to increase brain levels of tryptophan and serotonin, even though protein contains tryptophan but carbohydrate does not (Wurtman, Hefti, and Melamed 1981). Because serotonin-responsive neurons participate in the onset and maintenance of sleep, meals with a high ratio of carbohydrate to protein would be expected to increase sleepiness. The results of the few behavioral tests of this hypothesis have not been definitive (Lieberman, Spring, and Garfield 1986).

Caffeine. About three-fourths of the caffeine consumed in the United States is in coffee. Of the types of coffee regularly consumed in the United States, drip-method coffee usually contains the highest amounts of caffeine, about 112 mg per cup, and instant coffee the least, about 60 mg per cup. A cup of tea made with a tea bag contains about 42 mg of caffeine, and a typical serving (12 oz) of a cola beverage contains about 38 mg of caffeine (Roberts and Barone 1983).

Caffeine classically has been considered to have stimulant-like effects on behavior, and it has clear behavioral and pharmacologic effects at high doses. However, considerable controversy exists concerning its effects at the lower doses present in ordinary food and drink. The scientific literature on the behavioral effects of caffeine is quite extensive and quite contradictory. Many studies have failed to detect any effects on mood, such as increased alertness and improvements in vigilance, with even high doses of caffeine, while others have shown rather large effects as measured by tests of performance (Curatelo and Robertson 1983; Raebel and Black 1984). The most likely effects of moderate doses of caffeine are an improvement in aspects of performance (such as vigilance) and an increase in feelings of alertness, but these effects almost certainly depend on the individual's usual level of caffeine intake and inherent sensitivity to this substance.

Childhood Hyperactive Behavior

Numerous unconfirmed reports have found effects of various food and food constituents on children. Some of the more common ones are discussed below. Behavioral responses to food allergies are reviewed in the chapter on infections and immunity.

Food Colors. The childhood behavior problem most commonly discussed in relation to nutrition is termed Attention Deficit Hyperactivity Disorder, or, more popularly, hyperactivity. This condition is characterized by problems of inattention, excessive motion, impulsivity, learning disabilities, and related problems of conduct.

The contention that food additives, especially artificial dyes and colors, are causes of childhood hyperactivity (Feingold 1975) has stimulated many studies of the behavioral toxicity of food additives in children, notwithstanding the implausibility that such a wide variety of chemical structures would lead to a common result. A statistical analysis of the results of 23 of these studies concluded that artificial colors have, at most, a negligible effect on the behavior of children (Kavale and Forness 1983). This conclusion is consistent with that of other reviewers (Mattes 1983; Rumsey and Rapoport 1983; NIH 1982; Lipton and Golden 1984). At most, a few predisposed preschool and school-aged children may be adversely affected by artificial colors (Connors 1984b; Rimland 1983; Weiss et al. 1980). Because it remains possible that a few children may respond to diets that eliminate food colors, and such diets are not harmful, there is no reason to advise against therapeutic trials of food additive avoidance in individual cases.

Sugar. Sugar, by elevating brain levels of serotonin, would be expected to have a calming effect on behavior (Glinsmann, Irausquin, and Park 1986). Nevertheless, the suggestion that sugar consumption induces hyperactive behavior is an old one (Seham and Seham 1929; Randolph 1947; Rinkel, Randolph, and Zeller 1951), and many parents have been reported to believe that sugar is a cause of uncontrolled behavior in their children (Crook 1975). Data to support this idea are limited. One retrospective review of glucose tolerance curves of hyperactive children found that 75 percent of 261 hyperkinetic children had abnormal glucose tolerance curves following a 5-hour glucose tolerance test (Langseth and Dowd 1978). Other studies have not found abnormal glucose tolerance curves. An association was suggested between destructive agressive behavior and sugar intake in hyperkinetic children, but not in other normal 4-to 17-year-old children, based on 7-day food diaries kept by the mothers and videotaped observations of behavior by trained observers blinded to the protocol (Prinz, Roberts, and Hantman 1980). Another study noted an inverse relationship between sugar consumption by children and standardized measures of intelligence and school achievement (Lester, Thatcher, and Monroe-Lord 1982). None of these studies has shown a cause-and-effect relationship between sugar and behavior.

One way to study cause and effect, in contrast to correlation and association, is with a double-blind challenge study in which subjects are exposed to a test substance or to a placebo and the results compared. To date, however, only short-term challenges have been carried out; their results show little effect. For a group of 21 boys whose families responded to an advertisement seeking children with adverse behavioral reactions to dietary sugar loads, the ingestion of sugar produced a slight but significant *decrease* in gross motor activity (as would be expected on neurochemical grounds), and no differences were found in attentional measures (Behar et al. 1984). One hyperkinetic 5-year-old male and his mother both became frustrated, hyperactive, and difficult to control after a double-blind challenge with sugar in lemonade. However, not 1 of 50 other hyperkinetic children tested in the same way responded to a sugar challenge (Gross 1984).

The effects of acute challenges of sucrose in comparison to the artificial sweetener aspartame in grade school children were compared using 37 behavioral (playroom observation and examiner ratings) and cognitive (learning and memory tasks) measures (Wolraich et al. 1985). No differences in any measure of performance were found. No systematic change in activity was observed in eight school-aged children exposed to three differ-

ent doses of sucrose or to an aspartame placebo, and no clear effect was found on the Continuous Performance Task (Ferguson 1984).

To date, the only double-blind challenge that has reported an increase in activity after consumption of sugar was a pilot study of 13 psychiatrically ill children given regular orange juice or juice with sugar added in the form of sucrose or fructose (Connors and Blouin 1983). A subsequent study of 37 children who were psychiatric inpatients appears to suggest that during classroom observation *less* motor activity is seen with the sucrose and fructose challenges compared with aspartame (Connors 1984a). Overall, acute challenges with dietary sugar have failed to show that sugar causes hyperactivity, inattention, or impulsiveness (Rapoport 1986; Ferguson, Stoddard, and Simeon 1986).

Caffeine. Caffeine has been a concern of consumer groups because of possible deleterious effects upon children's behavior (Rumsey and Rapoport 1983). In a series of studies of the effects of caffeine in normal grade school children, habitual dietary caffeine intake was found to be a significant predictor of behavior (Elkins et al. 1981; Rapoport, Elkins, et al. 1981; Rapoport, Jensvold, et al. 1981; Rapoport 1983; Rapoport et al. 1984). Children who habitually consumed greater amounts of caffeine became more anxious and difficult to arouse when they were deprived of caffeine. When children were challenged with caffeine, the habitually high consumers felt little effect, but children who normally consumed little caffeine experienced adverse effects. Because no caffeine was consumed for 2 weeks preceding the challenge in this study, these effects are not likely to be due to caffeine tolerance, but instead suggest a possible physiologic basis for caffeine effects in children.

Considerable research has been conducted on the possible therapeutic effects of caffeine on behavior in children. In an uncontrolled cross-over trial with hyperactive children that compared the effects of caffeine, methylphenidate, and no treatment, caffeine significantly improved behavior (Schnackenberg 1973). In one study, caffeine has also been reported to improve the reaction times of hyperactive children (Reichard and Elder 1977), but not in more carefully controlled studies (Huestis, Arnold, and Smeltzer 1975; Garfinkel, Webster, and Sloman 1975; Firestone et al. 1978; Connors 1979). Comparisons of caffeine with stimulants such as amphetamine or methylphenidate have consistently found the prescription agents to be superior (Garfinkel, Webster, and Sloman 1975; Gross 1975; Huestis, Arnold, and Smeltzer 1975; Arnold et al. 1978; Firestone et al. 1978). Thus, a therapeutic role for caffeine in hyperactivity is uncertain.

Hypoglycemia

Hypoglycemia (low blood sugar) can occur either after a fast (fasting hypoglycemia) or several hours after the consumption of a meal (reactive hypoglycemia). Many individuals believe they suffer from reactive hypoglycemia because they experience symptoms of weakness, confusion, and irritability after eating sugars or other carbohydrate foods. However, it has not been possible to document an association between these symptoms and low blood sugar or insulin levels, and most authorities believe that symptoms are due to causes unrelated to blood sugar levels (Green 1981). Some authors believe a high percentage of patients referred with symptoms of hypoglycemia have emotional disorders rather than actual hypoglycemia (Johnson et al. 1980; Ford, Bray, and Swerdloff 1976).

True reactive hypoglycemia is diagnosed by an oral glucose tolerance test in which the administration of a large dose of glucose is followed by a collection of blood samples at hourly intervals for the next 5 hours. These tests are often unreliable (Lev-Ran and Anderson 1981; Charles et al. 1981). The generally accepted dividing line between normal and abnormal blood sugar of 50 mg/dl in whole blood may be too high, because lower levels have been observed in many individuals who experience no hypoglycemic symptoms (Hofeldt, Adler, and Herman 1975; Cahill and Soeldner 1974). Only when symptoms of hypoglycemia such as sweating, tremor, anxiety, and irritability occur at the same time as the documented low blood sugar level can a valid diagnosis of reactive hypoglycemia be made. Such a diagnosis may indicate the early presence of a disease such as diabetes.

Antisocial Behavior

Before the 1970's, interest in a possible relationship between diet and criminal behavior was generally limited to food faddists, but more recently, scientists have given serious attention to this matter (Hippchen 1978, 1981; Reed 1977; Rimland 1981; Rimland and Larson 1981; Schauss 1980; Schoenthaler 1983b). Advocates of a link between diet and criminality do not agree on a single mechanism by which diet might influence criminal behavior. Among the suggested explanations are reactive hypoglycemia, food allergies, and other undocumented adverse reactions to food, to vitamin and mineral deficiencies, and to toxicities (Feingold 1979; Green 1976; Hippchen 1978, 1981; Rimland 1981; Rimland and Larson 1981; Schauss 1980; Schmidt, Brajkovich, and Asch 1981; Schoenthaler 1983a, 1983b). Experts in criminology and psychiatry have reviewed these claims and have strongly concluded that no evidence for such a connection exists. The studies that purport to show such a link are seriously flawed, lack

appropriate controls, and are subject to bias (Gray and Gray 1983; Gray 1986; Pease and Love 1986).

Implications for Public Health Policy

Dietary Guidance

General Public

Behavioral factors clearly influence food selection, dietary change, and chronic disease risk, but research in this area is still too preliminary to draw more than a few implications for the general public; exceptions generally apply to specific chronic disease conditions. Similarly, beyond the dietary guidance implications presented in the chapter on obesity, current evidence is insufficient to recommend specific dietary changes to prevent or treat the eating disorders—anorexia nervosa, bulimia, and pica. Sugar, certain food additives, and caffeine have been suggested as predisposing dietary factors to the development of behavioral disorders in children and adults, but evidence is weak and contradictory, and there is no reason to expect that a reduced intake of these substances would affect the incidence or severity of behavioral disorders. In addition, current evidence does not support any implications at present about the effects of amino acid precursors of neurotransmitters on behavior.

Special Populations

Studies in patients with eating disorders and other chronic disease conditions (reviewed in other chapters of this report) emphasize the importance of modification of diet-related behavior in these conditions. Such patients should receive advice from qualified health professionals on the application of dietary principles appropriate for their conditions. Although evidence linking dietary caffeine, refined sugars, and food additives to behavioral disorders is uncertain, their elimination from the diet will not impair nutritional status and can be recommended to patients on an individual trial basis.

Nutrition Programs and Services

Food Labels

Evidence related to the role of dietary factors in behavioral disorders holds no special implications for food labeling policies.

Food Services

Evidence related to the role of dietary factors in behavioral disorders currently holds no special implications for change in policies related to food programs beyond those suggested by the *Dietary Guidelines for Americans*.

Food Products

Evidence related to the role of dietary factors in behavioral disorders holds no special implications for change in policies related to food products at this time.

Special Populations

Patients with eating disorders should be provided with ready access to counseling and assistance in the development of diets that provide safe and adequate levels of energy and nutrients.

Research and Surveillance

Research and surveillance issues of special priority related to the role of behavior in the prevention of diet-related chronic disease and to the role of diet in behavioral disorders should include investigations into:

- Behavioral factors that influence food selection patterns and dietary change.
- The most effective behavioral methods to encourage appropriate dietary changes.
- Behavioral factors that increase the risk for diet-related chronic disease.
- Behavioral factors that increase the risk for obesity, anorexia nervosa, bulimia, and pica.
- The prevalence of these eating disorders among different groups.
- Behavioral techniques effective in treatment of these disorders.
- Effects of foods and nutrients on etiology and treatment of behavioral disorders.
- Behavioral interventions that increase the long-term effectiveness of health promotion and chronic disease treatment programs.

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Chapter 15

Maternal and Child Nutrition

Further it must be known that the children must be fed only milk and pap until they have grown the front teeth. Then one can give them somewhat stronger food—bread softened with milk or in a meat or pea broth.
Bartholomaus Metlinger
Kinderbuch (1473)

Introduction

The health and productivity of our society have roots in the quality of the reproductive experience and the subsequent nurturing strategies of parents and childhood caretakers. Much can be done to enhance the well-being of mothers and infants, and adequate nutrition during pregnancy and lactation is an important component of this process. Societies throughout history have recognized the unique needs of pregnant and lactating women and have made special provisions for their health care and nutritional needs.

This chapter reviews key issues related to the nutrition of pregnant women and lactating mothers and their infants, children, and adolescents and to the improvement of their health and survival. It also discusses aspects of chronic disease prevention that especially concern these younger age groups.

Historical Perspective

Although the unique health status of pregnant women has long been recognized, dietary recommendations for this group have reflected incomplete knowledge about human reproduction and growth and nutrition. Likewise, while a healthy, vigorous infant has always been the desired outcome of pregnancy, only recently has nutrition been recognized as influencing that outcome.

Infants were weighed at birth during Talmudic times, but it was not until the 17th century that the French obstetrician Mauriceau recognized the health

significance of adequate birth weight (IOM 1985). Mauriceau's ideas did not gain currency, perhaps because his estimate of 15 lb as a normal birth weight was obviously incorrect. It was not until the 19th century that birth weights, on the basis of their variability, were used as indicators of nutritional status and physical growth (IOM 1985).

Beliefs about the effects that various foods might have on the mother or child influenced dietary recommendations for pregnant women in the 19th century. For example, to prevent a child from having an unpleasant disposition, pregnant women were cautioned against eating salty, acidic, or sour foods. Obstetrical problems also influenced dietary recommendations. During the time of the Industrial Revolution, rickets commonly impaired normal pelvic bone formation. As a result, women who had had rickets in childhood faced major risks in childbirth, and both maternal and infant mortality were high. To combat this problem, Prochownick, a German physician, prescribed a fluid-restricted, low-carbohydrate, high-protein diet for the last few weeks of pregnancy. Because the infants of women who followed this diet were smaller and more easily delivered, it became a standard recommendation for women throughout pregnancy, one that persisted even when rickets, the original reason for it, was no longer a problem (Worthington-Roberts, Vermeersch, and Williams 1985).

In the early 20th century, scientists began to study the relationship of low birth weight (LBW) to shortened gestation and to infant mortality. After World War I, attempts to relate food shortages to reduced birth weights were inconclusive. In 1930, the Finnish pediatrician Yllpo suggested that infants were at high risk below a birth weight of 2,500 g (about 5.5 lb). The World Health Organization subsequently adopted this standard, despite recognition that birth weight below this level is not synonymous with prematurity (IOM 1985).

Although research on diet and pregnancy did not begin until the 1930's, obstetric practitioners voiced strong opinions about what pregnant women should—and should not—eat. Obstetrical authorities commonly warned the pregnant woman against accepting either advice to ". . . eat largely because she is eating for two" or to ". . . eat sparingly because if she does not her baby will be too large" (Danforth 1933), holding the view that the weight of the unborn child could not be influenced by diet except within very narrow limits. At the same time, pediatricians argued that the mother's health and nutritional status did indeed influence the size of the newborn child. Studies conducted by the Research Laboratory of the Children's Fund of Michigan demonstrated that the mother's nutritional state before and at the time of conception and the adequacy of her diet during pregnancy

influence the well-being of the infant. There was an upswing of research in maternal nutrition in the 1940's, influenced by the impact of wartime food shortages on maternal health (Egan 1987). Some of the famine studies during World War II showed a marked fetal impact from extreme food deprivations of the mother, but correlational studies were inconsistent in relating nutritional intake to birth outcomes (IOM 1985). There was sufficient interest and concern in the United States about the relationship of maternal nutrition to problems of prematurity, congenital malformations, and infant mortality to stimulate the National Academy of Sciences to appoint a Committee on Maternal Nutrition and Child Feeding in 1946. Its charge was to "implement improved health of the nation through better coordination of scientific advances in the field of obstetrics and pediatrics." The Committee's 1950 report, *Maternal Nutrition as It Relates to Child Health—An Interpretive Review*, served as the chief reference for maternal and child health nutrition programs for many years (Egan 1987).

Uncertainties about the role of nutrition in the management of pregnancy led to discussion between the service community and the research community in 1966 that resulted in formation of a Committee on Maternal Nutrition of the National Academy of Sciences. In 1970, the Committee issued a hallmark research report, *Maternal Nutrition and the Course of Pregnancy*, stimulating the following:

- Significant changes in clinical practices related to the routine restriction of weight gain and sodium intake during pregnancy.
- Reaffirmation of the priority needs of pregnant women and infants in supplemental food programs.
- Development, adoption, and dissemination of policy statements and guidelines related to nutrition and maternal health by professional organizations.
- Increased emphasis on training of nutrition personnel as well as on education in nutrition for physicians.
- Increased funds for research on maternal and perinatal nutrition, and renewed interest of the National Institutes of Health in this area (Egan 1987).

Maternal and infant nutrition was a focus of the White House Conference on Food, Nutrition, and Health in 1969, and its Conference Panel on Pregnant and Nursing Women and Young Infants identified adequate diet as one factor "known to be necessary for favorable outcomes of pregnancy" (White House Conference 1969). The panel recognized the increased and special needs of pregnant and nursing women and infants and con-

cluded that optimal nutrition for women throughout life is the best way to promote infant health. In 1970, the White House Conference on Children called for expansion and improvement of existing food programs as well as promotion of nutrition education in the schools. In 1971, the White House Conference on Youth demanded Federal food assistance for all young Americans in need, and a National Nutrition Education Conference later that year also focused attention on the nutritional needs of adolescents (Egan 1972).

Federal Maternal and Child Nutrition Programs

Despite scientific uncertainties about the relation among nutrition and human reproduction, growth, and development, Federal programs have addressed the nutritional needs of mothers and children since early in this century (Egan 1977). The Children's Bureau issued dietary advice to parents and teachers and conducted nutritional surveys of low-income children (Egan 1977). School feeding programs began in the early 1900's when free, compulsory, and universal education was instituted. These programs were also supported by philanthropic organizations, local school districts, and private donors. Several States authorized schools to serve meals at cost, and a few States even served meals at reduced or no cost to needy children (CBO 1980). Increasing Federal involvement in these programs resulted from the burden on local and State entities during the 1930's. An amendment to the Agricultural Act of 1933 established a fund to purchase surplus agricultural commodities for donation to needy families and to child nutrition programs, including school lunch programs. The Social Security Act of 1935 authorized grants to the States for health services for mothers and children and established the basis for a national program of nutrition services (including assessment, counseling, referral, and followup) for this population (Select Panel 1981).

When the supplies of surplus commodities declined during World War II, Federal involvement in child feeding programs shifted to general income assistance. To avoid the uncertainties of congressional appropriation of cash subsidies, the National School Lunch Act, authorizing permanent grants-in-aid to States, was enacted in 1946. To receive cash and commodity assistance, the States had to operate school lunch programs on a nonprofit basis, provide free or reduced-price lunches for needy children, and serve lunches that would meet specified Federal standards (CBO 1980).

The Child Nutrition Act of 1966 enlarged the scope of Federal efforts by establishing numerous programs to expand food assistance year round to children of all ages and to provide assistance to pregnant women and

infants. For the first time, high-risk families enrolled in comprehensive maternity and infant health projects and children and youth projects received direct nutrition services as an integral part of their health care (Egan 1977). These programs and policies led to authorization of the Special Supplemental Food Program for Women, Infants, and Children (WIC) by Congress in 1972. Modified versions of many of the Federal food assistance programs that developed during the 1960's and 1970's remain in place today.

U.S. Department of Agriculture Programs. Current food assistance programs of the U.S. Department of Agriculture (USDA) include:

- School Breakfast and Lunch Programs: help schools to serve nourishing, low-cost meals to children and to provide free or reduced-price meals to children from low-income families.
- Summer Food Service Program: helps communities serve meals to needy children when school is not in session. Operates in areas where the concentration of low-income families is high.
- Child Care Food Program: subsidizes meals and snacks for children up to age 18 in nonresidential child care programs.
- Special Supplemental Food Program for Women, Infants, and Children: provides selected foods rich in specific nutrients, nutrition education, and health care referrals to pregnant, lactating, and postpartum women and children up to age 5. Participants must be certified as nutritionally at risk and of low income.
- Commodity Supplemental Food Program: distributes certain agricultural commodities at no cost to supplement the diets of low-income infants, children under 6 years, and pregnant and postpartum women who are vulnerable to malnutrition.
- Special Milk Program: makes it possible for school children to purchase milk at reduced price or receive it free; subsidizes milk served to children in schools, day care institutions, and summer camps.
- Food Stamps: provide eligible individuals and households with coupons free of charge that can be exchanged for food at authorized food stores. The redemption value of the food stamps depends on the household's size and financial circumstances. Food stamps are meant to supplement what a family spends on food.

Although there are intrinsic limitations in methods, evaluations of the school feeding and WIC programs have generally shown that they improve the health and nutritional status of the target populations (see Systems Development Corporation 1983; Rush 1985).

Nutrition Programs of the U.S. Department of Health and Human Services (DHHS). Nutrition services are an important component of many of the health and social service programs administered by DHHS. These programs include:

- Title V Maternal and Child Health Program: provides for nutrition assessment, dietary counseling, nutrition education, and referral to food assistance programs to women of childbearing age, infants, preschool and school-aged children, adolescents, and children with special health care needs served through a wide range of health care programs. In addition, it supports training in nutrition for nutrition personnel and other health professionals who lead the development of nutrition services. It supports nutrition projects of regional and national significance to advance and improve nutrition services for mothers and children.
- Medicaid-Early Periodic Screening, Diagnosis, and Treatment: requires assessment of the nutritional status of eligible children and provision of appropriate referral and treatment services.
- Head Start: provides preschool children from low-income families with nutritious meals and snacks; provides nutrition education for the children and their families; and provides training and technical assistance in nutrition for Head Start staff.
- Primary Care-Community Health Centers, Migrant Health Programs: provide nutrition services as an integral component of these comprehensive health care programs.

Nutrition Education Programs. Both USDA and DHHS sponsor nutrition education programs targeted to parents and children. Major programs are the USDA Extension Service's Expanded Food and Nutrition Education Program and Food and Nutrition Program, the Nutrition Education and Training Program of the Food and Nutrition Service, and the educational component of the WIC program. DHHS funds maternal and child nutrition education programs through the programs administered by its various agencies: the health care programs of the Health Resources and Services Administration and the Indian Health Service of the Public Health Service, and the Head Start Program of the Administration on Children, Youth, and Families of the Office of Human Development Services (Select Panel 1981).

National Goals and Recommendations

Within the past decade, Federal reports and conferences have established goals and produced recommendations designed to improve the nutrition and health of mothers and children. Some of these goals and reports are listed below.

Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention. This report defines broad goals for the improvement of health and reduction of mortality rates among infants, children, and adolescents. Nutrition is included as a key health promotion strategy to achieve these goals (DHEW 1979).

1990 National Health Objectives. At least 35 of the 226 specific objectives to achieve the goals defined by *Healthy People* are related to nutrition and the health of pregnant women, infants, children, or adolescents (DHHS 1980). Table 15-1 presents a selection of these objectives.

Table 15-1
Selected National Objectives to be Achieved by the Year 1990 Related to Maternal and Child Nutrition[a]

Pregnancy and Infant Health

- Reduce the national infant mortality rate (deaths for all babies up to 1 year of age) to no more than 9 deaths per 1,000 live births
- Ensure that no county nor racial or ethnic group of the population has an infant mortality rate in excess of 12 deaths per 1,000 live births
- Reduce the maternal mortality rate to no more than 5 per 100,000 live births for any county or for any ethnic group
- Reduce to no more than 5 percent of all live births the percentage of low birth weight babies (2,500 g and under)
- Ensure that 85 percent of women of childbearing age can state the special nutritional needs of pregnancy and can understand the hazards of alcohol use during pregnancy and lactation
- Ensure that virtually all infants receive adequate primary health care, including nutrition services, when needed

Fluoridation and Dental Health[b]

- Eliminate cariogenic foods from school vending machines and school breakfast or lunch programs
- Ensure that at least 95 percent of school children and their parents are able to identify the principal risk factors related to dental diseases and be aware of the importance of fluoridation in controlling these diseases

Misuse of Alcohol[b]

- Reduce the proportion of adolescents 12 to 17 years old who report acute drinking-related problems during the past year to below 17 percent
- Increase the proportion of women of childbearing age who are aware of the risks associated with drinking during pregnancy to greater than 90 percent
- Increase the proportion of high school seniors who recognize the risk of alcohol intoxication to 80 percent or more

Table 15-1 (continued)

Nutrition
• Increase the proportion of women who breastfeed their babies to 75 percent at hospital discharge and to 35 percent at 6 months of age
• Increase the proportion of school cafeteria managers who are actively promoting the USDA/DHHS *Dietary Guidelines* to more than 50 percent
• Ensure that all States include nutrition education as part of required school health education at elementary and secondary levels
Physical Fitness and Exercise[b]
• Increase the proportion of children and adolescents ages 10 to 17 participating regularly in appropriate physical activities to more than 90 percent

[a] Some objectives apply to more than one category.
[b] These issues are discussed further in the chapters on dental diseases, alcohol, and obesity, respectively.

Source: U.S. Department of Health and Human Services 1980.

Better Health for Our Children: A National Strategy. A chapter of the report of the Select Panel for the Promotion of Child Health emphasizes the importance of nutrition in maternal and child health and gives specific recommendations for improved information and education, health care services, and research in nutrition for this population (Select Panel 1981).

Surgeon General's Workshop on Maternal and Infant Health. This report recommends that nutrition services become integrated into all maternal and child health programs, that maternal and child health professionals receive improved training in nutrition, and that further research be conducted on infant feeding patterns, the development of dietary patterns and tastes, and the role of social and cultural factors in human nutrition (DHHS 1981).

Surgeon General's Workshop on Breastfeeding and Human Lactation. This report recommends specific strategies to promote breastfeeding through improved public and professional education, health care systems and support services, and research (DHHS 1984).

Significance for Public Health

Although the precise contribution of nutrition to maternal and infant health cannot yet be distinguished from genetic, environmental, or behavioral factors that affect risk, an inadequate diet during pregnancy increases the probability of a LBW infant, who, in turn, has an increased risk of mor-

bidity and mortality. Well-nourished mothers who gain appropriate amounts of weight during pregnancy generally give birth to heavier, healthier babies. Poorly nourished mothers who eat well and gain adequate weight during pregnancy can greatly improve their chances of giving birth to healthy infants. Diet is also critical in the control of diabetes, hypertension, and gastrointestinal disorders when such conditions are present during pregnancy.

Infant Mortality

In the United States, the infant mortality rate (the number of deaths of infants under 1 year of age per 1,000 live births) has declined rather steadily throughout this century, largely due to improvements in control of infectious diseases, health care, and nutrition. In 1900, the rate was about 100 deaths per 1,000 births; by 1978 it had declined to 13.8 and by 1985 to 10.6 (NCHS 1987c). Recent information suggests that the rate of decrease is slower than it has been in the past, as indicated by a provisional rate of 10.4 for 1986 (Kleinman 1987). Infant mortality rates in several industrialized countries are considerably lower—for example, 6.5 and 6.6, respectively, for Finland and Japan in 1983 (NCHS 1986). However, rates among countries are not strictly comparable due to differences in definitions.

Although marked improvements in infant survival have occurred among all racial and ethnic groups, the infant mortality rate among black Americans remains nearly twice as high as that among white Americans. From 1978 to 1985, the infant mortality rate among whites fell from 12.0 to 9.3 per 1,000, and that among Native Americans fell from 13.7 to 9.1 per 1,000. The rate among black Americans, however, was 23.1 in 1978; it declined, but in 1985 it was still 18.2—nearly twice the rate of whites (NCHS 1987b).

Low Birth Weight

In the United States, the most important factor contributing to the infant mortality rate is a low birth weight—less than 2,500 g, or 5.5 lb. Low birth weight occurs as a result of birth prior to 37 weeks' gestation, intrauterine growth retardation, or both. Infant deaths and illnesses increase sharply as birth weight declines within the normal weight range and even more sharply below 2,500 g. They are highest among infants of very low birth weight (VLBW), below 1,500 g. LBW infants are at increased risk for developmental handicaps, birth defects, respiratory and other infectious diseases, behavior problems, and complications of medical interventions. These conditions greatly increase the emotional and financial burden to the infant's family and to the Nation (IOM 1985).

Although overall rates of infant mortality have decreased greatly, the prevalence of LBW has declined more slowly. In 1971, babies with weights below 2,500 g accounted for 7.6 percent of all live births; in 1985, they accounted for 6.8 percent. Infants of moderately low birth weight (1,500 to 2,500 g) accounted for over 5.5 percent of all live births in 1985 and those of VLBW for over 1.2 percent. Together, the 6.8 percent of infants born at weights less than 2,500 g are responsible for 67 percent of all infant deaths during the first month of life and approximately 60 percent of all infant deaths (NCHS 1987a).

Much of the higher infant mortality among black Americans is explained by the high proportion of LBW infants born to this group. LBW infants comprised 12.4 percent of all black births in 1985. For Americans of Puerto Rican descent, the percentage of LBW infants was 9.1. It ranged from 6.2 to 6.9 percent for Americans of Japanese, Filipino, other Asian and Pacific Island, and American Indian ancestry, and from 5.6 to 5.8 percent for Mexican, Cuban, and other white Americans. The lowest percentage of LBW (5.3 percent) occurred among Chinese Americans (Secretary's Task Force 1985). Of special concern in these figures is the continuing racial disparity in birth weight. Between 1973 and 1983, rates of moderately low birth weight decreased more among whites than among blacks. Overall rates of VLBW decreased, but they actually increased among blacks (Kleinman and Kessel 1987).

Risk Factors for Low Birth Weight

Medical, social, behavioral, and dietary factors before and during pregnancy contribute to the risk for LBW. Medical risk factors include a previous reproductive history that includes many pregnancies, anemia, hypertensive disorders of pregnancy, inadequate weight gain, or delivery of a LBW infant; low prepregnancy weight; chronic illnesses such as diabetes or hypertension; and poor weight gain during pregnancy. Social, demographic, and behavioral risk factors have been identified as low socioeconomic status, low educational level, minority race, single marital status, adolescence, inadequate prenatal care, and use of drugs, alcohol, or cigarettes.

Dietary risk factors include an inadequate intake of calories or essential nutrients such as protein, vitamins, and minerals. Evidence indicates that the more of these risk factors present, the greater the risk to mother and child (IOM 1985). Because these risk factors interact and affect one another, it is difficult to determine the role of nutrition separate from these other risk factors.

Estimates of Cost

The personal cost of the death or severe illness of a LBW infant is incalculable. Quantitative estimates of the economic costs of care of LBW infants have been published. In 1987, the average hospital cost was estimated at $12,000 to $39,000. Costs increase, however, as birth weight falls; the average cost for a VLBW surviving infant is $31,000 to $71,000. For infants born at under 750 g, the average hospital stay was 98 days, and the costs ranged as high as $150,000 (OTA 1987). In 1984, the rehospitalization rate during the first year of life was 38.3 percent for VLBW infants and 19 percent for moderately LBW infants. Such infants remained rehospitalized an average of 16.2 and 12.5 days, respectively. In addition, nearly 20 percent of LBW infants who survive will have long-term morbidity during the first year that requires medical care (IOM 1985). Even taking into consideration the increased costs of providing adequate prenatal care, the savings to the Nation from prevention of even a small proportion of LBW infants would be considerable.

Scientific Background

Pregnancy and Lactation

Normal pregnancy is accompanied by anatomical and physiologic changes that are necessary to promote fetal growth and development and prepare the mother for labor, birth, and lactation. Many of these changes are apparent in the early weeks of pregnancy.

Physiologic. During both pregnancy and lactation, hormonal changes affect retention, utilization, and excretion of nutrients (Hytten and Leitch 1971). These changes lead to physiologic adjustments that result in expansion of blood volume and accumulation of fluid. They include an increase in cardiac output, heart rate, and basal metabolic rate. Preparation of the mammary glands for lactation begins during pregnancy, when the duct system enlarges and the alveolar cells proliferate. Lactation is initiated and maintained by hormonal changes that occur in response to the infant's sucking stimulus. Milk proteins, lipids, and lactose are synthesized by the alveolar cells. Stored fats are secreted into the milk, as are a variety of nutrients and other compounds. Although recent evidence suggests that lactation is associated with physiologic changes that conserve energy and reduce the need for increased energy intake (Butte, Garza, Stuff, et al. 1984), additional studies are needed to evaluate this matter (Lawrence 1985).

Biochemical. During pregnancy, decreases in plasma concentrations of albumin, most minerals, and most water-soluble vitamins occur as a result of the dilution effect of the expanded plasma volume. Because expansion in red cell mass is not as great as the expansion in plasma volume, the hematocrit, which is the percentage of red blood cells in a sample of centrifuged blood, typically drops during pregnancy. Other nutrients, however, increase in plasma concentration, perhaps as a result of improved intestinal absorption.

Physical. During pregnancy, body weight, lean body tissue, and fat increase. Increases in tissue fluid levels are most significant in the third trimester, but women vary substantially in the timing and degree of fluid accumulation. After childbirth, blood volume and extracellular fluids return to prepregnant levels. The uterus also returns to normal size, but breast size remains enlarged throughout lactation. Loss of the body fat stores accumulated during pregnancy occurs gradually and is usually complete by the time the nursing infant is about 6 months old (Lawrence 1985).

Normal Growth and Development

In humans, intrauterine growth and development require about 40 weeks of gestation. From the third month until term, fetal weight increases nearly 500-fold, from about 6 g (0.2 oz) to 3,000 to 3,500 g (6.5 to 7.6 lb) at birth.

Infants. Immediately after birth, weight is lost, but birth weight is usually regained by the 10th day. After this time, weight increases at a rapid but decelerating rate. Most infants double their birth weight by the age of 4 months and triple it within 1 year. Length increases by 50 percent during the first year. These changes are accompanied by changes in body composition. Fat accumulates rapidly; by 6 months, it makes up about 25 percent of the total body weight. During the second 6 months, the relative increase in lean body mass is much greater than the increase in fat (Fomon et al. 1982).

Children and Adolescents. The very rapid rate of growth in infancy is followed by slower growth during the preschool and early school-age years. Weight gain approximates 2.5 kg/year until 9 to 10 years of age. Length increases by an average of 11 to 12 cm in the second year, about 7 cm during each of the next three. Children become leaner between 6 months and 6 years, after which a gradual increase in fat thickness occurs in both males and females until puberty; females have a relatively greater body fat content than males at all stages of development (Fomon et al.

1982). The brain reaches 50 percent of its adult size by age 2, 75 percent by age 4, and 100 percent by age 6 to 10. Body growth is measured by increases in length and weight; skin-fold measurements may be used to evaluate body fat. The heights and weights for representative samples of boys and girls have been used to establish growth reference curves, developed by the National Center for Health Statistics (NCHS) (Hamill and Moore 1976; Hamill et al. 1977; Hamill et al. 1979). As a general rule, growth patterns follow percentile lines on these growth charts.

When growth performance for a given child is measured at regular intervals and plotted on such charts, unusual changes in weight and height percentile can identify children who are at nutritional risk from either under- or overnutrition. Growth patterns are highly individual, however, and average growth rates do not always apply to individual children. This observation is especially applicable in adolescence.

The velocity of physical growth in adolescence is second only to infancy. The most rapid period of growth in adolescence is known as the growth spurt. It precedes menarche in females and spermatogenesis in males. The age at which peak growth occurs is later and the growth spurt more intense in males than in females. There are also differences in its timing and length. The growth spurt usually begins between ages 8 to 12 in females and ages 10 to 14 in males; peak growth velocity occurs at ages 10 to 14 in females and 12 to 16 in males (Lucas, Rees, and Mahan 1985). Linear growth stops toward the end of adolescence, usually between the ages of 14 to 16 in females and 16 to 18 in males (Tanner 1962). The magnitude and duration of growth vary widely among adolescents, making chronologic age an unsatisfactory index of nutritional needs. Instead, individual body size, stage of sexual maturation, and current rate of growth must be considered.

Key Scientific Issues

- Role of Dietary Factors in Maternal Health
- Role of Dietary Factors in Fetal Health
- Role of Dietary Factors in Infant Health
- Role of Dietary Factors in the Health of Children
- Role of Dietary Factors in the Health of Adolescents
- Role of Dietary Factors in Chronic Disease in Childhood

Role of Dietary Factors in Maternal Health

Nutritional Needs of Pregnant and Lactating Women

Extra energy and nutrients are needed to support the growth of maternal tissues, such as the uterus and breast, and the increased metabolic demands of pregnancy as well as the growth of the fetus and placenta. During lactation, the energy and nutrients provided in the milk, and those required for its production, must be replaced.

Weight Gain. Research has demonstrated that both maternal prepregnancy weight and weight gained during pregnancy are important determinants of infant birth weight. Inadequate weight gain during pregnancy and low prepregnancy weight combined with low weight gain are associated with lower-than-average infant birth weights and greater risks for fetal or neonatal death and neonatal disease; these problems decline as weight gain increases.

Such associations do not necessarily prove causality, however; healthy infants of average birth weight have been born to women whose weight change during pregnancy ranged from loss to high gain. For this reason, and because genetic and behavioral factors other than weight gain also influence infant birth weight, it has been difficult to define the optimal weight gain during pregnancy for women of varying prepregnancy weights. Most studies that have correlated average weight gain with birth outcome in normal weight adult women with normal pregnancies have found the optimal weight gain to fall within the range of 22 to 27 lb (Naeye 1979; Rosso 1985), yet one-fifth of white adult women and one-fourth of black adult women did not gain this much weight during normal pregnancies of 40 or more weeks' duration in 1980 (Taffel 1986). When all pregnancies in this study, regardless of length of gestation, were considered, one-third of black mothers gained no more than 20 lb, and black mothers were nearly twice as likely as white mothers to gain less than 16 lb (20 percent as compared with 11 percent). Nevertheless, most of these women gave birth to healthy babies.

The influence of prepregnancy weight on birth outcome also makes it difficult to define an optimal weight gain; a low weight gain by women with a low prepregnancy weight is associated with the highest incidence of LBW, but higher weight gains during pregnancy reduce the risk (Taffel 1986). This relationship may not hold for adolescents, however. Although the mean weight gain of adolescent women during normal pregnancy has been shown in several studies to average about 35 lb, their risk of having a

LBW infant was still higher than that for adult women (Meserole et al. 1984; Frisancho, Matos, and Flegel 1983; Garn et al. 1984; Loris, Dewey, and Poirier-Brode 1985).

The effect on infant birth weight of differing levels of weight gain by obese women during pregnancy is also uncertain. Obesity during pregnancy is linked to an increased risk of maternal complications such as hypertensive disorders, gestational diabetes, infections, and surgical deliveries (Abrams and Laros 1986; Kliegman and Gross 1985; King 1986; Garbaciak et al. 1985). Obesity is also associated with higher rates of infant mortality (Naeye 1979). These risks are reduced when obese women do not gain more than 24 lb during pregnancy (Naeye 1979; Kliegman et al. 1984; Abrams and Laros 1986; Garbaciak et al. 1985), but the lower limit of weight gain that can produce optimal birth outcome has not been defined. This issue is important because caloric restriction and diet-induced weight loss in pregnant obese women has been associated with reduced infant birth weight (Naeye 1981; Campbell and MacGillivray 1975; Grieve, Campbell-Brown, and Johnstone 1979), suggesting that obese women should gain at least some weight during pregnancy (Campbell 1983).

Energy. The recommended intake of energy during pregnancy includes an increment of 300 kcal/day over the energy allowances for nonpregnant women (NRC 1980). This amount was obtained by calculating the total energy cost of synthesizing maternal and fetal tissues and dividing this figure by the number of days of pregnancy (Hytten and Leitch 1971). Although the 300 kcal/day increment has been widely accepted, actual measurements of the energy balances of pregnant women in several international populations have demonstrated that they may consume as few as 50 kcal/day over prepregnancy energy intake levels yet gain weight normally and produce infants of normal birth weight (Durnin 1987). Although the reason for this discrepancy is not yet known, preliminary observations suggest that the metabolic needs of pregnant women do not increase significantly (Durnin et al. 1985; McNeil and Payne 1985; Saha 1986). Nevertheless, caloric supplementation of pregnant women in a poor community where the average caloric intake was 1,500 kcal/day increased the average birth weight and reduced the incidence of LBW infants (Lechtig et al. 1975).

Recent investigations show that lactating women also require fewer calories than the 500 kcal/day calculated as needed above prepregnant energy levels (Butte, Garza, Stuff, et al. 1984). Present knowledge thus does not permit the precise definition of caloric requirements during pregnancy and lactation (Worthington-Roberts, Vermeersch, and Williams 1985).

Protein. The RDA for protein during pregnancy includes an additional 30 g/day beyond the 44 g/day recommended for nonpregnant women (NRC 1980). Protein is abundant in the American diet, and inadequate intake during pregnancy is reported infrequently. Studies that have associated diets containing 20 percent of total calories from protein (as compared with the 12 to 14 percent usually recommended) with a higher risk of premature deliveries and neonatal mortality suggest that protein intakes significantly higher than those recommended may be harmful (Rush, Stein, and Susser 1980a, 1980b).

Vitamins and Minerals. The RDA for vitamins and minerals for pregnant or lactating women include increased levels above those for nonpregnant women (NRC 1980). In healthy women with normal pregnancies, vitamin and mineral needs can usually be met by consuming an adequate diet. With the possible exceptions discussed below, supplements, although usually recommended, have not been associated with measurable health improvements in this population (Hemmiki and Starfield 1978).

American women may have a low intake of dietary folate. Some European studies have suggested an association of folate deficiency (along with deficiencies of other vitamins) with the development of neural tube defects. These observations stimulated clinical trials in which folate and multivitamin supplements appeared to reduce the risk of neural tube defects in subsequent children born to women who had previously given birth to infants with these defects (Smithells et al. 1981; Smithells et al. 1983; Laurence et al. 1981). These studies, however, were poorly controlled and flawed methodologically (Dobbing 1983). A recent report has found no difference in folate or vitamin B_{12} concentrations in blood samples from early pregnancy taken from mothers of infants with or without neural tube defects (Molloy et al. 1985).

The need for iron is increased during pregnancy, with about 500 mg needed to increase the number of maternal red blood cells, about 600 mg needed for the fetus and placenta, about 200 mg needed to replace normal maternal losses, and another 200 mg needed to replace the red blood cells lost during delivery. Because menstruation ceases for 9 months, about 300 mg of iron are saved, and the total additional iron needed for a pregnancy with a normal delivery is about 1,200 mg (King 1986), or about 4 mg/day. As discussed in the anemia chapter, iron deficiency occurs infrequently in the general population. Nevertheless, the National Research Council recommends an iron supplement of 30 to 60 mg/day to prevent depletion of iron stores during pregnancy and lactation (NRC 1980). Even when women are not anemic, they may complete pregnancy with low iron reserves (Taylor et

al. 1982). Clinical studies indicate that iron absorption increases progressively throughout pregnancy (Lind 1982). Although as much as 90 percent may be absorbed under these defined experimental conditions, the true efficiency of dietary iron absorption under normal situations of food intake is unknown (King 1986). For these reasons, pregnant women should be evaluated periodically to determine their level of iron stores and should receive supplements when stores are low (Romslo et al. 1983).

The RDA for zinc includes a 5 mg/day increment during pregnancy over the 15 mg/day recommended for nonpregnant women (NRC 1980). Zinc deficiency is teratogenic in rats (Hurley 1980, 1981), and abnormal brain development and behavior have been described in the offspring of zinc-deficient monkeys (Sandstead et al. 1977, Sandstead et al. 1978). Evidence from human populations suggests that the rate of fetal malformations and other poor outcomes of pregnancy may be higher in populations where zinc deficiency has been recognized (Sever and Emanuel 1973; Cavdar et al. 1980; Bergmann, Makosch, and Tews 1980; Jameson 1976; Soltan and Jenkins 1982; McMichael et al. 1982; Kiilholma et al. 1984; Buamah, Russell, and Bates 1984). However, conflicting reports have also been published (Mukherjee et al. 1984; Hunt et al. 1984; Ghosh et al. 1985), and questions remain about satisfactory measures of zinc status. The role of zinc deficiency in the adverse outcome of human pregnancy remains uncertain at present (Swanson and King 1987), and supplements are not recommended.

Adolescent Pregnancy

Maternal age influences fetal and infant mortality rates and birth weight. Mothers 15 years of age or younger (approximately 60,000 per year) have increased rates of pregnancy-induced hypertension and premature delivery, are more likely to deliver infants of LBW, and have higher rates of fetal loss and infant mortality (AAP Committee on Nutrition 1985b). In 1985, among live-born infants in the United States with birth weights under 2,500 g, 0.5 percent were born to mothers under 15 years of age and 6.7 percent to those 15 to 17 years of age (NCHS 1987c). A high proportion of adolescent mothers are nonwhite and of low socioeconomic status (IOM 1985). While nutrition is by no means the only issue in caring for the pregnant adolescent, it is a controllable risk factor that can be reduced by programs that provide support, prenatal care, and extra food (Heald and Jacobson 1980).

Disorders During Pregnancy

Pica. Pica, a persistent compulsion to eat unsuitable substances of little or no nutritional value, is a recognized complication of pregnancy. Although

the pica of pregnancy most often involves consumption of dirt or clay (geophagia) or of starch (amylophagia), compulsive ingestion of many other nonfood substances has been noted. Examples include ice, burnt matches, hair, stone or gravel, charcoal, soot, cigarette ashes, mothballs, antacid tablets, milk of magnesia, baking soda, coffee grounds, and the inner tubes of tires. The practice of pica is not new, nor is it limited to any geographical area, race, or culture. The medical implications of pica are not well understood. Inadequate absorption of iron is the hazard most commonly attributed to pica. Other less commonly reported complications include congenital lead poisoning resulting from the consumption of wall plaster (Pearl and Boxt 1980) and small bowel obstruction from the ingestion of laundry starch (Worthington-Roberts, Vermeersch, and Williams 1985). These issues are discussed in more detail in the chapter on behavior.

Hypertension. Preeclampsia and eclampsia are hypertensive conditions induced by pregnancy. Preeclampsia is characterized by a rise in blood pressure, generalized edema that may cause sudden, large weight gain from retained water, and loss of protein in the urine. Eclampsia is the most severe form of the disorder, characterized by convulsions that may lead to coma. Both present serious health risks to mother and fetus (Lindheimer and Katz 1985). Pregnancy-induced hypertension occurs among young women (especially those under 15 years), primiparas, especially older primiparas, and those who are underweight or of low socioeconomic status (Pritchard and MacDonald 1980). The cause of these conditions is uncertain. Whether dietary variables may be part of the cause cannot be determined from available data. Hypertension existing before pregnancy may also adversely affect pregnancy.

Diabetes. Infants born to women with diabetes are at greatly increased risk for prematurity, congenital defects, excessively high birth weight, respiratory distress syndrome, and other conditions that increase overall mortality, especially when the mother's blood glucose levels remain high during pregnancy (see chapter on diabetes). Risks of maternal complications are also increased by established diabetes. These problems are reduced by maintaining strict control of blood glucose levels before and throughout pregnancy (Freinkel, Metzger, and Potter 1983); dietary counseling is important in helping patients to achieve such control (Fuhrmann et al. 1983).

In some women who are not otherwise diagnosed as diabetic, pregnancy is associated with significant alterations in carbohydrate metabolism such that overnight fasting leads to lower-than-normal blood sugar and insulin levels and carbohydrate consumption leads to higher-than-normal levels

(Kalhan and Hertz 1985). These changes, which are most marked near the end of pregnancy, are referred to as gestational diabetes (Second International Workshop 1985). Because current diagnostic methods cannot easily distinguish between established and gestational diabetes, it is uncertain whether gestational diabetes itself—in the absence of preexisting undiagnosed diabetes—increases risks to mothers and infants (Scherger and Hudson 1985.)

All authorities agree that diabetes screening is indicated for pregnant women with risk factors for overt diabetes: a previous history of gestational diabetes, a large-for-gestational-age infant, excess amniotic fluid during pregnancy, excretion of sugar in urine, increased thirst or urination, or recurrent vaginal or urinary tract infections. Because diabetes screening can identify diabetes in mothers who may not have been diagnosed previously and who might benefit from preventive services, various authorities recommend screening for all pregnant women (Second International Workshop 1985; CDC 1986), including administration of an oral glucose tolerance test between the 24th and 28th weeks of pregnancy, or earlier for women with risk factors. Others, however, believe that current understanding of gestational diabetes is insufficient to justify universal screening at this time (Scherger and Hudson 1985). Dietary components of prenatal care of women found to have diabetes or gestational diabetes are discussed in the chapter on diabetes.

Role of Dietary Factors in Fetal Health

Nutritional Needs of the Fetus

Because no one animal model is appropriate for all studies of the human fetus, and because direct investigation of the fetus is limited by ethical and technological considerations, knowledge of the nutrient needs of the human fetus is fragmentary. This section reviews information about fetal and placental nutrient requirements and their response to maternal nutrition.

Energy. Current evidence indicates that glucose and amino acids, rather than fatty acids, are the primary metabolic fuels for the fetus. Fetal energy requirements increase during pregnancy to a maximum estimated from 110 kcal/day (Widdowson 1981) to 150 kcal/day (Rosso 1983) near term. These are modest values when compared with the mother's estimated energy requirement of 2,000 to 2,800 kcal/day (Widdowson 1981).

The glucose concentration in the maternal circulation is always higher than that in the umbilical vein, and maternal glucose levels greatly influence the

rate of glucose transfer across the placenta. For example, in a woman with diabetes and chronic hyperglycemia, larger amounts of glucose than normal are transported to the fetus. Conversely, during maternal caloric restriction, the rate of transfer may be markedly reduced. The placenta uses about half of the oxygen and glucose that are removed from maternal circulation (Nichols and Nichols 1983), and there is some evidence that the glucose needs of the placenta are met preferentially to those of the fetus (Jones and Rolph 1985).

Protein. A fetus near term requires about 6 g (Widdowson 1981) to 8 g (Rosso 1983) of protein per day. Most of this comes as small amounts of essential and nonessential amino acids received continuously from the placental circulation. The free amino acid concentrations in the umbilical artery and vein are higher than those in the mother's blood, indicating that amino acid transport across the placenta is an active metabolic process. Presumably, active transport of amino acids protects the fetus against inadequate maternal protein intake. Another source of protein occurs in amniotic fluid the fetus swallows. This could amount to as much as 750 mg/day. Animal studies indicate that glucose and amino acids can be taken up from amniotic fluid more rapidly than can be accounted for by swallowing alone (Charlton 1984). Administration of nutrients directly into the fetal stomach can normalize the birth weight and length of fetuses born to nutritionally deprived dams (Charlton and Johenger 1985).

Vitamins. Vitamin requirements of the human fetus have not been established. Fat-soluble vitamins cross the placenta by simple diffusion, so that maternal dietary intake would be expected to influence fetal levels. Most water-soluble vitamins are transported from the placenta to fetus by active uptake processes, so that fetal blood vitamin concentrations are higher than those in maternal blood. Although specific vitamin deficiencies have been shown to induce reproductive loss and developmental defects in experimental animals, similar data for human fetuses are not available.

Fetal Risk From Vitamin A. Isotretinoin is a vitamin A acid that is known to cause birth defects or developmental disability in 25 percent of children exposed to it in the first trimester of pregnancy. There are case reports of birth defects associated with large doses of vitamin A. Moreover, vitamin A is well known to cause birth defects in laboratory animals. It has been suggested that women who are pregnant or likely to become pregnant should avoid taking supplements containing more than the RDA level (see introduction and background chapter) for pregnant women (CDC 1987).

Minerals. Mineral requirements of the fetus, estimated from studies on fetal body composition, seem to be higher during the last few weeks of pregnancy than at any other time during prenatal or postnatal development (Widdowson 1981). Little is known, however, about the specific needs for individual minerals. In experimental animals, prenatal calcium deficiency causes rickets in the infant. In animals and humans, iron is stored in fetal red blood cells, and term infants are born with ample reserves. Because premature infants have a smaller red cell mass, they are at increased risk for iron deficiency after birth.

Effects of Other Dietary Factors

Alcohol. During the past 15 years, health researchers have become aware that excessive alcohol consumption adversely affects fetal development. Fetal alcohol syndrome (FAS) was first described among infants born to women who were chronic alcoholics (Jones 1973). These infants exhibited specific abnormalities of the eyes, nose, heart, and central nervous system; irritability and hyperactivity after birth as a result of alcohol withdrawal; and impaired physical and mental development despite nutritional rehabilitation. The minimum level of alcohol consumed during pregnancy that causes FAS has not been established. Some studies show that even one or two alcoholic drinks per day are associated with higher rates of spontaneous abortion, premature detachment of the placenta, and LBW infants (Council on Scientific Affairs 1983). Other studies, however, find that this level of alcohol intake during pregnancy does not increase congenital malformations (Mills and Graubard 1987). Because it is difficult to obtain accurate information about alcohol intake (see chapter on alcohol), this issue is not easy to resolve. Thus, as a prudent measure, the Surgeon General has suggested that women avoid alcohol use during pregnancy (FDA 1981).

The mechanism by which alcohol injures the fetus has not yet been defined. Alcohol can cross the placenta and produce direct toxic effects. Another possible mechanism may be the induction of nutrient deficiencies similar to those that have been shown to produce fetal abnormalities in experimental animals (Hurley 1980).

Although the adverse effects of maternal alcohol consumption on fetal development have been known for more than a decade, a significant number of women still consume alcohol while they are pregnant. For example, one study of women delivering in a large urban hospital reported that 82 percent consumed alcohol during pregnancy (Lillien, Huber, and

Rajala 1982). Because pregnancy course and outcome can be significantly improved if problem drinkers change their habits after conception (Rosett 1983; Rosett, Weiner, and Edelin 1983), routine health and prenatal care should include counseling about the hazards of alcohol use.

Caffeine. Caffeine, which is contained in many widely consumed beverages, does cross the placenta and reach the fetus. Caffeine is an animal teratogen, but there is no clear epidemiologic evidence of a similar effect in humans. Exposure of the pregnant rat to bolus doses of caffeine by intubation, approximately 80 mg/kg or above, results in signs of maternal toxicity, increased resorptions, decreased fetal weight and size, teratogenic effects involving limbs, and skeletal ossification deficiencies (Collins et al. 1981). At doses as low as 6 mg/kg, there is little evidence of maternal or fetal toxicity, although the offspring do display delayed skeletal ossification, a condition that has been shown to be reversible (Collins et al. 1987). The importance of the dosing method in producing teratogenic and other effects is reflected in that caffeine given to pregnant rats at doses of 204 mg/kg in the drinking water results in no teratogenic effects, although signs of maternal and fetal toxicity occur at doses of 87 mg/kg/day, and delayed skeletal ossification occurs at doses as low as 27 mg/kg/day (Collins et al. 1983).

Other studies in rodents have also been conducted to determine the effects of perinatal exposure to caffeine on the neurobehavioral development of offspring. Evidence indicates that gestational exposure of rodents to caffeine either in drinking water or by intubation may affect neurofunctional development at doses of approximately 25 mg/kg/day or greater (Glavin and Krueger 1985; Butcher, Vorhees, and Wootten 1984; Holloway and Thor 1982; West et al. 1986; Peruzzi et al. 1983).

Human studies have also produced inconsistent results. A study of 5,200 maternity cases in Germany reported lower birth weights in women with "high" coffee consumption, regardless of cigarette smoking, socioeconomic class, age, or number of children (May and Netter 1974). A survey of 800 Mormon households found that women who drank coffee had a higher rate of spontaneous abortions, but this effect was not related to dose (Weathersbee, Olsen, and Lodge 1977). Japanese researchers studied the effects of caffeine ingestion in a sample of 9,921 healthy women pregnant for 6 months or longer and reported that women who drank more than five cups of coffee per day had a higher incidence of premature labor, fetuses small for gestational age, and infants with birth defects, but this study did not control for socioeconomic variables (Furuhashi 1985). Other recent reports have found caffeine intake to be associated with increased risk of late first

and second trimester spontaneous abortion (Srisuphan and Bracken 1986) and reduced infant birth weight (Martin and Bracken 1987).

Other studies, however, have suggested that coffee drinking has little or no effect on fetal health. A study of over 20,000 pregnancies absolved coffee drinking from contributing to fetal defects or other untoward outcomes of pregnancy (Van den Berg 1977). An analysis of interview and medical record data for over 12,000 pregnant women evaluated the relation between coffee consumption and adverse outcomes of pregnancy, controlled for smoking and other relevant variables, and found no effect on birth weight, gestation period, or birth defects (Linn et al. 1982). Similarly, a case-control study of over 200 infants with selected birth defects found that the caffeine consumption patterns of their mothers did not differ significantly from those of control mothers (Rosenberg et al. 1982). Finally, an examination of almost 500 cases of birth defects recorded in Finland showed no difference in coffee consumption between the mothers of these infants and control mothers (Kurppa et al. 1982). Although data from human populations do not provide significant evidence that caffeine affects pregnancy outcome, the Food and Drug Administration advises pregnant women to eliminate or limit consumption of caffeine-containing products as a precautionary measure (FDA 1980).

Role of Dietary Factors in Infant Health

Nutritional Needs of Normal Infants

The nutritional requirements of normal infants have been investigated to the extent possible with this population, and RDA's have been established (NRC 1980). These recommendations are largely based on analyses of human milk and on the nutrient content of foods that healthy, thriving infants consumed. A number of studies have measured nutrient needs directly. The best measure of the adequacy of an infant's diet is the growth rate in length and weight. This is usually evaluated by plotting the data from repeated measurements over time on standard NCHS charts (Roche and Hines 1980; Baumgartner, Roche, and Hines 1986).

Energy. Infants require three to four times greater amounts of energy per kilogram of body weight (90 to 120 kcal/kg/day) than do adults to support their relatively high metabolic rate and needs for growth (Heird and Cooper 1988). Energy requirements of individual infants are determined by body size and composition, rates of physical growth, and activity patterns. The RDA of 115 kcal/kg/day in the first 6 months and 105 kcal/kg/day for the second 6 months meets the needs of most normal, well-nourished infants, but infants' needs vary considerably, and the energy intake of any one

infant may vary from day to day. Normal infants appear to adjust intake to needs, provided the mother is sensitive to cues of satiation: loss of interest in food, releasing the nipple from the mouth, or turning the head from the nipple or pushing the bottle or cup away. Many infants who are growing normally consume less energy than RDA levels. One study, for example, found the average intakes of breastfed infants to decline from 110 kcal/kg/day at 1 month to 71 kcal/kg/day at 4 months (Butte, Garza, Smith, et al. 1984).

Water. The evaporative, fecal, and urinary water losses determine water requirements for infants. Evaporative losses in healthy, full-term normal infants range from 30 to 70 ml/kg/day. Fecal losses average 1 to 4 ml/kg/day (up to 10 ml/kg/day in breastfed infants) but can increase suddenly and vary greatly in infants with diarrhea. Because of their large surface area relative to mass, infants lose proportionately more water by skin evaporation than do adults. Infants also have less renal concentrating capacity than adults. Thus, infants are vulnerable to water imbalance. Nevertheless, breast milk and infant formulas provide adequate water, and healthy infants rarely require supplemental water except in very hot weather (AAP Committee on Nutrition 1985b). Instead, dehydration problems are most likely to occur during episodes of vomiting, diarrhea, or fever, when dehydration can occur so suddenly as to constitute a medical emergency (Fomon 1974).

Protein. Protein requirements are also proportionately greater in infants than in adults. Dietary protein must be sufficient to support increases in body protein that range on average from 3.7 g/day for the first month in males and 3.3 g/day for the first month in females down to 1.8 and 1.7 g/day, respectively, for months 9 to 12. These needs generally can be met by protein intakes of about 1.8 g/100 kcal for infants during the first month of life, decreasing to 1.2 g/100 kcal for infants 4 to 6 months of age (Fomon et al. 1986). The Infant Formula Act of 1980 established a minimum standard for the protein content of infant formulas, 1.8 g/100 kcal, which is based on a protein equivalent in nutritive quality to casein (AAP Committee on Nutrition 1976). The RDA of 2.2 g/kg for the first 6 months and 2.0 g/kg for months 7 to 12 also considers protein quality (NRC 1980).

Fat and Carbohydrate. Because dietary fat is a concentrated source of the calories needed to meet infants' high energy needs, infants should consume 3.8 to 6.0 g of fat per 100 kcal, or 34 to 54 percent of total calories (Fomon 1974). Dietary fat is required for normal brain development. Three percent of total calories should be provided by linoleic acid, an essential fatty acid (AAP Committee on Nutrition 1976). Carbohydrate should supply 30 to 60 percent of the total daily energy intake in infancy.

Vitamins and Minerals. Although infant requirements for micronutrients are not as well defined as those for energy and protein (Heird and Cooper 1988), RDA's have been established for many vitamins and minerals (NRC 1980). Full-term infants who obtain breast milk from a well-nourished mother will receive most necessary vitamins (AAP Committee on Nutrition 1985b), although, under some circumstances, vitamins D and K are exceptions. If breastfed infants have limited exposure to sunlight, vitamin D supplementation may be required to prevent rickets (Reeves, Chesney, and DeLuca 1982). Human milk is low in vitamin K, and this vitamin should be routinely administered parenterally to all infants at birth to prevent bleeding disorders (AAP Committee on Nutrition 1985b). Infants fed a commercially available formula that is properly prepared should receive an adequate intake of vitamins (AAP Committee on Nutrition 1976).

The bioavailability of minerals generally is greater from human milk than it is from formulas. The RDA for calcium is designed to meet the need of formula-fed infants, who retain 25 to 30 percent of the calcium in cow milk-based formula. Breastfed infants retain about 65 percent of the calcium consumed. Studies suggest that the bioavailability of zinc from human milk is 41 percent, compared with 28 percent from cow milk, 31 percent from cow milk formulas, and 14 percent from soy formula (Sandstrom, Cederbald, and Lonnerdal 1983).

Iron deficiency is the most common nutrient deficiency in infancy (see chapter on anemia). Rapidly growing infants absorb 49 percent of the iron in human milk, 10 percent of the iron in cow milk, and 3 percent of the iron in iron-fortified formulas (Saarinen, Siimes, and Dallman 1977). For this reason, some authorities believe that breastfed infants do not need additional iron until the age of about 6 months (Saarinen 1978). Current recommendations are that infants begin consuming iron-fortified cereals at 4 to 6 months of age to prevent anemia (Garry et al. 1981; AAP Committee on Nutrition 1985b). Because human milk is low in fluoride and because enamel development in permanent teeth is significant during the first year of life, a fluoride supplement may be desirable for children who do not have access to adequately fluoridated drinking water (see chapter on dental diseases). Requirements for other minerals have been reviewed (AAP Committee on Nutrition 1985b).

Infant Feeding

The available information on infant feeding has been reviewed extensively and was the subject of a 1984 report commissioned by the Assistant Secretary for Health (Task Force 1984).

Human Milk. Human milk is the food of choice for infants. It provides appropriate amounts of energy and nutrients, it contains factors that provide protection against infections, and it rarely causes allergic responses.

Breastfeeding of the newborn in the hospital increased from 24.7 percent in 1971 to 62.5 percent in 1984, but only 27.5 percent of infants are still breastfed by 6 months of age (Martinez and Kreiger 1985). Rates of breastfeeding are highest among mothers who live in the western part of the United States, have had at least some college education, are from upper income families, and are white. Numerous investigations and reports have discussed the unique values of human milk, trends in rates of breastfeeding in the United States, and methods for promoting breastfeeding (DHHS 1984).

Table 15-2 compares the average content of selected nutrients in human milk, infant formulas, and other kinds of milk used to feed full-term infants (AAP Committee on Nutrition 1985b). The nutrient content of human milk reflects the maternal diet, the time of day the milk is expressed, and the length of time the mother has been breastfeeding. Protein concentrations, for example, decrease from the first week through the sixth to ninth month (Anderson, Atkinson, and Bryan 1981), and the concentrations of iron, copper, and zinc also decrease during that period (Vuori and Kuitunen 1978; Siimes, Vuori, and Kuitunen 1979).

Fat provides about 50 percent of the calories in human milk, most in the form of triglyceride, with the fatty acid pattern reflecting the maternal diet. Linoleic acid provides an average of 4 percent of the calories in human milk. The cholesterol content averages 20 mg/100 ml but varies considerably, and values up to 47 mg/100 ml have been reported (Jensen, Hagerty, and McMahon 1978). Lactose is the major carbohydrate. Human milk has a lower content of the amino acids tyrosine and phenylalanine and a higher content of taurine and cystine than cow milk.

The concentrations of water-soluble vitamins in human milk generally reflect the maternal dietary intake and nutritional status. Providing folate supplementation to a woman deficient in this vitamin increases milk folate levels (Cooperman et al. 1982). Vitamin B_{12} deficiency has been reported in breastfed infants whose mothers are strict vegetarians (Johnson and Roloff 1982). As noted above, breastfed infants require supplemental vitamin K at birth and may require vitamin D supplementation if exposure to the sun is inadequate.

Table 15-2
Content of Selected Nutrients in Human Milk, Commercial Formulas, and Other Milks Used for Feeding Normal Full-Term Infants

Nutrient	Per Liter	Mature Human Milk[a] (21.6 ± 1.5 kcal/oz)	Milk-based Formulas[b] (20 kcal/oz)	Soy Protein-based Formulas (20 kcal/oz)	Whole Cow Milk (20 kcal/oz)	Skimmed Milk (11 kcal/oz)	Goat Milk (21 kcal/oz)
Protein	g	10.5 ± 0.2	15	18–21	34	35	37
Fat	g	39.0 ± 0.4	36–38	36–39	37	2	43
Carbohydrate	g	72.0 ± 0.25	69–72.3	66–69	48	50	46
Calcium	mg	280 ± 26	400–510	630–700	1,219	1,270	1,380
Phosphorus	mg	140 ± 22	300–390	420–500	959	1,050	1,140
Sodium	mEq	7.8 ± 1.7	7–10	9–15	22	23	23
Potassium	mEq	13.4 ± 0.9	14–21	19–24	38	44	54
Chloride	mEq	11.8 ± 1.7	11–14	11–15	27	31	44
Iron	mg	0.3 ± 0.1	1.1–1.5 (12–12.7)[c]	12–12.7	0.4	0.4	0.5
Estimated renal solute load	mOsm	73	92–105	122–138	226	240	269

[a] Average values with standard deviations for comparison.
[b] Values listed are subject to change. Refer to product label or packaging for current information. Milk-based formulas contain lactose, and soy protein-based formulas do not.
[c] Iron content of iron-fortified formulas.

Source: Adapted from the American Academy of Pediatrics Committee on Nutrition 1985b.

In addition to nutrients, human milk contains antibodies and other anti-infective factors that are thought to protect infants against gastrointestinal infections. For example, lactoferrin may slow bacterial growth by depriving infective organisms of necessary iron. Lysozymes may destroy bacterial cell membranes after they have been inactivated by peroxidases and ascorbic acid present in human milk. Secretory immunoglobulins in milk protect against organisms that infect the gastrointestinal tract (Welsh and May 1979). Perhaps most important, breast milk fosters colonization of the infant digestive tract with protective *Lactobacilli*. In addition, a number of other cellular and soluble factors may provide specific and nonspecific defenses against infectious agents (Ogra and Greene 1982).

Infant Formulas. The Food and Drug Administration specifies the nutrient composition of commercial infant formulas (CFR, Title 21, Section 107.100—Nutrient Specifications). As suggested by Table 15-2, infant formulas are designed to simulate human milk. Manufacturers modify cow milk by replacing its fat with vegetable oils that are well absorbed, diluting it to a more appropriate concentration of minerals and other solutes, heating it to improve protein digestibility, and adding vitamins and minerals. Soy-based substitutes are available for infants who develop allergic or other sensitivities to substances in cow milk-based formulas. Soy formulas contain isolated soy protein, methionine, corn syrup or sucrose, vegetable oils, vitamins, minerals, carnitine, taurine, and stabilizers. Other products are available for infants who cannot tolerate either soy or cow milk. When properly prepared, commercial formulas support normal growth and development. Errors in preparation, however, have resulted in medical problems. Inadequately diluted formula increases the concentrations of calories, protein, and solutes circulated to the kidney for excretion and can increase levels of sodium and other substances in blood, resulting in disturbances of acid-base balance and toxic symptoms (Chambers and Steel 1975). Overdiluting the formula reduces the level of sodium and other salts in the blood, thereby causing adverse reactions (Partridge et al. 1981), and it does not provide adequate energy and nutrients for growth.

Imitation Milks. Substitute or imitation milks inadequate in calories and nutrients are not suitable for feeding to infants (AAP Committee on Nutrition 1984). Malnutrition has been observed in infants fed a formula made of barley water, corn syrup, and whole milk (Fabius et al. 1981) and in those fed nondairy creamer (Sinatra and Merritt 1981).

Cow Milk. Unmodified whole cow milk is inappropriate to feed to young infants because it causes occult bleeding from the gastrointestinal tract in some infants, leading to anemia and, occasionally, to allergies (see chapter

on infections and immunity). Its lipids are less digestible than the lipids of human milk or most vegetable oils, and its concentrations of minerals and other solutes nearly exceed the excretory capacity of the immature kidney (AAP Committee on Nutrition 1983b). Intestinal blood loss has been noted in younger infants and those who have consumed large volumes of milk, although this usually presents no problem after the age of 6 months or so (Fomon et al. 1981). As indicated in Table 15-2, cow milk has a higher renal solute load than either human milk or infant formulas. By 6 months of age, the kidneys of most normal infants have matured and can excrete excess solutes sufficiently. If infants receive at least one-third of their calories from foods and consume no more than 1 liter of milk per day, there is little disadvantage to the use of whole cow milk after 6 months of age (AAP Committee on Nutrition 1983b). Sometimes, however, infants consuming whole cow milk may not receive adequate dietary iron to meet their nutritional requirements (Tunnessen and Oski 1987).

For infants, 2-percent and nonfat milks are deficient in energy, essential fatty acids, and certain vitamins, and they contain excessive protein and minerals per calorie provided. They are not recommended during the first year of life (AAP Committee on Nutrition 1985b; Fomon et al. 1977). When supplemented with vitamin C and iron, evaporated milk formula (3 oz of evaporated milk, 4.5 oz of water, 2 tsp of corn syrup) is an acceptable, low-cost substitute for infants less than 6 months of age (Fomon et al. 1979).

Goat Milk. Goat milk should be used carefully during infancy because it is low in iron, folate, and vitamins B, C, and D (AAP Committee on Nutrition 1985b). It requires supplementation with these nutrients. As shown in Table 15-2, solute concentration is even higher than in cow milk (Harrison et al. 1979).

Solid Foods. By the age of 4 to 6 months, infants have usually matured enough to sit and to control movements of the head, tongue, lips, and jaw. They can indicate when they do and do not want to eat. At this point, feeding pureed solid foods becomes appropriate. The recommended routine is to introduce single-ingredient foods to the diet, one at a time, at weekly intervals (AAP Committee on Nutrition 1980a, 1985b). Iron-supplemented cereals are usually the first foods added. If properly prepared and stored, pureed foods made at home are nutritionally equivalent to those prepared commercially. By the age of 1 year, foods should provide more than 50 percent of the energy intake of infants (Montalto, Benson, and Martinez 1985). Salt need not be added to foods prepared for normal infants, and sugar should be added sparingly, or not at all. Infants should not be fed hot dogs, nuts, grapes, popcorn, uncooked carrots, round

candies, and similar food items that can cause choking (AAP Committee on Nutrition 1985b).

Low Birth Weight Infants

Infants born prematurely or after intrauterine growth retardation are at high risk for malnutrition and may require special feedings. Before 26 weeks of gestation, the fetus's gastrointestinal system is too immature to digest proteins, fats, or lactose. Fully competent digestive processes do not develop until about 32 to 36 weeks of gestation. Infants born prior to 32 to 34 weeks of gestation may not be able to suck effectively. LBW infants may have medical problems such as necrotizing enterocolitis (a potentially lethal bacterial infection of the intestine), fluid and electrolyte imbalances, and respiratory distress syndrome (difficulty exchanging oxygen and carbon dioxide due to immature lungs) that increase needs for energy and nutrients (AAP Committee on Nutrition 1977). Whether the goal of nutritional support for such infants should be to maintain normal (AAP Committee on Nutrition 1985a) or slower-than-normal weight gain (Keen and Pearse 1985; Steen 1985) is as yet undecided. The challenge is to provide adequate calories and nutrients in a form that the immature digestive and excretory systems can handle and that does not cause complications.

Providing 95 to 160 kcal and about 3 g of protein per kg per day (maintained at about 10 percent of calories ingested as the infant grows), 2 to 4 percent of calories as linoleic acid, 40 to 50 percent of calories as carbohydrate, and sufficient water to compensate for the unusually high losses from skin helps achieve adequate nutrition for LBW infants (Heird and Cooper 1988). Mineral and electrolyte intake may also need to be adjusted to compensate for these infants' unusual requirements (AAP Committee on Nutrition 1985a). Human milk and formulas designed for full-term infants contain insufficient calcium and phosphorus to meet the needs of LBW infants and must be supplemented to permit adequate bone growth and mineralization (Greer, Steichen, and Tsang 1982). Because iron supplements increase susceptibility to vitamin E deficiency, recommendations for iron supplementation in the LBW infant are cautious, advising 1 mg of iron per 100 kcal (Heird and Cooper 1988). Recommendations for vitamins are generally the same as those for full-term infants, although fat-soluble vitamins may pose special problems due to poor fat absorption. Preventing bone disease in LBW infants depends not only on adequate calcium and phosphorus, but also on an intake of at least 500 IU of vitamin D per day (AAP Committee on Nutrition 1985a). Vitamin E requirements may be higher for LBW infants than for term infants. Although 15 to 30 IU of supplementary vitamin E per day has been suggested for LBW infants

(AAP Committee on Nutrition 1985a), the data are not sufficient to support firm recommendations (CDC 1984). The recommendation for folate in LBW infants is 50 μg/100 kcal (Heird and Cooper 1988). This vitamin must be added separately to liquid multivitamin preparations because of its instability (AAP Committee on Nutrition 1985a).

Methods for meeting nutritional goals for LBW infants usually include a combination of human milk (from the mother or pooled from other sources); other special supplements, formulas, or products fed by mouth or tube (enteral nutrition); or intravenous feeding (parenteral nutrition). Milk from mothers of LBW infants contains more energy; has higher average concentrations of protein, fat, and sodium; has lower concentrations of lactose and phosphorus; and contributes to a more rapid growth rate than does milk produced by term mothers (Anderson, Atkinson, and Bryan 1981; Atkinson et al. 1980; Atkinson, Bryan, and Anderson 1981; Chessex et al. 1983; Gross et al. 1981; Schanler and Oh 1980). Human milk also has the advantage of passive transfer of antibodies. Some LBW infants can be nourished adequately on their mother's milk, whereas others thrive better when provided with additional supplements. One such supplemental product, a human milk fortifier that contains protein, carbohydrate, calcium, phosphorus, trace minerals, and vitamins, has been associated with improved growth and prevention of bone demineralization in LBW infants (Ronnholm, Spila, and Siimes 1982).

Special formulas for LBW infants contain more protein, calcium, and phosphorus than formulas for term infants (Atkinson 1983). Although the composition of these formulas varies, all can support growth (AAP Committee on Nutrition 1977; Gross 1983). The composition of several formulas for premature infants are provided in a publication of the American Academy of Pediatrics Committee on Nutrition (AAP Committee on Nutrition 1985a).

Parenteral nutrition is often used in the first few days or weeks of life to support anabolism in LBW infants who cannot tolerate full enteral nutrition. Amino acids are usually used as the nitrogen source, and concentrations administered are limited to those that do not produce elevated plasma levels or the accumulation of ammonia in the blood (Heird and Cooper 1988). Glucose concentration must be adjusted to prevent hyperglycemia and local irritation of peripheral veins. Excessive lipids must be avoided to mitigate hyperlipidemia. Vitamins, minerals, and electrolytes must be added to meet individual requirements (AAP Committee on Nutrition 1983a, 1985b).

Cholestasis, or a suppression of the flow of bile, is a common complication of prolonged parenteral nutrition in LBW infants. While the etiology of this condition is unknown, the degree of prematurity and length of time on parenteral nutrition are important correlates (Gibbs 1980). Lack of oral feedings may also play a role. Although this complication is often reversible when parenteral administration is discontinued, it may progress to hepatic toxicity, cirrhosis, and liver failure (Reynolds 1985).

Role of Dietary Factors in Child Health

Energy

The energy requirements of children are determined by their individual basal metabolic rates, rates of growth, and activity patterns. Therefore, appropriate intakes for children of the same age, sex, and size vary. The RDA's recommend a range of energy allowances that average 105 kcal/kg/day for children 1 year of age to 80 kcal/kg/day for children 2 to 10 years of age (NRC 1980). Higher levels of energy intake are required to compensate for inadequate body weight due to low birth weight, growth retardation, or other factors (Ashworth and Millward 1986).

Nutrients

Children need protein for the maintenance of body tissues, changes in body composition, and synthesis of new muscles. During growth, the protein content of the body increases from about 15 percent at 1 year to 18 to 19 percent by 4 years, which is also the value for adults (Fomon et al. 1982). Estimates of protein needs for growth range from 1 to 4 g/kg/day (Ashworth and Millward 1986). The RDA decreases from 1.8 g/kg/day at 1 year to 0.8 g/kg/day at 18 years (NRC 1980).

Inadequate intakes of vitamins and minerals will be reflected in slow growth rates, inadequate mineralization of bones, and very low body reserves of the micronutrients. Clinical signs of vitamin deficiency in children are reported infrequently. The most common mineral deficiency, iron, appears to be declining, although children from low-income families are at greater risk (see anemia chapter). With the relatively low prevalence of clinical signs of vitamin and mineral deficiency in the general population of children, there is no evidence that supplementation is necessary for this group (AAP Committee on Nutrition 1980b). Although vitamin and mineral supplements increase the quantity of these nutrients in the diet (Cook and Payne 1979), they have not been shown to improve biochemical indices of nutrient status in children who are already well nourished (Breskin et al. 1985). For this reason, recommendations on vitamin and mineral supple-

mentation for children target those at high risk, those from socioeconomically deprived families, and those who have poor appetites or eating habits (AAP Committee on Nutrition 1980b).

Eating Patterns

Preschool children are a nutritionally vulnerable group. Their growth rate is slower than it was in infancy and their nutritional needs in relation to body size proportionately reduced. Thus, they often want and eat relatively little food. Food intake can be reduced even further by the increasing independence (expressed as refusals to eat) and immature feeding skills that are characteristic of very young children. Despite these problems, surveys have indicated that, with the exception of a small subgroup, American preschool children are in relatively good nutritional health. Children of lower socioeconomic status are at higher risk of inadequate nutrient intakes (especially iron deficiency) and poorer growth. Although parents have the main responsibility for providing adequate and appropriate food for preschool children, day care providers supply an increasing proportion of the food that children consume.

Parents continue to be the main influence on the food intake of school-aged children, although an increasing proportion of the diet is consumed in schools, day care centers, and fast food restaurants (Select Panel 1981). Between the ages of 4 and 6, children increase the varieties of foods they are willing to eat (see behavior chapter). Snacks become an important source of calories and nutrients (Crawford, Hankin, and Huenemann 1978) and may contribute as much as one-third of calories and fat, one-fifth of the protein, and nearly one-half of the carbohydrate 10-year-old children consume (Farris et al. 1986). These patterns emphasize the need for parents and schools to provide appropriate meals and snacks and guidance in food choices. Of special concern is the need to encourage appropriate levels of daily physical activity (Select Panel 1981) and choice of nutritious snacks that do not promote tooth decay.

Role of Dietary Factors in Adolescent Health

Energy and Nutrient Requirements

Energy and nutrient requirements are directly related to the stage and rate of growth, and demands are greatest during the peak velocity of growth. Because individuals enter adolescence at different ages and have different rates of growth for different time periods, it is difficult to establish specific nutrient requirements for individuals. Few studies have been conducted on the nutritional needs of adolescents, and the RDA's are established mainly

by extrapolation from adult age groups (NRC 1980). For most nutrients, RDA's are similar to those for adults. The RDA's provide a wide range of energy intakes for two age groups, 11 to 14 years of age and 15 to 18 years of age (NRC 1980). However, many girls experience their peak growth velocity before the age of 11.

The RDA for calcium, 1,200 mg/day, is higher for adolescents than for adults and is designed to meet the needs of the adolescent who is growing at the fastest rate. Achieving maximum bone mass during the teens and twenties can reduce the risk of developing osteoporosis later in life (Lucas, Rees, and Mahan 1985; see chapter on skeletal diseases). The higher RDA for iron for adolescent males is also related to rapid growth, which is accompanied by increases in blood volume, muscle mass, and iron-containing enzymes. Although there are few data on the zinc requirements of adolescents, this population may be at risk for marginal intakes (Mahan and Rosebrough 1984). Vitamin requirements are correlated with growth demands rather than age. For example, males have higher needs for folate than females, and the values for both sexes increase with physical maturity (Daniel, Gaines, and Bennett 1975).

Eating Patterns

The growth spurt of adolescence demands significant increases in calories and nutrient intake to support the rapid growth rate and increased body size. In early adolescence, children still depend on their parents for food, but by the end of adolescence they are largely independent (Select Panel 1981). Irregular eating patterns are common in adolescence, reflecting this growing independence from the family and the teenager's increasingly busy social life and athletic, academic, and vocational activities. Breakfast and lunch are often skipped or eaten on the run. Snacking is characteristic of this age group and contributes significantly to nutrient intake; these snack foods are often higher in calories, fat, and sugar—and lower in vitamins, minerals, and fiber—than foods consumed at family meals (Hampton et al. 1967; Pao 1980). Because lifetime dietary patterns are established during these years, adolescents should be encouraged to choose nutritious foods, to develop good eating habits, and to maintain appropriate levels of physical activity (Select Panel 1981).

Role of Dietary Factors in Chronic Disease in Childhood

Several chronic diseases have special implications in the nutrition of infants, children, and adolescents. Some of these are discussed elsewhere in this Report. Childhood hyperactivity (or attention deficit disorders) and eating disorders such as anorexia nervosa and bulimia, for example, are

reviewed in the chapter on behavior, and juvenile diabetes is reviewed in the diabetes chapter. Children with chronic disease and other handicapping conditions frequently require therapeutic diets accompanied by intensive nutrition counseling and support (see, for example, Baer 1982). Discussion of issues related to most of these conditions is beyond the scope of this Report, but a few examples follow.

Coronary Heart Disease

The relationship between diet in infancy, childhood, and adolescence and the development of adult atherosclerosis and coronary heart disease (see chapter on coronary heart disease) is of great current interest. Within the past 5 years, cholesterol-lowering diets for children with elevated blood cholesterol levels (Consensus Development Panel 1985), as well as for those with normal levels (Weidman et al. 1983), have been recommended to prevent onset of the adult disease. These recommendations are that all children older than 2 years adopt a diet that reduces dietary fat intake to 30 percent or less of calories, saturated fat to less than 10 percent of calories, and daily cholesterol intake to 250 to 300 mg or less. However, other groups have advised against specific recommendations because they find insufficient evidence for the safety and efficacy of such diets in children (AAP Committee on Nutrition 1983c, 1986).

Increasing evidence suggests that atherosclerosis begins in childhood. Cholesterol concentrations, which are lower in cord blood than in maternal blood, rise after infants begin to be fed. Infants fed human milk or cow milk have higher blood cholesterol levels at age 6 months than do those fed formulas containing vegetable oils, but these differences are reduced once cholesterol-containing foods are added to the diet (Farris et al. 1982). By the age of 1 year, blood cholesterol levels correlate with dietary intake of saturated fat and cholesterol; they rise rapidly during the first 2 years of life (Berenson et al. 1979). Blood cholesterol levels at age 6 months are correlated with levels at age 7 years (Freedman et al. 1987). Childhood blood cholesterol levels have a strong genetic component, and children whose parents have high levels are two to three times more likely to be in the 95th percentile for blood cholesterol than children of parents with low to normal levels (Berenson et al. 1979).

Atherosclerotic plaques have been identified in the coronary arteries of young soldiers killed in the Korean and Vietnam wars (Strong 1986) and in adolescents and even younger children who suffered accidental death (Velican and Velican 1980). Children in the United States exhibit higher blood cholesterol levels and have a higher dietary intake of fat and cholesterol than children in populations with lower heart disease rates (Weidman

et al. 1983). Measurements of other heart disease risk factors such as high blood pressure (Burke et al. 1987) or obesity (Harsha et al. 1987) made in early childhood are highly correlated with those made in the same children at age 7. Thus, pediatricians have been urged to identify and to treat children with elevated blood cholesterol levels (Wynder et al. 1983; Consensus Development Panel 1985).

On the other hand, no data are available from prospective studies to demonstrate that feeding cholesterol-lowering diets to children can either support normal growth and development or reduce later heart disease rates. Thus, the American Academy of Pediatrics (AAP) recommends that children's diets follow current dietary trends with moderation, including decreased consumption of saturated fats, cholesterol, and salt and an increased intake of polyunsaturated fats (AAP Committee on Nutrition 1986). It also stresses that current data indicate that no changes in the current diet for infants and children under the age of 2 are necessary. Whether a diet consisting of 30 percent of calories from fat should be advised for the general population of children over age 2 remains controversial, but a fat intake over 40 percent of calories is excessive (La Rosa and Finberg 1988). Until better data are available, the AAP recommends screening high-risk children for early detection and treatment for heart disease risk factors such as high blood cholesterol, high blood pressure, and obesity (AAP Committee on Nutrition 1986).

Obesity

The increased rate of pediatric obesity in the United States is an important public health issue (Gortmaker et al. 1987). Childhood obesity can lead to adult obesity and all its complications; currently, insufficient information is available about the causes and prevention of early onset of obesity (see chapter on obesity).

The cause of obesity in infants is poorly understood. Speculations that formula feeding and early introduction of solid foods might be responsible are not supported by research studies (Ferris et al. 1980; Dubois et al. 1979), and no differences in subsequent fatness have been observed among children who were breast or bottle fed (Fomon et al. 1984). Both genetic and environmental factors are involved (see obesity chapter). A recent study of adopted children, for example, found a strong correlation of body weights to the weight of the biologic rather than the adoptive parents (Stunkard et al. 1986). Lower-than-normal activity levels are also related to childhood obesity (Berkowitz et al. 1985). One study observed a direct relationship between body weight and number of hours spent watching television (Dietz and Gortmaker 1985).

Studies examining the role of early infant obesity as a risk factor for later obesity are also inconsistent. Some studies found that most obese infants become thinner as they grow older and concluded that early weight gain does not predict later obesity (Shapiro et al. 1984). Others have found that body weights at the age of 1 year strongly predict body weights at age 7 (Harsha et al. 1987). Nearly all studies agree, however, that the correlation between childhood obesity and later obesity increases as children grow older (AAP Committee on Nutrition 1981). These and other issues related to obesity are reviewed in the chapter devoted to that topic.

Cognitive Performance

LBW infants are at greater risk for developmental disorders than are normal-weight infants (Parkinson, Wallis, and Harvey 1981). Infants with early intrauterine growth retardation (prior to 26 weeks' gestation) are at greater risk than infants whose growth retardation begins after 26 weeks' gestation (Fancourt et al. 1976). Early intrauterine growth retardation is associated with less successful school performance, lower intelligence, and more behavioral and other handicaps (Harvey et al. 1982).

The role of maternal and early infant malnutrition, as distinguished from other causes of fetal and infant growth retardation, is uncertain. Animal and human studies have shown that severe malnutrition during fetal growth and early infancy retards brain cell division and alters nerve myelination, but cognitive and behavioral effects of less severe nutritional deprivation cannot easily be distinguished from other environmental effects.

Data from populations in which malnutrition is endemic indicate a relationship between growth retardation of infants and young children and low performance in mental development tests (Lasky et al. 1981). Children with protein-energy malnutrition in infancy who were tested at ages 5 to 11 years had poorer academic performance than children who were well nourished in infancy, which is reflected in classroom behavior problems such as lack of attention, poor memory, poor motivation, and easy distractibility (Galler, Ramsey, and Solimano 1984). However, socioeconomic disadvantages as well as poor nutritional status could cause these problems. Children subjected to prenatal malnutrition because of war-induced famine or to acute periods of malnutrition during infancy can overcome nutritionally induced growth deficits and can exhibit cognitive function levels that correlate most strongly with the parents' educational status (Stein et al. 1972; Beardslee et al. 1982). Malnourished children adopted by socioeconomically advantaged families have been able to catch up in mental development (Graham and Adrianzen 1972).

Studies of the relationship between maternal nutritional supplementation and the behavioral development of offspring have produced inconsistent results. In some studies, no differences in cognitive function occurred among offspring of women who did or did not receive nutritional supplements (Rush, Stein, and Susser 1980a, 1980b; Higgins 1976), but others have reported significant benefits of improving prenatal nutritional status (Villar et al. 1984).

As discussed in the anemia chapter, lower mental and behavioral test scores improved relative to controls among iron-treated iron-deficient infants only when the amount of iron administered corrected both the anemia and biochemical indices of iron deficiency (Lozoff et al. 1987). Short-term studies on the effects of omitting breakfast on cognitive performance have reported that adequate nutrition benefits learning (Pollitt, Leibel, and Greenfield 1981, 1983; Conners and Blouin 1982/83). Well-nourished children ages 9 to 11 who skipped breakfast displayed higher rates of inaccurate responses to problem solving.

Inborn Errors of Metabolism

Early identification and nutrition intervention can help prevent subsequent mental retardation in infants born with many kinds of metabolic disorders. All States have screening programs to detect newborns with inborn metabolic disorders (Infant Metabolic Diagnostic Laboratory 1987). Such children require long-term dietary management. One example of such a disorder is phenylketonuria (PKU) (AAP Committee on Genetics 1982).

PKU results in excessive and potentially toxic blood levels of the amino acid phenylalanine. The goals of therapy are to provide adequate intakes of energy and nutrients but only enough phenylalanine to maintain normal growth and development. Meeting these goals requires special formulas and food products with reduced phenylalanine content, as well as considerable support from health professionals (Trahms 1984). Current recommendations are to continue the phenylalanine-restricted diet throughout the reproductive years, because experience with its discontinuation at ages ranging from 4 to 10 years indicates progressively decreasing cognitive functioning, learning difficulties, poor attention span, and behavioral difficulties (Smith et al. 1978; Koch et al. 1982; Holtzman et al. 1986). Evidence suggests also that phenylalanine restriction during pregnancy improves the outcome for women with PKU and their infants (Mabry, Denniston, and Coldwell 1966; MacCready and Levy 1972; AAP Committee on Genetics 1985; Drogari et al. 1987).

Implications for Public Health Policy

Dietary Guidance

General Public (Including Children and Pregnant Women)

Assessment of nutritional status is an integral part of maternity care at the beginning of pregnancy and periodically throughout pregnancy and lactation to provide continuing monitoring and recommend appropriate intervention.

Evidence related to the role of diet in maternal and child health indicates that well-nourished mothers produce healthier children. Intake of sufficient energy and nutrients to attain optimal nutritional status, including appropriate weight before pregnancy and adequate weight gain during pregnancy, improves infant birth weight and reduces infant mortality and morbidity. Avoiding potentially toxic substances such as alcohol or drugs during pregnancy seems to improve infant birth weight and health, but the evidence regarding low exposures to these agents is not conclusive. Information on appropriate dietary intake, with consideration of ethnic and cultural food habits, should be provided as early as possible to pregnant women and to women expecting to become pregnant.

Evidence related to the role of diet in infancy indicates that breast milk is the optimal food for infants. Whenever possible and as early as possible, health professionals should provide guidance and support to pregnant women and new mothers on the importance of breastfeeding and on methods for its initiation and maintenance. Mothers who cannot or choose not to breastfeed should receive information about appropriate formulas.

Consuming the appropriate amount and form of energy and nutrients for developmental age is important for good health, as is early education about lifelong dietary patterns that help prevent disease. Parents should guide their children in developing positive eating behaviors and on age-appropriate food patterns that meet nutritional requirements but avoid excessive intake of fat, sodium, and sugar. Parents should also help adolescents develop healthy eating habits and should emphasize the importance of including sufficient quantities of low-fat, nutritious foods in meals and snacks.

Special Populations

Some factors present at the onset of pregnancy place women at increased nutritional risk. These include: adolescence, short interconceptional peri-

od, poor reproductive performance, economic deprivation, food faddism, substance use, chronic systemic disease, and inadequate or excessive prepregnant weight (below 85 percent or above 120 percent of standard weight for height). Other nutritional risk factors such as anemia and inadequate or excessive weight gain may develop during pregnancy.

Attaining appropriate prepregnancy body weight and nutritional status, gaining adequate body weight, and avoiding alcohol during pregnancy are important for all women. Qualified health professionals should provide close nutritional monitoring and individualized counseling to women appropriate to their educational level and cultural food habits before and throughout pregnancy.

Specialized professional counseling on feeding should be provided to parents of LBW infants, other infants at high risk, and infants who require special formulas. Parents of children who are at high risk because of developmental disorders, inborn errors of metabolism, physical disabilities, or chronic disease should also receive ongoing professional advice on appropriate diets and feeding methods. Because children from families with a history of diet-related chronic disease have a high risk for such conditions, they should be evaluated for these conditions. Children of families whose blood cholesterol, blood sugar, or blood pressure exceed appropriate levels should be advised on dietary and other means to reduce these risk factors.

Physicians, nurses, and other health professionals caring for children and women of childbearing age should receive education and training in nutrition assessment, nutrition intervention for prevention of disease, and promotion of maternal and child health.

Nutrition Programs and Services

Nutrition Services

Evidence related to the role of nutrition in maternal, infant, and child health suggests that all health care programs for these groups should provide nutrition services, especially to those people at special health or economic risk. Such services include nutrition assessment, dietary counseling, nutrition education, and referral.

Food Products

Evidence related to the role of dietary factors in maternal and child health suggests that food manufacturers should develop nutritious, low-fat, low-

salt, low-sugar snack food products for children and adolescents. Quality and safety of infant formulas and other infant foods require continued monitoring to prevent untoward health consequences.

Special Populations

Pregnant women, infants, and children with diet-related disease conditions and physical disabilities that impair food intake should receive counseling and assistance in dietary management. Low-income families should have access to an adequate diet. Those with poor education, limited understanding of English, and different cultural patterns require nutrition education approaches appropriate to their needs.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in maternal, infant, and child health should include investigations into:

- The amounts of energy and essential nutrients pregnant women must consume to achieve optimal birth outcome and promote long-term maternal health.
- The optimal weight gain during pregnancy.
- The diet during pregnancy that best prevents complications of chronic disease conditions in the mother.
- The effects of potentially toxic dietary factors such as alcohol on fetal health.
- The optimal feeding methods and diet for improving growth and development of LBW infants.
- The diet in childhood that will best prevent later development of chronic disease conditions.
- The influence of nutritional status on teratogenic outcomes, particularly neural tube defects.
- Nutritional care for optimal development of infants and children with special health care needs due to chronic illness or developmental disorders.
- Effective educational methods to teach parents how to develop good dietary practices for themselves and their children.
- Effective educational methods for teaching good nutritional practices to children and adolescents.

- Effective strategies to integrate nutrition screening, education, and intervention services into health care programs.
- The impact of social changes on nutritional status, including those related to meal sources and eating patterns.

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Chapter 16

Aging

. . . If thou well observe
The rule of not too much, by temperance taught
In what thou eat and drink, seeking from thence
Due nourishment, not gluttonous delight,
Till many years over thy head return:
So may thou live, till like ripe Fruit thou drop
Into thy Mother's lap, or be with ease
Gathered, not harshly plucked, for death mature.
John Milton
Paradise Lost, Book XI (1667)

Introduction

Life expectancy at birth is now 75 years, compared with about 47 years at the beginning of this century (NCHS 1988). The average age and the proportion of the older population are also increasing. Individuals over age 65 now comprise 12 percent of the population, compared with 4 percent in 1900. This percentage is expected to rise to 21 percent by the year 2030. People who survive to old age are living longer. For example, persons reaching age 65 in 1984 had an average life expectancy of an additional 17 years (19 years for women and 14.5 years for men), and life expectancy at age 65 has increased 2.5 years just since 1960 (NCHS 1986). This increased life expectancy for older Americans is resulting in an even more rapid growth in the populations over age 75 and over age 85.

The lack of a satisfactory definition of old is a problem. What is old? Who is old? When does one become old? Clearly, physiologic age is not the same as chronologic age. On the other hand, numerous attempts to find a simple and accurate indicator of physiologic age have not yet yielded a satisfactory instrument. This discussion employs simple chronologic cutoffs, recognizing, however, that there is tremendous heterogeneity within the populations over 65, over 75, and over 85. The general term older will refer to Americans over age 65.

Historical Perspective

Nutritional issues are prominent in the history of gerontology, and dietary advice for the aged can be traced back as far as recorded history. The field of nutrition and aging can be divided into studies in humans on dietary adequacy, requirements, guidelines, etc. and studies in animal models aimed at retarding the aging rate via diet. This chapter discusses the human studies but does not examine in detail the large amount of literature on animals.

Certain theories about the basic causes of aging are related directly to nutrition. One theory proposed at the beginning of this century, for example, was that the gradual accumulation of toxins secreted by intestinal bacteria caused aging and that eating certain types of yogurt could prevent this accumulation (Mechnikova 1921). Aldous Huxley satirized this theory in his novel *After Many a Summer Dies the Swan*, in which a character eats raw carp in an attempt to populate his intestines with the "good" microorganisms of this long-lived fish. More recent theories attribute aging to the gradual oxidation of membrane lipids throughout life and promote consumption of compounds with antioxidant properties (Harman 1982). Dietary caloric restriction without malnutrition in rodents and other diverse animals substantially prolongs lifespan and retards most aspects of biologic aging (Masoro 1985; Weindruch and Walford 1988). Dietary restriction is effective in rodents when started in early life or mid-adulthood. This result has been reproduced many times since it was first described in the 1930's (McCay, Crowell, and Maynard 1935), but underlying mechanisms remain vague. Dietary restriction is attracting broad attention because it provides the best model now available to study the biology of decelerated aging. How calorie-restricted regimens affect aging in primates is not well known.

Older persons are susceptible to extravagant claims for the effects of nutritional manipulations and supplements. Nutritional science provides an important service by evaluating these claims and limiting the damage resulting from such quackery (see chapter on dietary fads and frauds).

In the past two decades, the scientific community has increased attention on the nutritional status of older people. Although specific nutritional problems have been documented among older Americans, the relationship of diet to morbidity and mortality in this age group is not always clear. What is clear is that prevention of many of the health problems of old age must necessarily begin much earlier in life.

This chapter reviews age-related physiologic, psychologic, and socioeconomic changes that can influence nutritional status of older Americans; discusses issues related to the nutritional requirements of older persons; and describes the effects of nutritional deficiencies on the health of the older population.

Significance for Public Health

Although not inevitable, health and mobility often change and decline with advancing age. The increasing life expectancy at age 65 observed throughout this century suggests that diet, exercise, and other personal and socioeconomic factors can help prolong good health for most people (Rowe and Kahn 1987). Nevertheless, the chances are great that an individual in the eighth or ninth decade of life will be limited in activity and require health and social services. Many older Americans suffer from arthritis, heart disease, hypertension, hearing loss, diabetes, obesity, gastrointestinal conditions, liver disease, and cancer and other chronic diseases. More than 60 percent of people over age 65 have high blood pressure and approximately 30 percent have heart disease. Heart disease, cancer, and stroke account for over three-quarters of the deaths among older persons and 50 percent of all days of bed confinement (U.S. Senate 1987/88; NCHS 1986).

Such chronic conditions as well as dementia prevent functional independence and increase the need for dietary and other long-term care services. In 1985, for example, more than 5 million persons over age 65 needed special care to remain independent, and this figure is expected to exceed 7 million by the year 2000. Nearly 3 million older Americans residing outside institutions have been estimated to require assistance with basic activities related to food consumption such as shopping, meal preparation, or eating (Posner and Krachenfels 1987). One survey has estimated that three-fourths of all patients receiving home health care require therapeutic diets and could benefit from the services of trained nutrition professionals (Gaffney and Singer 1985).

The total costs of health care for older persons are not known precisely. In 1986, health expenditures made up 29 percent of the nearly $270 billion paid by the Government for programs and services for the older population, but older Americans still disbursed an estimated average of 15 percent of their personal income for health care (U.S. Senate 1987/88).

One difficulty in determining the effect of nutrition on the health of older Americans is that there are no recent national food consumption and

nutritional status data on this group, and hence no data on national trends. Currently available national data come from the Nationwide Food Consumption Survey (NFCS) conducted in 1977–78 and the National Health and Nutrition Examination Surveys (NHANES I and II) conducted from 1971–74 and 1976–80 (see chapter on dietary patterns and practices). Some of this information will be discussed below in the section on energy and nutrient status of the older population. New national data on food consumption and/or nutritional status of older individuals will be provided by the U.S. Department of Agriculture's (USDA's) 1988 NFCS and DHHS's NHANES III, which began data collection in 1988. In addition, plans are being developed to conduct a special survey of food consumption of older persons as part of USDA's Continuing Survey of Food Intakes by Individuals.

Policy Background

Nutrition Services and Programs

Until the early 1970's, nutrition services for the older population, with the exception of food stamps, were based almost exclusively in hospitals and long-term care facilities and included routine dietary screening, nutritional status assessment, dietary counseling, oral or intravenous nutritional support, and food service. These services continue to be provided. Because they are not usually reimbursable under current cost-containment guidelines, they are especially vulnerable to fiscal constraints (Posner and Krachenfels 1987).

In 1973, in response to the growing population of older Americans, to rising health care costs, and to greater interest in preventive health care, the Nutrition Program for the Elderly was established under the Administration on Aging to expand food and nutrition services from the hospital to include communities and homes. Current Federal programs support the functional independence of older individuals in ambulatory care centers, adult day care centers, hospices, and home settings. These food and nutrition activities include the USDA's Food Stamp Program, which serves more than 2 million older Americans, and two programs administered by the Nutrition Program for Older Americans—Congregate Meals, which also serves about 2 million individuals, and Home-Delivered Meals, which serves 0.5 million. Despite limitations in size and scope, these programs have been demonstrated to improve the dietary intake and nutritional status of participants (Czajka-Narins et al. 1987).

Surgeon General's Workshop on Health Promotion and Aging

The 1988 Surgeon General's Workshop on Health Promotion and Aging addressed nutrition and aging issues (DHHS 1988). The workshop report regarding nutrition and aging was based on the premise that "good nutritional status is essential for a high quality of life and food contributes to the quality of life through psychological, social, as well as physical mechanisms." This premise is based on the assumptions that older people vary greatly in their social, economic, and lifestyle situations, functional capacity, and physical conditions; that nutrition policy should be crafted from a multidisciplinary framework; that a critical shortage of knowledgeable personnel in the areas of nutrition education, research, and service now exists; and that because the research base for nutrition of older Americans is evolving, specific recommendations must be periodically reviewed and updated.

The workshop report identified priorities related to (1) sound public education tailored to the special concerns of old age, such as multiple drug regimens, appropriate energy intakes, and the effects of existing chronic diseases on nutritional status; (2) professional education on geriatric concerns integrated into the core curriculum, inservice training, and continuing education of dietitians and other health care professionals; (3) counseling provided by credentialed nutrition professionals in institutional or community-based programs providing health services to older adults; and (4) appropriate financing for nutrition services delivered to older people as part of routine and long-term care.

Key Scientific Issues

- Effects of Aging on Nutritional Status
- Evaluation of the Nutritional Status of the Older Population
- Effects of Nutritional Deficiencies on the Older Population

Effects of Aging on Nutritional Status

Aging is accompanied by a variety of physiologic, psychologic, economic, and social changes that may compromise nutritional status. All of these changes do not necessarily occur in all individuals, however, and many older people remain in excellent health until very old age. Older persons have a high prevalence of chronic disease, use medications heavily, and are relatively sedentary. Many of the seemingly inevitable consequences of aging may actually be caused by these other factors (Letsov and Price

1987). The role of exercise in the health of older persons has been reviewed recently (Smith, Smith, and Gilligan 1988).

Physiologic Changes

Many physiologic functions, including the senses of smell and possibly taste, decrease with age (Schiffman, Mors, and Erickson 1976; Kamath 1982; Smith, Smith, and Gilligan 1988; Chauhan et al. 1987). These changes may result in decreased appetite as well as impaired utilization of nutrients and limitations of function.

Dental problems, common in old age, decrease the ability to chew certain foods (Albanese 1978). Physical disabilities such as diminution of vision may make eating less pleasant (Roe 1985). Although the decreases in basal metabolic rate and physical activity noted with increasing age in some studies reduce nutrient needs, older people may still consume insufficient calories and essential nutrients (McGandy et al. 1966; McGandy 1986). Decreased physical activity also may predispose individuals to the development of osteoporosis (see chapter on skeletal diseases).

Changes such as osteoarthritis, which affects 16 million people in this country, can affect mobility and decrease an older person's ability to purchase and prepare food (Garetz 1976). Another possible hindrance to adequate nutrition in the aged is malabsorption, which can be caused by a decrease or absence of gastric acid secretion and by interactions with medications commonly prescribed for older persons (Butler and Lewis 1977; Russell 1986; Roe 1985; Hathcock 1987). Whether these changes contribute to nutrient deficiencies in older people has not been established, nor is it known whether such changes are related more to the use of medications, to poor health, or to sedentary lifestyle than to age itself (Letsov and Price 1987). Recent studies, for example, have demonstrated that exercise prevents or delays the onset of musculoskeletal disabilities in older adults (Lane et al. 1987).

Psychologic Changes

The most common psychologic factor affecting nutrition is depression (Garetz 1976). Of all psychiatric diagnoses, depression is most strongly correlated with increased morbidity and mortality, regardless of the age of the subjects (Widgor and Morris 1977; Nielsen, Homma, and Bjorn-Henriksen 1977), and is most often related to chronic disease and to poverty, which are common among older persons. At least 30 percent of noninstitutionalized men and women over the age of 65 live alone (Todhunter 1976; AARP 1985). Neither institutionalization nor solitary

living necessarily induces depression, but such life changes may be associated with poor self-esteem, which, in turn, can lead to significant changes in eating patterns (Letsov and Price 1987). Depression is one psychiatric disorder that can be treated successfully, but recent advances in therapy are not disseminated to health professionals widely or rapidly enough to make maximum impact (NIA 1987).

Economic and Social Changes

Older Americans as a group have a lower economic status than other adults in the United States (U.S. Census Bureau 1977; U.S. Senate 1987/88). Although the percentage of older individuals living below the poverty level (12.4 percent in 1984) has decreased substantially over the past two decades and is now less than the percentage of those under 65 living in poverty (14.7 percent in 1984), poverty continues to be too high. The decline in income most often results from retirement from the workforce, the effects of inflation on fixed incomes, death of a wage-earning spouse, or failing health (U.S. Senate 1987/88). Income and health status have been found to be important determinants of life satisfaction in the older population (Chatfield 1977). Low income is also a major risk factor for inadequate nutrition in older individuals (DHEW 1974; Guthrie, Black, and Madden 1972).

Most older people do not live in institutions, but older Americans as a group are more likely to be institutionalized temporarily or permanently (Kane 1984). Although institutional food is likely to meet minimal standards for nutrient content, factors such as a lack of choice or limited day-to-day variety may increase the risk of inadequate consumption. Many residents of nursing homes consume a therapeutic diet (NCHS 1981) that may further discourage adequate intake. An important issue for demented institutionalized individuals is that they may not consume the food, not that the menu is inadequate (Sandman et al. 1987).

Evaluation of the Nutritional Status of the Older Population

Methodological Issues

Assessing the nutritional status of the older population—and other populations—requires clinical studies to evaluate physical signs of nutritional health or disease, dietary studies to evaluate nutrient intakes with accepted standards, and laboratory investigations to provide data about quantities of particular nutrients in the body or to evaluate certain biochemical functions that are dependent on an adequate supply of a particular nutrient. Because use of a single measure is rarely sufficient to establish the level of malnutrition in a population, nutritional assessment is best accomplished using a

combination of these methods. The greater the number of measurements yielding values below standard, the more likely a population is to suffer from poor nutritional status.

Nutritional status evaluation of older people is complicated, and a number of methodological caveats should be kept in mind when evaluating the results. Clinical and dietary standards for younger adults may not be appropriate for older persons, yet few data are available on nutritional requirements or recommended intakes of older adults. The Recommended Dietary Allowances (RDA's), for example, were developed largely from research on the nutrient needs of young healthy people. The present standards for adults over age 50 are, for the most part, identical to those for people ages 23 to 50 (NRC 1980). Because these standards fail to consider the great heterogeneity of adults whose ages may differ by as much as 50 years (Schneider et al. 1986) and because they were often not developed from actual measurements on older populations, their appropriateness for older Americans is not known (Suter and Russell 1987).

Collection of dietary data in older individuals based on recording or recalling food eaten over a specified period of time is complicated by an increased prevalence of dementia and forgetfulness in older persons, which may result in underreported nutrient intakes (Beaton 1985; Hunt et al. 1983). It has also been difficult to separate behavioral changes in dietary intakes from the effects of aging processes on dietary and nutritional status. For example, 70 percent of a sample of older subjects indicated some change in food habits in recent years for health reasons, changes in living status, beliefs, or finances (Todhunter 1976). The Ten State Nutrition Survey found that two-thirds of the older population had changed their diets in the 4 years before the study (DHEW 1972). Male participants in the Baltimore Longitudinal Study of Aging reduced their cholesterol intake significantly during the period 1961–75 (Elahi et al. 1983). Whether advice from health professionals is responsible for such changes has not been established. However, these changes need to be considered when making inferences about the effects of aging processes on nutrition in older persons taken only from surveys conducted at a single point in time.

Similar issues apply to use of laboratory tests, body measurements, and body weights to assess the older population's nutritional status. Evaluation of height and weight measurements to define obesity, for example, is complicated by the loss of stature that accompanies aging (Bowman and Rosenberg 1982). Measurements of actual heights, weights, and body skinfolds in older populations have led to the development of standards substantially different from those for younger adults (Frisancho 1984).

Health status also affects such measurements; nutritional measures of older homebound individuals differ significantly from those of younger and less restricted groups (Sherman et al. 1983).

It is also difficult to make generalizations about clinical signs of undernutrition in older persons. For example, changes in subcutaneous tissue and skin that occur normally with age may mask clinical signs of vitamin deficiency (McClean, Dodds, et al. 1976). However, NHANES did not find high percentages of older people with biochemical indications of nutrient deficiencies.

Perhaps the most serious problem in nutritional status assessment of older people is the lack of correlation between dietary intake data and clinical and laboratory assessment methods. For example, over the past 20 years, several comprehensive nutritional surveys that included persons over age 60 have been performed in this country (DHEW 1972, 1974; Agricultural Research Service 1972; USDA 1980; DHHS 1983). All of these studies have identified a substantial proportion of older men and women who fell below the RDA for calories—as well as for protein, vitamins, calcium, and iron (Bidlack, Kirsch, and Meskin 1986; Young and Rivlin 1982). However, estimates of obesity from anthropometric (body) measurements generally show an increase in percent of body fat for both sexes as age increases (Schlenker et al. 1973). NHANES I (DHEW 1974) and the Ten State Nutrition Survey (DHEW 1972) found obesity to be a substantial problem in the aged, especially in women. The findings of diminished calorie intake and increased obesity are difficult to reconcile. The contradiction may result from differences in criteria for evaluating the adequacy of dietary versus biochemical data (DHHS/USDA 1986), the diversity of the study populations, diminished physical activity among many older persons, or as yet unknown metabolic factors. However, it is well established that body composition changes in older people: the extremities lose fat that is redistributed to the trunk, and lean body mass is lost. Thus, the term obesity in older populations may need redefinition.

Energy and Nutrient Status of the Older Population

Bearing in mind the methodological considerations discussed above, this section highlights results from clinical, laboratory, anthropometric, and dietary assessments of energy and nutrient status of the older population.

Energy. The national dietary and food consumption surveys conducted during the 1970's reported lower energy intakes among older persons than among younger adults (DHEW 1979a; DHHS 1983; USDA 1984), a finding

that has been supported by smaller studies. A study of male executives in the Baltimore Longitudinal Study of Aging, for example, found a steady decline in average energy expenditure from 2,700 kcal/day at age 30 to 2,100 kcal/day at 80 years of age. The decline in energy expenditure was attributed to reduced physical activity (400 kcal) and to a 200 kcal decline in basal energy metabolism as a result of a reduction in lean body mass with age (McGandy et al. 1966). Aging was also inversely associated with energy intake among 180 male participants (35 to 74 years old) in the same study of aging (Elahi et al. 1983). A 4-year longitudinal study of free-living healthy older men and women whose average age was 71 showed a decline in energy intake of 162 and 152 kcal, respectively, to an average energy intake of 2,118 kcal/day for men and 1,545 kcal/day for women (Garry, Goodwin, and Hunt 1985). These levels of energy intake were determined from 3-day diet records and were substantially higher than those recorded for older subjects between 65 and 74 years of age in NHANES I and II and in the 1977–78 NFCS (DHEW 1979a; DHHS 1983; USDA 1984).

NHANES I reported lower caloric intake among older black Americans than among white Americans (DHEW 1979a), as did the 1977–78 NFCS for older black versus white men (USDA 1984). NHANES II did not present data by race within age, sex, and income groups because the number of black persons within those groups was too small to provide reliable estimates (DHHS 1983). However, NHANES II indicates that the percentages of overweight women are greater than men, although both sexes increase in weight until late mid-life when rates plateau and then decline into old age. Black women become overweight earlier in life than whites, but weight patterns of black males are similar to their white counterparts. Of the approximately 3,500 older persons examined in the NHANES I sample, which is representative of the U.S. civilian, noninstitutionalized population between 65 and 74 years of age, the mean energy intakes for the white and black males were 1,828 and 1,571 kcal/day, respectively; for white and black older females, the mean energy intakes were 1,319 and 1,186 kcal/day (NCHS 1977). These energy intakes represented 77 percent of the RDA's for white females and 69 percent for black females. The percents of the RDA standard were 75 and 64 for white and black males, respectively. Even when a conservative estimate of the 67 percent of the RDA standard is used, about 50 percent of the individuals 65 years and older met this level of intake. These levels were related to income: energy intake for those with income below the poverty level was less than the population mean regardless of sex and race. These surveys were conducted on healthy free-living individuals; most surveys of institutionalized older individuals have reported even less energy intake than that of individuals living at home (Stiedemann, Jansen, and Harrill 1978; Harrill and Cervone 1977; Jordan 1976).

Although it is difficult to interpret dietary intake studies of older Americans because of methodological problems, existing studies almost always reveal decreases in energy intake with age that may also be influenced by income, race, food preference, and drug use. A low-calorie diet may not impair health as long as the nutrient density of the diet is high and can provide adequate amounts of essential nutrients. However, this issue has not been examined in great detail because nutrient requirements in old age remain largely unkown.

Consequently, the increasing level of obesity among older persons, as indicated by higher weight-for-height with age (Frisancho 1984), requires explanation. Whether the inconsistency between reported low energy intake and increasing body weight is due to measurement errors, inappropriate standards, loss of height with age (Bowman and Rosenberg 1982), or lack of physical activity has not been established.

Protein. A 30-day continuous metabolic balance study of seven men and eight women over 70 years of age who consumed RDA levels of protein and energy found that about half were unable to maintain nitrogen balance on this level of protein (0.8 g of protein/kg/day). The results suggested that higher intakes were required (Gersovitz et al. 1982) to meet protein requirements. Other studies that examined protein requirements of older persons have also concluded that protein requirements may be higher (Munro 1983) even though mean protein intake usually exceeds the RDA (Brown et al. 1977; Jordan 1976; McClean, Weston, et al. 1976; Grotkowski and Sims 1978; Garry, Goodwin, Hunt, Hooper, et al. 1982; McGandy et al. 1986). Other studies reported lower protein intakes: at least 24 percent of the women in nursing homes and 29 percent in private homes consumed less than the RDA for protein (Jansen and Harrill 1977; Justice, Howe, and Clark 1974), and in another study, 12 percent of the men and 40 percent of the women living at home failed to meet this criterion (Jordan 1976). Because the RDA for protein includes a substantial safety margin and because clinical measurements have rarely found signs of protein deficiency among healthy older persons, it is not possible to conclude from these data that persons with intake below the RDA are protein deficient or that they would benefit from additional protein intake.

Calcium. Older people, especially Caucasian women, lose bone mineral and have a higher incidence of fractures than younger persons (Seeman and Riggs 1981). The mechanism behind the age-related loss of bone calcium is discussed in the chapter on skeletal diseases. Metabolic and absorptive factors as well as low intake may contribute to chronic negative calcium balance (Heaney, Recker, and Saville 1978; Horsman et al. 1980; Spencer,

Kramer, and Osis 1982). Reduced efficiency of intestinal calcium absorption (Avioli, McDonald, and Lee 1965; Gallagher et al. 1979; Alevizaki, Ikkos, and Singuelakis 1973; Bullamore et al. 1970; Ireland and Fordtram 1973) may be due to inadequate dietary intake (Heaney, Recker, and Saville 1977; Vinther-Paulsen 1981; Garry, Goodwin, Hunt, Hooper, et al. 1982; Omdahl et al. 1982; Koplan et al. 1986), age-related changes in gastric acidity, and/or interactions of intestinal constituents such as fiber, bacteria, and other nutrients. Perhaps in some individuals a negative effect on calcium nutriture may be caused by age-related changes in hormonal control (parathyroid hormone, calcitonin, prolactin, steroids, growth hormones), aberrations in vitamin D metabolism, and imbalances of protein, phosphorus, alcohol, and electrolytes with calcium (Riggs and Melton 1986).

The RDA for calcium of 800 mg/day (NRC 1980) may not be sufficient to maintain calcium balance in populations consuming Western-type diets (Heaney, Recker, and Saville 1978; Matkovik et al. 1979; Recker and Saville 1977; Recker and Heaney 1985; Consensus Development Panel 1984).

NHANES and NFCS reported mean intakes of about 700 to 720 mg for older men and 540 to 590 mg for older women (DHEW 1979a; DHHS 1983; USDA 1984). Other surveys have also reported that dietary calcium intake by older people is often marginal. For example, 43 percent of women in nursing homes failed to get two-thirds of their calcium requirement (Stiedemann, Jansen, and Harril 1978; Brown et al. 1977). Women living at home consumed even less calcium than those in nursing homes (Brown et al. 1977). One study reported that women, on the average, consumed only two-thirds of the RDA for calcium (Grotkowski and Sims 1978). Whereas some studies have reported similarly low calcium intakes among men (660 mg/day) (Brown et al. 1977; McClean, Weston, et al. 1976), others have found that intakes among older males equaled or exceeded the RDA of 800 mg/day (Stiedemann, Jansen, and Harrill 1978; Grotkowski and Sims 1978). Older people may have reduced calcium intake because they avoid dairy products containing lactose, to which they are intolerant (Goodwin, Hunt, et al. 1985; Heaney et al. 1982).

Iron. As with people of all ages, the frequency with which anemia occurs in the older population and determination of its etiology depend on the criteria used for diagnosis (see chapter on anemia). Few data on the iron status of older persons in the United States are available, and most studies report conclusions based on hemoglobin and hematocrit values with, at most, only one other index of iron nutrition (Lynch et al. 1982). One

national study—NHANES I (DHEW 1979b) and three regional studies (O'Neal et al. 1976; Fisher, Hendricks, and Mahoney 1979; Htoo, Kofkoff, and Freedman 1979), for example, found that more than 10 percent of older white men were anemic (when a hemoglobin level less than 14 g/dl was considered diagnostic). When a hemoglobin level less than 12 g/dl was used to identify anemia in women, these same studies found older white women to have a lower prevalence of anemia than men. These studies included older men who were not screened for diseases that can greatly reduce red blood cell production, such as chronic infections, renal disease, and neoplasms that result in chronic blood loss. Such data may indicate that the standard for low hemoglobin levels for men are too high, although age-related lower testosterone levels may reduce hematopoiesis and might also account for this difference (Lipschitz, Mitchell, and Thompson 1981).

Another study examined biochemical measures of iron status in healthy older persons and concluded that anemia or impaired iron status was no more prevalent in this population than in younger healthy adults when identical criteria were used to assess iron nutritional status (Garry, Goodwin, and Hunt 1983). A later longitudinal study revealed significant variability in the population mean values for all biochemical measures of iron nutriture except plasma iron; however, none of the changes suggested an increased risk of anemia. Comparison of older subjects who took iron supplements with those who did not showed no clinically significant differences in the biochemical measures of iron status (Garry, Goodwin, and Hunt 1985).

Because iron stores or reserves, as determined by plasma ferritin measurements, increase with age, studies that examine only dietary intake of iron in older people need to be interpreted cautiously (Casale et al. 1981). Low dietary iron intake at one point in time does not necessarily increase the risk for anemia because iron may still be available from body stores and because absorption increases when intake and stores are low. In addition, the type of iron and other components of a meal such as ascorbate also influence the amount absorbed (see anemia chapter).

Some clinicians believe that an increased incidence of anemia in some older people, compared with younger groups, is a direct and common physiologic response to aging (Lipschitz, Mitchell, and Thompson 1981). Evidence that bone marrow erythroid precursors are reduced in some anemic older individuals supports this theory; whether this reduced blood-forming capacity is due to aging *per se* or to some age-associated phenomenon such as chronic disease or use of medications is not certain (Lipschitz et al. 1984). Studies of very old healthy individuals find little evidence of

anemia and, therefore, support the contention that this condition is rare in healthy older people (Zauber and Zauber 1987).

Data from NHANES II are illustrative here. The mean iron intakes for men ages 65 to 74 years were 14.1 mg (about 1.4 times the RDA) and the prevalence of impaired iron status correspondingly low. The values for women of the same age were 10.2 mg, or about equal to the RDA for women age 55 and over, with a corresponding low prevalence of impaired iron status (DHHS 1983; LSRO 1984).

B Vitamins. Vitamin deficiency may be a result of decreased dietary intake, absorption defects, decreased hepatic avidity for folate in Laennec's cirrhosis, decreased storage and conversion to active metabolic forms, or excessive utilization, destruction, or excretion (Cherrick et al. 1965).

No comprehensive study of all the vitamins and their related enzyme systems has been conducted, perhaps because laboratory facilities and analytical technology are not sufficient to do all the necessary biochemical evaluations (Brin and Bauernfeind 1978). Most studies have examined the status of one or two vitamins. For example, a Boston study of older subjects reported that 37 percent had inadequate blood levels of riboflavin and 21 percent had low thiamin levels (Davidson et al. 1962). Biochemical pyridoxine deficiency in older individuals has also been noted in enzyme functional tests (Hoorn, Filkweert, and Westerink 1975). A number of studies have indicated a great risk for vitamin deficiencies in older persons on the basis of low dietary intakes, but such deficiencies are not always confirmed by biochemical or clinical results (Garry and Hunt 1986). In addition, interpretation of biochemical parameters is hampered by lack of data on normal standards for the older population (Kirsch and Bidlack 1987). For example, a New Mexico study revealed that more than one-fourth of the older population consumed less than 75 percent of the RDA's for folate and vitamins B_6 and B_{12} from diet alone (Garry, Goodwin, Hunt, Hooper, et al. 1982). However, biochemical studies failed to confirm that these individuals were at risk for developing clinical symptoms associated with low intakes of these vitamins (Garry, Goodwin, and Hunt 1984). Intake of vitamin supplements may explain part of this apparent discrepancy, although analysis showed little statistical difference in mean dietary intake for those individuals taking a specific supplement compared with those who did not take the supplement (Garry, Goodwin, Hunt, Hooper, et al. 1982).

Vitamin C. Studies have shown that the total body pool of ascorbic acid reaches a maximum of approximately 20 mg/kg and that this level can be

achieved at a steady state plasma concentration of 1.0 mg/dl (Kallner, Hartman, and Hornig 1979). Women require an intake of 75 mg/day and men require an intake of 150 mg/day to achieve this ascorbic acid level in plasma (Garry, Goodwin, Hunt, and Gilbert 1982). This finding was supported by a clinical trial that showed that a daily intake of 60 mg was insufficient to maintain this plasma concentration (VanderJagt, Garry, and Bhagavan 1987). The clinical significance of maintaining maximal plasma ascorbic acid levels, however, has not been determined.

Some studies have reported low vitamin C intake and blood levels in both institutionalized and free-living older persons (Leevy et al. 1965; Davidson et al. 1962). Other studies reported intakes significantly greater than RDA levels and very few individuals with clinical symptoms of hypovitaminosis C (Garry, Goodwin, Hunt, and Gilbert 1982; Garry, Goodwin, Hunt, Hooper, et al. 1982). For instance, one study found that less than 2 percent of 270 free-living and healthy older persons over 60 years of age were at risk for developing clinical symptoms of hypovitaminosis C, as measured by plasma vitamin C concentrations below 0.2 mg/dl (Garry, Goodwin, Hunt, and Gilbert 1982). The mean steady state plasma vitamin C level for persons not taking supplemental vitamin C was 1.02 mg/dl—a level reported to be sufficient to maintain a maximal body pool. Additional supplemental intake had little effect in raising plasma levels. Mean intakes of vitamin C from the diet in that population were 137 mg/day and 142 mg/day for women and men, respectively—approximately 2.4 times the RDA (Garry, Goodwin, Hunt, Hooper, et al. 1982). In addition, over half were taking supplemental vitamin C—mean levels of approximately 600 mg/day.

Vitamin A. Vitamin A deficiency does not seem to be a particular problem in older persons. Although NHANES I and NHANES II reported that about half the study population over age 65 had vitamin A intakes at or less than two-thirds of the RDA, only 0.3 percent of the NHANES I older population had low vitamin A blood levels (Bowman and Rosenberg 1982; DHHS 1983). Serum vitamin A was not available for adults from NHANES II (LSRO 1985). Whether vitamin A supplement use can account for the observed discrepancy is unknown, but similar data suggest that older individuals can maintain normal vitamin blood levels even with reportedly low dietary intakes (Yearick, Wang, and Pisias 1980; Garry et al. 1987).

Vitamin D. Previous studies have revealed a generally lowered vitamin D status in older people, chronically ill individuals (Petersen, Hall, and Briggs 1981; Weisman et al. 1981), and those living in institutions (Weisman et al. 1981; Corless et al. 1979; Vir and Love 1978) with little or no exposure to sunlight (Lund and Sorensen 1979; Baker, Peacock, and Nordin 1980;

Lawson et al. 1979). Because the vitamin D endocrine system is the major regulator of intestinal calcium absorption (Christakos and Norman 1978), a reduced vitamin D status might promote a negative calcium balance in older people (see chapter on skeletal diseases).

Two recent studies in the United States have found dietary intake of vitamin D to be approximately 50 percent of the RDA for older subjects (Garry, Goodwin, Hunt, Hooper, et al. 1982; Lee, Lawler, and Johnson 1981), and inadequate intake (especially of vitamin D-supplemented dairy products) was well correlated with low blood levels of 25-hydroxyvitamin D (Omdahl et al. 1982). However, ultraviolet light induced endogenous production of vitamin D is the main external factor in maintaining adequate vitamin D status. Because sunlight exposure activates vitamin D precursors in skin, it has been recommended that older people obtain at least minimal sunlight exposure (10 to 15 minutes) two or three times a week (Holick 1986). Increased sun exposure may help compensate for aging skin's decreased capacity to produce these precursors (MacLaughlin and Holick 1985; Holick 1986). Supplements may be necessary to compensate for inadequate sunlight exposure due to seasonal variation in northern latitudes (Bouillon et al. 1987). Moderation in sun exposure should be recommended because overexposure to the sun is a strong risk factor for skin cancer.

Vitamin E. There is no evidence that older individuals are deficient either in dietary intake or tissue levels of vitamin E (Kelleher and Losowsky 1978; Vatassery, Johnson, and Krezowski 1983; Garry and Hunt 1986), despite statements that megadose vitamin E supplements retard the aging process and prevent atherosclerosis and cancer (Bieri, Corash, and Hubbard 1983). Therapeutic doses of vitamin E have prolonged survival of red blood cells in some inherited hemolytic anemias (Corash, Spielburg, and Bartsocas 1980), but its use to treat or prevent other conditions has not been established (Bieri, Corash, and Hubbard 1983).

Nutritional Supplements. It has been estimated that 37 percent of American adults consume a daily multivitamin preparation, fueling a more than $2 billion per year industry (the Gallup Organization 1982; Herbert 1980; Koplan et al. 1986). NHANES II indicated that the persons most likely to take supplemental nutrients are less likely to need them, and those most in need of them are least likely to take them (Koplan et al. 1986). In older persons, vitamin use has increased dramatically in the past decade (Garry, Goodwin, Hunt, Hooper, et al. 1982; Scheider and Nordlund 1983). Whether such supplements improve the health of these people cannot be determined from existing data (Mann et al. 1987), but it is clear that

excessive supplementation may be harmful. High doses of the fat-soluble vitamins A and D are toxic.

Drug-Nutrient Interactions

Although older Americans constitute about 12 percent of the U.S. population, they use about 25 percent of all prescription drugs (Lecos 1984/85). This is not surprising because many chronic diseases associated with aging are managed with prescription drugs. Over half of the older people take at least one medication daily and many take six or more a day for multiple diseases (Lecos 1984/85). Cardiovascular drugs (e.g., diuretics) are most widely used by the aging population, followed by drugs to treat arthritis, neurologic disorders, and respiratory and gastrointestinal conditions. Many unwanted drug-nutrient interactions in older persons have been documented (see chapter on drug-nutrient interactions). The drug-nutrient interactions outlined in another chapter of this Report apply to the older person. However, this population requires special consideration because aging *per se* changes the absorption, disposition, and elimination of drugs. The older person with multiple diseases is at risk for additional drug-nutrient interactions linked to separate drug therapies for primary and secondary health problems. Even over-the-counter antacids, laxatives, analgesics, and vitamin and mineral supplements may result in unwanted drug-nutrient side effects in the older person (Roe 1985).

Effects of Nutritional Deficiencies on the Older Population

Morbidity and Mortality

Severe malnutrition—protein, calorie, vitamin, or mineral—is associated with increased morbidity and mortality, and the relationship of malnutrition to morbidity and mortality in older persons is of current interest. While less severe forms of malnutrition may be detrimental to health, the evidence has been more difficult to establish. Among severely ill or injured hospital patients of any age, protein-energy malnutrition greatly increases the risk for postoperative complications and overall morbidity and mortality (Mullen et al. 1979; Kaminski, Fitzgerald, and Murphy 1977). This association between nutritional status and survival does not prove a causal relationship because poor nutritional status may be the result of the illness or injury and not its cause. It is also difficult to demonstrate that moderate nutrient deficiencies increase morbidity and mortality.

Several investigators have tried to correlate blood levels of vitamin C, for example, with morbidity and mortality in an aging population. Among patients admitted to an acute care geriatric unit, those with low ascorbate

levels had a significantly higher mortality, but vitamin C supplements did not improve survival in these patients (Wilson et al. 1972, 1973). One prospective study reported dietary intake of vitamin C to be a significant predictor of mortality in an aging population (Hodkinson and Exton-Smith 1976), although it was not possible to separate cause from effect in this instance. Some older subjects with low vitamin C levels in blood exhibit clinical signs of scurvy (Andrews and Brook 1966), but some do not (McClean, Dodds, et al. 1976). Signs of scurvy may be slow to resolve with supplementation in older subjects (Andrews, Letcher, and Brook 1969). The clinical significance of this observation has not been established.

Immune Status

Considerable evidence documents an age-related decline in immune competence, characterized by losses in T-lymphocyte and other functions. Certain of these changes resemble those induced by malnutrition (Thompson, Robbins, and Cooper 1987), but whether malnutrition is a significant cause of depressed immune function in large numbers of older individuals is uncertain. The large number of rodent studies that describe well-nourished old animals regularly displaying weak immune responses argues against the hypothesis that immunosenescence is due to malnutrition (Shock et al. 1984).

As described in the chapter on infections and immunity, protein-energy malnutrition in individuals of any age alters the proportion of T cell types, depresses T cell function, impairs delayed hypersensitivity reactions, and impairs thymic factor activity. Such changes are strongly associated with increased susceptibility to infectious diseases (Mullen et al. 1979; Falchuk et al. 1977). Impairment of delayed hypersensitivity and thymic factor activity have also been documented for deficiencies of single nutrients (Beisel 1982). Severe malnutrition is clearly related to impaired immune function in some older people, and improved dietary intake can at least partially correct these impairments. Current evidence is insufficient, however, to decide which, if any, age-related losses in T cell function are caused by nutritional deficiencies or some other physiologic or environmental factor (Thompson, Robbins, and Cooper 1987). The possible role of zinc deficiency in loss of immune function in older people has received considerable attention (Sandstead et al. 1982; Gershwin, Beach, and Hurley 1983).

If nutritional deficiencies are related to impaired immune function in older people, correcting the deficiencies should improve this function. Among hospitalized patients, intensive nutritional support does increase immu-

nocompetence (Law, Dudrick, and Abdou 1973). Among older people, dietary supplements have been associated with improved antibody responses to viral vaccines (Chandra and Puri 1985), and several studies have reported improved immune function as a result of zinc supplementation (Duchateau et al. 1981; Thompson, Robbins, and Cooper 1987); others have not (Brader et al. 1988). Whether these effects represent correction of nutrient deficiencies or are secondary to some nonspecific effect of supplementation is uncertain (Goodwin and Garry 1983).

Nervous System and Cognitive Function

Whether mental functions necessarily decline with age is questionable, and whether dietary factors can influence mental status in older persons is also uncertain. Results of psychometric testing in older people vary depending on the group studied. Although large population studies have reported gradual decreases in many mental functions with age (Nandy and Sherwin 1977), healthy, active older subjects do not display significant decrements (Botwinick 1977). This discrepancy suggests that the reported decrements in mental function are not inevitable age-associated events; rather, such changes are secondary to the various diseases and physical conditions that frequently accompany aging (Palmore 1974).

Alzheimer's Disease

Alzheimer's disease affects between 2 and 3 million Americans. The prevalence of this disease increases with age; while only 5 to 8 percent of people age 65 and over are affected, 35 percent of those over age 85 are affected. The cost of institutional care alone for Alzheimer's disease patients is estimated to exceed $38 billion per year in direct costs and up to $80 billion per year if indirect costs are considered (Huang, Cartwright, and Hu 1988).

The causes of Alzheimer's disease have not been established, but potential risk factors include age, family history of Alzheimer's disease, and head injuries. Further studies are needed to determine the validity and reliability of these risk factors. Whether nutritional factors can alter the risk for this condition is not known. High concentrations of aluminum have been found in the neurofibrillary-containing neurons of deceased patients, suggesting a relationship between aluminum and Alzheimer's disease. Such foci are not observed in the brains of people who die from other causes (Perl and Brody 1980). Despite these observations, there is no evidence that renal dialysis or use of aluminum antacids, antiperspirants, or cookware increases the risk for Alzheimer's disease (Katzman 1986), and the significance of the increased brain aluminum concentrations is unknown. The roles of certain

dietary antioxidants and toxic amino acids (Spencer et al. 1987) are under study.

Because Alzheimer's disease is a neurodegenerative syndrome involving cell loss and dysfunction, and because there is evidence that nutrient variables can affect brain metabolism, it might be speculated that neurotoxins acquired through the food chain may be involved in brain cell death. Therefore, researchers and clinicians should consider nutritional factors in the etiology of Alzheimer's disease.

Implications for Public Health Policy

Dietary Guidance

General Public

Aging is accompanied by a variety of physiologic, psychologic, economic, and social changes that may compromise nutritional status. However, ways in which the aging process affects energy balance, specific nutrient requirements, and nutrient status remain to be fully elucidated. Older adults may not necessarily have the same nutritional requirements as younger adults, yet current estimates of the nutrient requirements of older persons are based almost entirely on values extrapolated from data from studies of younger adults. The ways in which nutritional status might influence changes in tissue and organ function change with age and may influence the relationships between dietary components and the occurrence of chronic diseases of old age. Until more appropriate age-specific RDA's are established, the current RDA's should continue to be used as standards for nutrient intake of healthy older persons.

Until more is known, older Americans should consume sufficient nutrients and energy and maintain levels of physical activity that maintain desirable body weight and may prevent or delay the onset of chronic disease. Because it is often difficult to maintain adequate nutrient intake on low-calorie diets, older people should be advised to maintain at least moderate levels of physical activity so as to increase caloric needs. Recommendations to the general population about calcium intake (see chapter on skeletal diseases) are true for older Americans. Because many of the chronic diseases common to older persons may originate earlier in life (see chapter on maternal and child nutrition), dietary guidance to prevent them should be provided throughout life (as discussed in other chapters).

Health promotion messages from the public and private sectors should utilize advanced communication techniques, recognizing different lifestyles, decrements in vision and hearing, different cultural experiences, and different learning styles that may be common to older people. Federal and State agencies should provide information about successful public-private sector models for nutrition, health promotion, and education for older adults—for example, Healthy Older People, Age Well, and OASIS (Older Adult Service Information System).

Special Populations

Sedentary older individuals should be counseled on appropriate methods to increase caloric expenditure. Older persons who do not (or cannot) consume adequate levels of nutrients from food sources and those with dietary, biochemical, or clinical evidence of inadequate intake should receive advice on the proper type and dosage of nutrient supplements. Such supplements may be appropriate for some older persons, but self-prescribed supplementation, especially in large doses, may be harmful and should be discouraged. Older people who suffer from diet-related chronic diseases should receive dietary counseling from credentialed health professionals, and those who take medications should be given professional advice on diets that minimize food-drug interactions.

Nutrition Programs and Services

Food Labels

Evidence related to the role of diet in the aged currently holds no special implications for change in policy related to food labeling, although the size of the type on the label is a factor for most older consumers. Information provided on food labels should be scientifically sound, understandable, and nonmisleading.

Food Services

Food services, especially those receiving Government funds, should be required to pay special attention to meeting the caloric and nutrient needs of older clients. Nutritional assessment and guidance should be done at hospital admission or enrollment in or discharge from institutional or community-based services for older adults (e.g., acute and long-term care inpatient services, hospital-based outpatient services, alcohol and drug treatment programs, community health services, and home-delivered meals programs).

Food Products

Evidence suggests that older people would benefit from food products that provide a high proportion of available nutrients to calories, that have taste appeal, and that are easy to prepare.

Special Populations

Older people who are homebound, who live in isolation, or who suffer from chronic disease have special needs for nutrition services that are tailored to their particular conditions. Considerable evidence supports the nutritional and health benefits of dietary, economic, and social support programs for the older population.

Research and Surveillance

Research on nutrition and aging currently focuses on two general areas—the nutritional requirements and status of aging people and the influence of diet on aging processes and related pathologies. Psychosocial interactions with nutrition cut across both areas.

Research and surveillance issues of special priority related to the role of nutrition in the aged should include investigations into:

- The nutrient and energy requirements of older adults, currently extrapolated from younger age groups.
- The effects of dietary restriction and overconsumption on longevity and age-related pathology.
- The interactions among nutritional status, lifestyle and behavior, and the environment in older Americans.
- The effects of nutrition on age-related impairment of the cardiovascular, gastrointestinal/oral, immune, musculoskeletal, and nervous system functions and on prevention and treatment of disorders of those systems.
- The effects of marginal nutrient and energy deficiencies on the mental and physical health of older persons.
- Interactions among nutrients and between nutrients and drugs in older adults.
- Development of data bases for use by pharmacists and dietitians in counseling older persons on drug-nutrient interactions.
- Age-specific methods and standards to assess the nutritional status and body composition of older adults.

- The educational methods and program strategies that best promote adequate food consumption by older persons.
- Improved methods to monitor the nutritional status of older populations and individuals, including institutionalized older adults, over time.
- The educational and public health strategies that can be used to eliminate nutrition-related health fraud directed toward older citizens.

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Chapter 17

Alcohol

Inflaming wine, pernicious to mankind,
unnerves the limbs,
and dulls the noble mind.
Homer
The Iliad, VI 261 (850 B.C.)

Introduction

Alcohol (ethanol) is of importance to nutrition because it provides energy and because its ingestion can affect the requirements for and the intake, digestion, absorption, transport, storage, metabolism, and excretion of many other nutrients. Few generalizations can be made regarding the effects of alcohol on nutritional status because these depend on complex interactions between the type, quantity, and duration of alcohol consumed and the overall nutrient intake from the diet. These interactions are highly dependent upon behavioral and socioeconomic factors and predisposing genetic factors. Chronically excessive alcohol use is often associated with symptoms, signs, and biochemical evidence of nutritional deficiencies, but these are largely the secondary effects of reduced consumption of other kinds of food and drink. The effect of moderate or occasional drinking is less well documented.

Historical Perspective

Fermented beverages have been consumed in most societies since antiquity, in part because fermentation provided one of the earliest methods of food preservation (Ghalioungui 1979). In some societies, indigenous foods that contained alcohol as a result of fermentation may have offered protection against the development of deficiencies of vitamins, amino acids, and other essential nutrients (Steinkraus 1979; Darby 1979).

Socioeconomic factors have always affected the pattern of alcohol abuse and its complications in different societies. In ancient Greece, for example,

wine drinking was confined largely to the upper classes, and beer drinking to the lower classes. In industrialized England of the 18th century, gin was the drink of the poor, while port was drunk by the affluent, whose episodes of gout were attributed to the contamination of port with lead.

Distilled spirits, in contrast to fermented foods and beverages, provide concentrated sources of alcohol and calories largely without other nutrients. Although the process of distillation was known at least as early as the fourth century B.C. (Ghalioungui 1979), the consumption of distilled spirits tended for centuries to be limited to the more affluent who also had access to varied diets. In Western Europe, distilled alcoholic beverages were not widely available to the poor until the Industrial Revolution. In England, government policies that liberalized controls on production and distribution of alcoholic beverages led to the widespread "gin epidemic," and further legislation was then required to prohibit sales and prevent adverse consequences (Roe 1979).

Out of this history grew a series of health and social reform movements, including the prohibitionist movement in the United States. In their efforts to change society's behavior, most health reform advocates focused on the extreme consequences of alcohol abuse, using selected medical and scientific data to support their arguments (Whorton 1982). This, in turn, led to distortions in understanding the nutritional consequences of alcohol use. For example, many studies examined the habits of accessible derelict or vagrant alcoholics or provided descriptive reports that were easier to obtain than biologic determinations of specific pathophysiologic mechanisms.

The attitudes toward alcohol of the 19th and early 20th centuries remain prevalent today, and many people are uncertain and misinformed about interactions between alcohol and nutrition. Recent efforts from the U.S. Department of Health and Human Services have focused on providing the scientific community and the public with current information about this area. Thus, alcohol consumption has been identified as a dietary practice in need of change in several Federal publications. Examples include those listed below.

Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention, 1979. This report recommends reducing misuse of alcohol. It includes information on prevention programs that stress the importance of educating the public on the effects of alcohol consumption,

altering the social climate of its acceptability, reducing individual and social stress factors that might increase consumption, and enforcing existing laws (DHEW 1979).

Nutrition and Your Health: Dietary Guidelines for Americans (second edition), 1985. One of the seven recommendations is "If you drink alcohol, do so in moderation." The discussion of this guideline emphasizes the caloric contribution of alcohol to the overall diet, especially for individuals who are overweight, but notes that one to two drinks daily appear to cause no harm in adults. It warns pregnant women that excessive alcohol consumption may cause birth defects at the same time that it acknowledges that the "level of consumption at which risks to the unborn occur has not been established" (USDA/DHHS 1985).

Promoting Health/Preventing Disease: Objectives for the Nation, 1980. These health objectives include specific recommendations for methods to reduce deaths due to alcohol-related behavior, accidents, and disease by the year 1990 (DHHS 1980).

Promoting Health/Preventing Disease: Public Health Service Implementation Plans for Obtaining Objectives for the Nation. This report identifies priority objectives for prevention of alcohol misuse and outlines Federal efforts in education, grant support, technical assistance, economic incentives, and research and surveillance measures aimed at achieving them. It also assigns to specific agencies the primary responsibility for each of the implementation steps and provides data on the anticipated date of initiation of each step (DHHS 1983).

The Sixth Special Report to the U.S. Congress on Alcohol Abuse and Health from the Secretary of Health and Human Services. This report provides the most comprehensive statement to date of current knowledge in the epidemiology of alcohol abuse and alcoholism; the genetics, psychobiologic effects, and medical consequences of alcoholism; the effects of alcohol on pregnancy outcome; the adverse social consequences of alcohol abuse; trends in treatment, research, and practice; and perspectives on prevention (DHHS 1987).

The 1990 Health Objectives for the Nation: A Midcourse Review, 1986. This report provides data on progress toward achieving the 1990 objectives for prevention of deaths due to alcohol misuse. Although it notes impressive achievements in reducing alcohol-related motor vehicle accident

fatalities and deaths due to cirrhosis, it stresses the importance of multidisciplinary approaches to prevention of the adverse health consequences of individual behavior associated with alcohol consumption (DHHS 1986).

Significance for Public Health

Although the nutritional elements of the public health impact of alcohol abuse are still being defined, in and of itself, misuse of alcohol is one of the most preventable health problems in the United States. As mentioned above, prevention of the adverse consequences of alcohol misuse is a major health objective for the year 1990 (DHHS 1986). Excessive alcohol intake is a prominent contributor to 4 of the 10 leading causes of death in the United States—cirrhosis of the liver, motor vehicle and other accidents, suicides, and homicides (NCHS 1986). As discussed in the cancer chapter of this Report, chronic alcohol abuse also increases the risk for oral, esophageal, liver, and other types of cancer.

In 1980, it was estimated that nearly 20,000 deaths could be directly attributed to alcohol use, from alcoholic liver disease, alcoholism, alcoholic psychosis, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic polyneuropathy, nondependent use of alcohol, and accidental poisoning by alcohol. Almost 78,000 fatalities could be indirectly attributed to alcohol use (Ravenholt 1984). In 1983, about 42 percent of all motor vehicle deaths were alcohol related. Problems such as homicides and automobile accidents that are indirectly related to alcohol consumption have the highest rates among young adult males ages 18 to 24. Excessive alcohol intake during pregnancy is estimated to cause birth defects in 1,400 to 2,000 babies annually. The costs of the medical and social consequences of excessive alcohol intake were estimated to be $117 billion in 1983 (DHHS 1987). In the late 1970's, 19 percent of adolescents reported problems related to drinking alcohol. Among adults over age 18, approximately 10.6 million are alcohol dependent and another 7.3 million experience alcohol-related adverse consequences (DHHS 1986).

Recent trends suggest that both the intake of alcohol and its adverse health consequences are declining in this country. Overall per capita ethanol consumption increased annually from 1977 to 1980, reached a plateau in 1980 and 1981, and then began an annual decline until 1985, when it was slightly below the 1977 level (Laforge et al. 1987). Beer consumption in 1985 was 3 percent above the 1977 level; wine consumption per capita increased over the entire period of 1977 to 1985, and in 1985 it was 31 percent higher than in 1977. Per capita consumption of spirits, however, declined over this

entire period, and in 1985 was 15 percent below the 1977 level (Laforge et al. 1987). There has also been a slow decline in deaths attributable entirely to alcohol-related causes since 1980 (Berkelman et al. 1986).

Scientific Background

Quantitative Aspects of Alcohol Consumption Among Individuals

Different units are used to record the quantity of alcohol intake among individuals. Commonly used units are grams or ounces of pure alcohol. There are approximately 15 g of alcohol in each of the following standard-sized drinks: 1–½ oz of 80 proof liquor, 5 oz of table wine, and 12 oz of beer (Pennington and Church 1985).

Consumption of Alcoholic Beverages

The proportion of U.S. adults who drink alcoholic beverages depends on both the region of the country and sociocultural background. Estimates of the various categories of drinkers in the population are usually based on survey information, and the estimated quantities consumed are often based on self-reports. Such surveys indicate that about 33 percent of the general population say they do not drink alcohol at all; 34 percent are light drinkers, who say they drink from one to three drinks per week; 24 percent are moderate drinkers, who report consuming fewer than two drinks a day; and 9 percent are heavy drinkers, who average two drinks a day or more (Moore and Gerstein 1981). In studies of the heaviest drinkers (i.e., alcohol abusers and alcoholics), the quantity of alcohol consumed is very difficult to ascertain, and clinical criteria for the diagnosis of alcoholism usually must depend on factors other than alcohol intake information (Task Force on Nomenclature and Statistics 1980).

Although this classification into light, moderate, and heavy drinkers seems reasonable and is used in this chapter, it is arbitrary and not universally accepted. For example, in the Honolulu Heart Study, consumption of two to three drinks per day was considered moderate, but, according to the above classification, it would be considered heavy consumption. The use of the Michigan Alcoholism Screening Test (a short questionnaire shown to be efficient in identifying alcoholics) and other alcoholism screening tests such as the Self-Administered Alcoholism Screening Test (Swenson and Morse 1975) may prove important in separating alcoholic from non-alcoholic persons by standard criteria rather than by self-reports.

Surveys also reveal wide regional variations, especially among the percentage of individuals who say they abstain completely from alcohol (e.g., 14

percent in western New York State, 32 percent in San Francisco). The percentage of heavy drinkers, adults who report drinking two drinks or more a day, ranges from 9 percent nationwide to 23 percent in Boston and 24 percent in western New York State (Barnes and Russell 1978; Wechsler, Demone, and Gottleib 1978).

The frequency of alcohol consumption reported by high school students differs from that reported by adults in national surveys. In a 1985 nationwide survey of about 17,000 high school seniors conducted by the National Institute on Drug Abuse, only 8 percent of seniors said they had never used alcohol. Nearly 5 percent of seniors drank every day, and 37 percent reported episodes of heavy drinking (five or more drinks per occasion) during the previous 2 weeks (DHHS 1987).

Categories of Beverages Consumed and Types of Drinkers

Since 1934, the consumption of alcohol in the United States, based on statistics from commodity sales, has increased almost continuously, and in 1984 the annual per capita intake in terms of absolute alcohol was 2.65 gal/person 14 years of age or older (DHHS 1987). As one-third of the U.S. adult population abstains from alcohol, those who drink consume an average of 1.3 oz of absolute alcohol per day. These distinctions become even more important when examined more closely: the heaviest drinking 5 percent of the population accounts for about 50 percent of total alcohol consumption, and the heaviest drinking 33 percent accounts for over 95 percent of total alcohol consumption. Given the presumed absence of impact of alcohol on the nutrition of the one-third of the population who abstain, and negligible impact on that of the one-third who are light drinkers, the group of primary interest from this perspective is this latter group.

Over time, consumption of the various types of alcoholic beverages has changed. Beer is now the most prevalent alcoholic beverage consumed, accounting for almost 50 percent of the alcohol consumption in the United States. Distilled spirits account for nearly 39 percent and wine for 12 percent. The wine industry was virtually dismantled as a result of Prohibition but has recently made significant advances in recapturing part of the market and appears to be continuing to increase its share of sales. The types of distilled spirits consumed have also changed with time; in recent decades, there has been a shift from whiskey to other forms of distilled spirits, such as gin and vodka.

Alcohol Abuse and Alcoholism

The essential feature of alcohol abuse is a pattern of pathologic moderate to heavy alcohol use for at least a month that causes impairment in social or

occupational functioning. The accepted diagnostic criteria, as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) of the American Psychiatric Association, are useful for such patterns of chronic, pathologic alcohol consumption (Task Force on Nomenclature and Statistics 1980). DSM-III criteria describe three main patterns of alcohol abuse: (1) regular drinking of large amounts, (2) regular heavy drinking but limited to weekends, and (3) episodic binges of heavy daily drinking lasting weeks or months, interrupted by long periods of sobriety. These criteria for the diagnosis of alcoholism also include either a pattern of pathologic alcohol use or impairment in social or occupational functioning and either central nervous system tolerance or withdrawal symptoms.

The number of Americans with alcohol problems is estimated to be as high as 18 million (DHHS 1987). In an outpatient medical setting using the Self-Administered Alcoholism Screening Test, the prevalence of abstainers was 13 percent and the prevalence of possible or probable alcoholism was 5.4 percent (Hurt, Morse, and Swenson 1980). The prevalence of alcoholism in general hospitals, estimated by using the Michigan Alcoholism Screening Test, was 18 percent for men and 5.5 percent for women (Moore 1971). In emergency room patients, the prevalence of alcoholism may be as high as 30 percent of patients during the evening hours (Rund, Summers, and Levin 1981). However, precise statistics for the prevalence of alcoholism are not available now, nor are they likely to become so in the near future, because alcoholism is diagnosed infrequently, especially in its earlier stages.

Physiology of Alcohol Use

Absorption. Alcohol is readily absorbed from all levels of the gastrointestinal tract, and blood concentrations rise rapidly after ingestion. Overall absorption of alcohol depends partly on the rate of gastric emptying. Food, particularly fat, delays gastric emptying and stimulates gastric secretion, thereby diluting the concentration of alcohol and blunting its rapid absorption into blood.

Absorption across the gut mucosa appears to occur as a result of passive diffusion. The rate of absorption varies as a function of the concentration gradient, the area and permeability of the absorbing surface, and the volume of regional blood flow (Kalant 1971). During the first 15 minutes after oral administration, maximum alcohol levels are rapidly found in the stomach, duodenum, and proximal jejunum; at 90 minutes, peak levels are found in the mid-jejunum. Alcohol levels in the ileum parallel those in the blood, suggesting that the ileal concentration results from passage of alcohol from the blood back into the lumen rather than from transit along the

small bowel (Halsted, Robles, and Mezey 1973). Infusion of alcohol directly into the duodenum, the first segment of the small intestine where most nutrients are absorbed, causes blood levels of alcohol to rise as high as those following direct intravenous administration, and these levels rise much more rapidly than those that occur when alcohol is infused into the stomach.

Distribution. Once absorbed, alcohol diffuses rapidly across capillary and other cell membranes and is distributed uniformly throughout all extracellular and intracellular body water. At equilibrium, the concentration of alcohol in all tissues is proportional to the tissue water content, so that differences in the volume of body water among people can help to explain why some individuals are apparently more susceptible than others to the pharmacologic and toxic effects of alcohol. Smaller, lighter people are more susceptible to the effects of alcohol than larger, heavier people simply because their fluid volume is less. For a given body weight, the volume of body water is less in females than in males, and less in older people than in younger people; therefore, a given dosage of alcohol can be expected to produce higher blood concentrations in women and older persons and to affect them more (Vestal et al. 1977).

Metabolism. Alcohol is metabolized by the liver first to acetaldehyde, then to acetate, and, finally, to carbon dioxide and water. Three separate enzyme systems can account for the initial oxidation of alcohol to acetaldehyde (Badawy 1978; Lieber 1984; Pirola 1978). Quantitatively, the most important system is that involving alcohol dehydrogenase, an enzyme found in the cytoplasm of liver cells. The acetaldehyde produced is rapidly oxidized to acetate by the enzyme acetaldehyde dehydrogenase, resulting in little accumulation of acetaldehyde in either the liver or blood.

Alcohol and acetaldehyde dehydrogenases exist in several forms, which oxidize alcohol and acetaldehyde at different rates. These enzyme variations may account in part for observed differences in rates of alcohol metabolism among individuals of different genetic backgrounds and may help explain, for example, why some people of Oriental or American Indian heritage have lower tolerances for alcohol consumption (DHHS 1985).

A second enzyme system located in the liver, called the microsomal ethanol-oxidizing system (MEOS), probably plays a relatively minor role in alcohol metabolism, at least at low concentrations, but it has significant activity at higher concentrations of alcohol. This system can be stimulated by chronic exposure to high levels of alcohol. This is associated with cross induction of the metabolism of other drugs, such as the anticonvulsants

hydantoin and phenytoin, the barbiturates, the sedative meprobamate, the tricyclic antidepressants, the phenothiazine tranquilizers, and oral anticoagulants (Pirola 1978). The inducibility of this system results in interactions between alcohol and other drugs that may alter the rate of disappearance of alcohol and other drugs from the body (see chapter on drug-nutrient interactions) and may activate a variety of hepatotoxic agents and carcinogens.

A third enzyme system, the catalase system, appears to be of minor importance in the metabolism of alcohol and is not stimulated by chronic consumption of alcohol. Several other minor metabolic pathways, such as glucuronide and sulfate conjugation and fatty acid esterification, have been identified, but their importance remains unclear.

Some of the metabolic consequences of alcohol consumption can be explained by shifts in oxidation-reduction balance that occur as a consequence of ethanol oxidation. Reduced nicotinamide-adenine dinucleotide (NADH) is produced as a result of the oxidation of ethanol by the alcohol dehydrogenase enzyme system and by the further oxidation of acetaldehyde to acetate. An increased supply of NADH relative to NAD may affect carbohydrate, lipid, and protein metabolism and account for alterations in the hepatic metabolism of steroids, biogenic amines, some drugs, and, perhaps, even some toxins. Other deleterious effects of alcohol ingestion have been attributed to aldehyde or its cytotoxic interactions with body proteins (Wickramsinghe, Gardner, and Barden 1987).

Excretion. More than 95 percent of the alcohol ingested is oxidized in the liver to carbon dioxide and water, and the remainder is excreted in the urine, feces, perspiration, and expired air.

Key Scientific Issues[a]

- Effect of Alcohol on Nutritional Status and Energy Balance
- Role of Alcohol in Diseases of the Liver
- Role of Alcohol in Diseases of the Nervous System
- Role of Alcohol in Cardiovascular Diseases
- Role of Alcohol in Reproductive Disorders

[a]The role of alcohol in cancer, diabetes, and osteoporosis is not covered here but is reviewed in the chapters devoted to those conditions.

Effect of Alcohol on Nutritional Status and Energy Balance

Whether alcohol injures organs directly because of its toxic effects on tissues or indirectly because of the nutritional deficiencies it causes has been a subject of debate for decades. In the mid-18th and 19th centuries, alcohol was considered a toxin and was classified with other poisons, such as arsenic, mercury, and ergot. The discovery of vitamins in the 20th century gave momentum to studies of the association between alcohol consumption and nutritional status, especially between 1920 and 1940. Similarities between complications of alcoholism such as those affecting the nervous system and various vitamin deficiency states led to the belief that most physical manifestations of alcoholism had a nutritional basis.

The malnutrition observed in alcoholics was proposed as the primary reason for the organ and tissue damage found so frequently in this population. Patients with severe alcoholic liver disease and ascites who were given a diet high in protein and B-complex vitamins had a better prognosis than those provided with a regular diet, and there was a significant association between the occurrence of nutritional deficiency and the occurrence of alcoholic cirrhosis (Patek and Post 1941). This finding suggested that eating a diet high in protein and B-complex vitamins would protect an individual from the effects of alcohol. Because so many nutritional deficiencies were observed in derelict alcoholics, the assumption naturally was made that similar but milder nutritional deficiencies were present in all other alcoholics.

By the early 1960's, however, many of the clinical consequences of alcoholism were shown to be the direct toxic effects of alcohol itself (Lieber 1966). Most recent evidence points to the toxic effect of alcohol or its metabolic byproducts as the primary mode of liver injury. In addition, possible genetic differences in predisposition to the direct toxic effects of alcohol have been recognized. The effects of alcohol on the nutritional status of nonalcoholic social drinkers remains to be defined.

Excessive alcohol intake increases the risk for malnutrition through a variety of pathophysiologic mechanisms, including direct and indirect alterations in both nutrient intake and requirements, digestion, absorption, transport, storage, metabolism, and excretion. For any nutrient, alcohol may affect one or more of these processes. The following sections summarize what is known about the most important interactions between alcohol and each major nutrient. The reported effects of alcohol vary greatly, depending on how much and how long it is consumed. In some cases,

marked differences among animal species have led to apparently contradictory and confusing experimental results.

Energy

At the turn of this century, Atwater determined that ethanol provides 7 kcal/g, and ever since then this amount has been used as the basis for calculating the contribution of alcohol to total energy intake (Passmore 1979). The use of this conversion factor assumes that the energy in alcohol is fully available to the body. Based on this conversion factor, only 3 to 7 percent of the calories consumed by all Americans over the age of 14 are derived from alcohol, but if nondrinkers are excluded, alcohol provides over 10 percent of the calories consumed by adult drinkers in the United States (Williamson et al. 1987).

Many observations suggest that the caloric contribution of alcohol is more complex than can be explained by the Atwater conversion values, and therefore, the concept of alcohol and energy balance has recently been revised. If, for example, alcohol provides an average of 20 percent of the calories in the diet of the average drinking American adult, then many alcoholics consuming much larger amounts ought to be obese. Instead, national data indicate that despite higher energy intakes, drinkers are no more obese than nondrinkers (Gruchow et al. 1985). Alcoholics tend to lose weight over time, and abstinence is commonly associated with a gain in weight (Morgan 1982). In one study, eight malnourished alcoholic patients lost an average of 9 lb while they were consuming at least 200 g (about 1,400 kcal) of ethanol daily for a minimum of 3 weeks. They then gained an average of 7 lb after abstaining from alcohol for 2 weeks and eating an adequate diet (Halsted, Robles, and Mezey 1971). In another study, alcohol was associated with a substantial reduction in weight among women (Williamson et al. 1987). The conclusion usually drawn from such studies is that alcoholics do not consume an adequate diet, which is often true.

Increasing alcohol intake while maintaining an adequate diet, however, does not necessarily lead to a weight gain. For example, when 56 alcoholic patients were admitted to a hospital and fed a diet of 2,600 kcal, those who received an additional 256 g, or 1,800 kcal, of alcohol each day experienced no greater weight gain than those who received the diet of 2,600 kcal alone (Mezey and Faillace 1971). Similarly, when alcoholic patients were fed diets supplemented with 2,000 kcal of alcohol, no consistent change in body weight occurred, but when the 2,000 extra kcal were provided as chocolate, there was a consistent weight gain (Pirola and Lieber 1972). This study showed that substitution of an equal number of kcal of alcohol for carbohy-

drate at a level of 50 percent of total kcal was followed by weight loss, and the same result was obtained at 25 percent of total kcal (McDonald and Margen 1976).

The mechanisms accounting for the apparent inefficiency in conversion of potential energy from alcohol are complex and incompletely understood (World et al. 1984). Metabolic rate, as measured by oxygen consumption, is higher in rats fed alcohol than in those fed the same number of calories as carbohydrate (Pirola and Lieber 1972). Alcohol increases oxygen consumption in normal human subjects and is reported to increase it even more in alcoholic persons (Lieber 1984).

Several mechanisms have been proposed to explain how the oxidation of alcohol could result in "inefficient" energy transfer. The MEOS pathway of alcohol oxidation requires a reducing equivalent, from nicotine adenine dinucleotide phosphate (NADPH), and results in the production of heat rather than high-energy phosphate bonds. Subsequent reduction of NAD to NADH during the oxidation of acetaldehyde to acetate would result in no net change in total reducing equivalents. Furthermore, the alteration in the ratio of NADH to NAD in the cell cytoplasm might temporarily shift various substrates to the more reduced state and thereby impair the flux of reducing equivalents into the mitochondria for subsequent oxidative phosphorylation. A third mechanism could result from abnormalities in mitochondrial membranes, but this would be more likely to occur in alcoholic individuals and therefore would not explain the acute increase in metabolic rate following alcohol ingestion in normal drinkers (Lieber 1984).

Recent studies on nonshivering and postprandial thermogenesis (Rothwell and Stock 1986) may cast some light on another possible mechanism to explain the observed rise in oxygen consumption following alcohol ingestion. Landsberg and Young (1984) have shown that sympathetic nervous activity plays a central role in the increased heat production following feeding and the reduced heat production associated with starvation. Alcohol ingestion, especially in large amounts, has been associated with increases in catecholamine levels, specifically norepinephrine (Beilin and Puddey 1984).

The caloric value of alcohol (at least when ingested in large amounts) cannot be regarded as equivalent to the caloric value of other dietary sources of energy, as measured by the synthesis of high-energy phosphate bonds. Loss of weight when alcohol is substituted isocalorically for carbohydrate and the failure to gain weight when an otherwise adequate diet is supplemented with alcohol have led to the suggestion that alcohol-derived

calories should be disregarded completely as an energy source in predicting dietary-induced changes in weight (World et al. 1984), but the factors may work differently by pattern of alcohol use.

For moderate drinkers, another factor that must be considered is the effect of alcohol on caloric intake from other foods, especially in individuals who are chronically dieting. Recently, the concept of the "restrained eater" has been developed (Herman and Polivy 1980). Briefly stated, the restrained eater attempts to maintain body weight at a lower-than-set-point level by chronically undereating. When obligated to eat, or when the self-restraint is temporarily suspended, rebound overfeeding occurs. This hypothesis is supported by studies in which volunteers were asked to taste an appealing food after some of them had been provided a preliminary dose of alcohol. Among restrained eaters, alcohol increased the amount of food consumed, but alcohol did not affect the subsequent intake of unrestrained eaters (Polivy and Herman 1976a, 1976b).

These findings are consistent with the frequent clinical observation that obese people have greater difficulty dieting and maintaining lower body weights if they continue to drink alcohol. Whether the signals involved are psychologic or biologic remains to be determined. Animal studies suggest that biologic signals may be responsible because similar overeating can be demonstrated in animals who have been underfed before testing (Herman and Polivy 1980).

Lipids

Abnormalities in lipid metabolism are common in both alcoholics and mild to moderate drinkers (Janus and Lewis 1978). Body fat stores usually are depleted when weight loss results from poor diets. Alcoholics with chronic pancreatitis and pancreatic insufficiency may not digest fat efficiently because of a reduced output of pancreatic lipases, the primary enzymes for digesting lipids. Hepatic insufficiency can also cause fat malabsorption due to impaired secretion of the bile salts that emulsify fats and make them more digestible and absorbable. In addition, abnormalities in intestinal mucosal cells have been found to occur as a direct result of alcohol toxicity and, more commonly, as an indirect result of malnutrition (Green 1983).

Carbohydrate

Differences among animal species and differences in experimental conditions have led to apparently conflicting results regarding the effects of alcohol on carbohydrate metabolism (Marks 1978). Two major syndromes warrant discussion: (1) impaired glucose tolerance and (2) alcohol-induced

hypoglycemia. These effects are of special concern in patients with diabetes mellitus.

Impaired Glucose Tolerance. Impaired glucose tolerance is most easily demonstrated if the dosages of alcohol are sufficient to increase sympathetic nervous system activity and, perhaps, to decrease peripheral uptake of glucose. Doses of alcohol sufficient to produce blood alcohol levels of approximately 80 mg of alcohol per 100 ml of blood and mild euphoria do not activate the sympathetic nervous system and do not greatly affect blood glucose concentrations (Marks 1978). Indeed, some studies have shown an improvement in glucose tolerance following alcohol ingestion. Mild fasting hyperglycemia has been observed in more than 20 percent of middle-class alcoholics at the time of admission for alcoholism treatment (Hurt et al. 1986). It appears that the conditions under which alcohol is consumed, the associated dietary intake, the level of alcohol consumption, the history of alcohol consumption, and the presence of organ pathology such as hepatic insufficiency are responsible for the wide variation in the effects of alcohol on glucose tolerance.

Hypoglycemia. A rare but often fatal complication of alcohol abuse is profoundly low blood sugar (Williams 1984). This condition usually occurs in the context of acute alcohol ingestion after minimal food intake for several days or more. Victims are found stuporous or deeply comatose, with blood glucose levels below 20 mg/100 ml of blood. It has been proposed that alcohol blocks gluconeogenesis by metabolic shifts that result in reduced conversion of gluconeogenic precursors into glucose and glycogen. In the absence of glycogen stores, profound hypoglycemia occurs. Alcohol-induced hypoglycemia can be produced experimentally in normal healthy volunteers by inducing them to fast for 36 to 72 hours before administering alcohol (Freinkel et al. 1965). Obesity, or pretreatment with corticosteroids, tends to blunt the hypoglycemic effect of alcohol. In contrast, malnutrition, adrenocortical insufficiency, thyrotoxicosis, and consumption of diets high in protein and low in carbohydrate increase sensitivity to the hypoglycemic effects of alcohol ingestion.

Diabetes Mellitus. The effects of alcohol on the management of diabetes have been reviewed (McDonald 1980). Of particular importance are alterations in the metabolism of oral hypoglycemic drugs. Sulfonylurea compounds stimulate insulin release from the pancreatic beta cells and, in turn, inhibit hepatic gluconeogenesis, thus augmenting the hypoglycemic effects of alcohol. Prolonged alcohol ingestion can stimulate hepatic metabolic pathways responsible for drug metabolism and thereby shorten the half-life

of certain drugs (see chapter on drug-nutrient interactions). In such cases, the effectiveness of these drugs diminishes with prolonged alcohol ingestion.

For example, alcohol can impair the action of oral hypoglycemic agents. Both phenformin—a drug no longer available in the United States, but used elsewhere—and alcohol inhibit the decarboxylation of pyruvate to acetyl-CoA and favor the reduction of pyruvate to lactic acid, which would tend to increase the risk for lactic acidosis. Patients who take chlorpropamide experience flushing and other symptoms similar to those induced by disulfiram (Antabuse) when alcohol is consumed. Evidence indicates that there are genetic predispositions to this drug-alcohol interaction. Finally, alcohol-related deteriorations in judgment may be especially serious for persons with insulin-requiring diabetes if inebriation leads to errors in insulin dosage, administration, and diagnosis. In rare cases, profound hypoglycemia with permanent neurologic deficit has occurred.

Protein

Data from animal studies suggest that low-protein diets, sufficient to produce protein malnutrition, affect the biosynthesis of the alcohol dehydrogenase enzyme system and the availability of other cofactors required for alcohol oxidation (Orten and Sardesai 1971). Furthermore, the ability of rats, and possibly humans, to oxidize alcohol varies with both the amount of dietary protein and the types of protein ingested. For example, egg and milk proteins have been found to be more beneficial in maintaining normal rates of alcohol oxidation than proteins from cereals or other plant sources. When measured by indicators such as degree of inebriation and incidence of death due to alcohol intoxication, however, a mixture of proteins from vegetable sources has been shown to provide protection comparable to that from animal protein alone (Lucas, Ridout, and Lumchick 1968).

Water-Soluble Vitamins

Thiamin. Poor dietary intake and poor selection of foods, frequently seen in alcoholics, reduce thiamin intake. Alcohol may interfere with absorption of thiamin, with its activation to thiamin pyrophosphate, or with the ability of thiamin pyrophosphate to combine with the enzymes for which it is a cofactor (Hoyumpa 1983). In addition, hepatic storage of thiamin may be reduced due to fatty infiltration of the liver, hepatocellular damage, or cirrhosis. Increased losses of thiamin from the body, as well as increased requirements due to increased metabolic demands, especially following

refeeding with carbohydrates, have been reported. Wernicke-Korsakoff's syndrome caused by thiamin deficiency in the alcoholic population is discussed later in this chapter.

Riboflavin and Niacin. Riboflavin deficiency has been documented in alcoholics, but the mechanism for this deficiency, other than a presumed inadequate intake, has yet to be delineated.

In the 1940's, reductions in mortality rates from 90 to 14 percent following therapy with niacin (nicotinic acid) were reported in a large series of alcoholic patients who presented with impaired consciousness, delirium, a particular type of muscular rigidity called cogwheel rigidity, and uncontrollable grasping and sucking reflexes (Jolliffe 1940, 1941). In some patients, paralysis of the eye muscles and memory defects developed during therapy. Although these symptoms were attributed to niacin deficiency, deficiencies of other nutrients, especially thiamin, were probably present as well.

Vitamin B_6. Evidence suggests that alcohol inhibits the absorption of vitamin B_6 (Baker et al. 1975) and its release from the liver (Sorrell et al. 1974). Alcohol also increases the rate of degradation of pyridoxal-5-phosphate, one of the active forms of vitamin B_6. However, the magnitude of vitamin B_6 deficiency, its contribution to morbidity, and the precise mechanisms involved in its effects on alcoholic persons are unknown.

Folate and Vitamin B_{12}. Folate deficiency is probably the most common vitamin deficiency observed in alcoholics. Conversely, alcoholism is probably the most common cause of folate deficiency in the U.S. adult population. As with other nutrients, many factors contribute to folate deficiency in alcoholics, although poor dietary intake is undoubtedly the major cause. Alcoholics with good diets are less likely to have a folate deficiency than alcoholics with poor diets. The type of alcoholic beverage typically consumed may be significant because beer contains considerably more folate than wine or distilled spirits.

Folate malabsorption has been reported to occur among alcoholics, but this condition may be secondary to the toxic effects of alcohol or to malnutrition, both of which can damage the intestinal mucosa and impair nutrient absorption. Accordingly, correction of folate deficiency has been followed by improved absorption both of folate and other vitamins and minerals.

Urinary excretion of folate is increased by alcohol intake, and its tissue utilization is decreased (Russell et al. 1983). Alcohol may directly inhibit

enzymes involved in folate metabolism. Several investigators (Sullivan and Herbert 1964; Lindenbaum 1977) have shown that alcohol antagonizes the ability of folate to reverse the megaloblastic bone marrow changes seen in deficiency states, but larger doses of folate can overcome this antagonism. The suppressive effects of alcohol have been shown to be present whether folate is given intravenously or orally, suggesting that a metabolic function subsequent to absorption is involved.

Others have observed that macrocytosis (large red blood cells) occurs frequently in alcoholics and that this symptom persists despite folate supplementation unless alcohol intake is curtailed. Because of the high prevalence of folate deficiency and related anemia in derelict alcoholics, some investigators have proposed that low concentrations of folate be added to inexpensive domestic wine and spirits as a way of preventing this deficiency (Kaunitz and Lindenbaum 1977). However, it should be noted that even though folate deficiency can cause macrocytosis, the macrocytosis often seen in heavy drinkers is usually not related to folate deficiency and is not corrected by administration of the vitamin. Instead, this macrocytosis appears to be due to the direct effect of alcohol on the architecture of the red cell and is correctable only with abstinence. Because this kind of macrocytosis is usually unaccompanied by anemia, the presence of macrocytosis without anemia is a useful clue to alcohol abuse.

Symptoms of vitamin B_{12} deficiency are much less common than those of folate deficiency in alcoholics. Among malnourished alcoholics with liver disease, the prevalence of vitamin B_{12} deficiency is similar to that seen among randomly selected municipal hospital patients. Indeed, in some studies, the circulating levels of vitamin B_{12} have been found to be higher in alcoholics than in normal controls (Bonjour 1980).

The major manifestation of either folate or vitamin B_{12} deficiency is macrocytic megaloblastic anemia. Macrocytic anemia, without megaloblastosis, is also seen in chronic liver disease. Megaloblastic changes in the intestinal mucosal cells of persons with folate or vitamin B_{12} deficiency may further impair nutrient absorption and bioavailability.

Ascorbic Acid (Vitamin C). Serum ascorbic acid levels have been found to be lower in alcoholics than in nonalcoholics, probably because of inadequate diets. However, some data suggest that even when diets are adequate, increasing levels of alcohol consumption are associated with lower serum levels of ascorbic acid. Whether ascorbic acid affects alcohol metabolism is uncertain, as is knowledge of the extent to which this interaction may have clinical significance (Bonjour 1979).

Fat-Soluble Vitamins

Vitamin A. Vitamin A, as a fat-soluble vitamin, requires for its absorption a certain level of fat in the diet and adequate quantities of pancreatic lipid-digesting enzymes (lipases) and bile salts in the small intestine. Some complications of alcoholism, such as pancreatic insufficiency and biliary insufficiency, can therefore lead to malabsorption of vitamin A. In addition, alcoholics with liver disease may have impaired storage or transport of vitamin A because of an inadequate synthesis of retinol-binding protein, the protein formed in the liver that transports vitamin A in the blood. Even moderate alcoholic liver disease is associated with severely decreased vitamin A concentrations, and these levels are reduced in the liver even when blood levels of vitamin A, retinol-binding protein, and prealbumin are normal (Leo and Lieber 1982).

The storage form of vitamin A, retinol, is oxidized to its active form, retinal, by retinol dehydrogenase, an enzyme similar to alcohol dehydrogenase. Impairments in the metabolism of vitamin A have been reported in alcoholics, and some evidence suggests that retinol and ethanol compete for the alcohol dehydrogenase enzyme in the liver, testes, and retina (Shaw and Lieber 1983). Experimental deficiencies of several nutrients, including vitamin A, have been shown to enhance carcinogen-induced tumors in laboratory animals. Whether vitamin A deficiency plays a role in the reported association between alcohol intake and certain types of tumors remains to be determined (Committee on Diet, Nutrition, and Cancer 1982).

Vitamin D. Vitamin D and its metabolites are involved in regulating calcium and phosphorus metabolism, bone formation and resorption, and various other physiologic functions, including some aspects of immune function. Alcoholics have been reported to have low circulating levels of vitamin D, especially 25-hydroxyvitamin D, the metabolite formed in the liver. Not surprisingly, alcoholic persons with liver disease have lower levels of this metabolite than persons without liver disease. Higher rates of osteomalacia and osteoporosis have been reported in alcoholics (see chapter on skeletal diseases). The specific mechanisms to account for these findings remain unclear. Certainly, conditions associated with fat malabsorption may lead to malabsorption of vitamin D. In addition, some evidence suggests that alcohol induces enzymatic changes in the liver that favor the production of inactive metabolites of vitamin D. As discussed below in the section on minerals, the actions of vitamin D are closely linked with the metabolism of calcium and phosphorus, the levels of which may be altered in response to heavy alcohol ingestion.

Vitamin E. Alcoholic persons may develop severe malabsorption of vitamin E due to pancreatic or biliary insufficiency, but actual reports of vitamin E deficiency in alcoholics have been uncommon (Losowsky and Leonard 1967). Available data suggest that vitamin E malabsorption occurs most commonly in the presence of cirrhosis and steatorrhea, or fat malabsorption (Leevy, Tanribilir, and Smith 1971). Whether antioxidants such as vitamin E protect against alcohol-induced fatty changes in the liver remains uncertain (French 1971).

Vitamin K. Evidence suggests that at least half of the vitamin K required by humans is normally synthesized by bacteria in the intestine. In rare cases, vitamin K deficiency may occur with fat malabsorption, which is common in alcoholics. In addition, persons with alcoholic liver disease demonstrate a variety of impairments in the synthesis of vitamin K-dependent and other blood clotting factors. Bleeding disorders are, therefore, common in alcoholics. Alcohol also has been shown to affect blood platelets, coagulation inhibitors, and fibrinolysis (Larkin and Watson-Williams 1984).

Minerals

Iron. Iron deficiency in alcoholics may occur as a result of repeated gastrointestinal bleeding or clotting disorders. Iron overload, with hemosiderosis, may occur because of increased iron intake, either from alcoholic beverages (especially certain wines) or from iron-containing vitamin-mineral supplements that are often taken because of otherwise unexplained anemia. Iron absorption may be increased due to the increased solubility of ferric iron in the small intestine caused by stimulation of gastric acid secretion by alcohol. Increased iron absorption has also been reported in persons with pancreatic insufficiency, folate deficiency, and cirrhosis. In addition, disorders in heme synthesis can result in iron deposition in bone marrow and other organs. Alcoholics may develop sideroblastic anemias, characterized by the presence of ringed sideroblasts, in which iron is deposited between the membrane folds of the mitochondria (Eichner and Hillman 1971). Such anemias may result from vitamin B_6 deficiency, usually in association with folate deficiency or other impairments in activity of enzymes involved in heme synthesis (Larkin and Watson-Williams 1984). Hepatic hemosiderosis also appears to occur more frequently in alcoholics and may be exacerbated by coexisting hemolysis, blood transfusion, or the prolonged administration of therapeutic iron. In most such cases, it is not possible to separate the causes from the consequences of iron deposition in the development of hepatic failure (Larkin and Watson-Williams 1984).

Magnesium. Low magnesium levels have been demonstrated in the blood, skeletal muscle, and heart muscle of alcoholics (Wheeler et al. 1977). Chronic alcohol use can result in both reduced intake and malabsorption of magnesium. Alcohol ingestion acutely increases the urinary excretion of magnesium. Because magnesium is necessary for certain thiamin-dependent enzymes, there has been speculation that magnesium plays a role in the development of some of the neurologic complications of alcohol abuse, including Wernicke-Korsakoff's syndrome (discussed later in this chapter). However, the data are inconsistent, and the precise role, if any, of magnesium remains to be determined (Thomson 1978). Finally, magnesium insufficiency can be associated with hypocalcemia, perhaps because hypomagnesemia causes resistance to parathyroid hormone and impairment of its secretion.

Calcium and Phosphorus. Alcohol ingestion increases urinary calcium excretion, but the mechanisms for this action have yet to be determined. The possible roles of magnesium, parathyroid hormone, and vitamin D in this effect are unclear. Chronic alcoholics may have low serum calcium levels, usually secondary to reduced serum albumin levels from malnutrition, liver disease, or acute pancreatitis. As noted above, vitamin D intake, absorption, and metabolism may also be impaired in alcoholics, resulting in abnormalities in phosphorus, calcium, and magnesium metabolism. For example, low levels of vitamin D impair calcium absorption. Low levels of dietary calcium result in increased urinary retention of calcium and increased urinary excretion of phosphate. By whatever combination of mechanisms, hypophosphatemia occurs in some alcoholics and is easily detectable by routine laboratory testing at the time of admission to the hospital, although its symptoms are similar to those seen in other syndromes associated with alcohol abuse. In some groups of alcoholics, mild hyperphosphatemia has been observed more frequently than hypophosphatemia (Hurt et al. 1986).

Zinc. Reduced concentrations of zinc have been found in the plasma, red blood cells, and liver of humans and rats following chronic alcohol ingestion. Alcohol appears to increase the urinary excretion of zinc, perhaps because of increased release of zinc from hepatic stores. Protein catabolism is also associated with increased urinary zinc losses. The effect of zinc deficiency on alcohol metabolism has not been established, but preliminary evidence suggests that zinc-dependent enzymes, such as those involved in vitamin A metabolism, may be inhibited by alcohol (Thomson 1978). Some alcoholic men with night blindness have required both zinc and vitamin A treatment to correct visual dysfunction (McClain et al. 1979), but

whether the origin of this problem is liver dysfunction or nutrient malabsorption is as yet uncertain.

Nutritional Status of Alcoholics

Three types of malnutrition may be observed in alcoholics (Lieber 1983): (1) primary malnutrition due to a decreased intake of nutrients, (2) secondary malnutrition caused by an impairment in the digestion and absorption of nutrients due to the effects of alcohol, and (3) tertiary malnutrition due to an alteration in the ability to convert nutrients to their active coenzyme forms, resulting in nutritional complications that potentiate the direct toxic effects of alcohol.

The nutritional status of alcoholics remains ill defined because of variations in the types of studies performed and the groups of alcoholics that have been studied. The derelict alcoholic has a different baseline nutritional status than the middle-class alcoholic, and findings derived from studying one group cannot necessarily be extrapolated to the other.

The preponderance of studies have examined indigent alcoholics who are readily available and willing to cooperate at least temporarily with researchers. These individuals are probably as different in the type and amount of alcohol and food consumed as they are in every other aspect of day-to-day living when compared with nonindigent and middle-class alcoholics. Although indigent alcoholics make up less than 5 percent of the total alcoholic population, there is a persistent misconception that this group is representative of the alcoholic population at large. The almost total exclusion of women in this population is an indication that indigent alcoholics are not representative of all alcoholics.

Because of the association of alcoholism with serious medical illnesses such as liver cirrhosis or pancreatic insufficiency, another tendency is to study the nutritional status of persons with these conditions rather than the much larger—and healthier—portion of the alcoholic population. A clear distinction needs to be made between each of these groups. For example, the dietary intake of a large group of hospitalized alcoholic patients has been reported to be poor when judged by "traditional standards" (Patek et al. 1975). The mean daily energy intake in this group was over 3,000 kcal, but more than 50 percent was derived from alcohol. All of these patients were hospitalized for the treatment of medical complications of alcoholism, and two-thirds had cirrhosis, a much higher prevalence than expected for the general alcoholic population (Lelbach 1975).

Individuals hospitalized in alcoholism treatment centers may also have severe alcohol-associated medical problems, but the primary reason for their hospitalization is alcoholism. Therefore, these patients are probably more representative of the overall alcoholic population. Despite the high proportion of caloric intake from alcohol in this group, only a few studies have reported evidence of malnutrition. Among a small group of male alcoholics in an inpatient alcoholism treatment program, total caloric intake was estimated to be 2,600 to 2,700 kcal, with alcohol providing 22 to 36 percent of calories (Neville et al. 1968). In a similar group of middle-class alcoholics, the mean intake measured by diet history at admission to an alcoholism treatment unit was 3,100 kcal, with alcohol accounting for 35 percent of the daily energy intake (Hurt et al. 1981). No severe nutritional deficiencies were found using anthropometric measurements and blood studies of protein status in a small group of alcoholic patients hospitalized in a veterans hospital alcoholism treatment program (Dickson et al. 1983). Despite adequate protein intake, alcoholic patients, with and without liver disease, had significantly lower body weights, triceps skin folds, and arm muscle circumferences than abstainers (Simko, Connell, and Banks 1982), but no assessment of the socioeconomic status of this group was included. Thirteen percent of nonindigent alcoholics in another study were malnourished, but because of the method used to analyze the anthropometric data, the percent was probably higher (Tomaiolo and Kraus 1980). In yet another study, 13 percent of low-income alcoholics and 10 percent of middle-income alcoholics were judged to be malnourished, but obesity occurred in 2 percent and 4 percent, respectively. This latter research suffered from the vagueness of the nutritional data, which was based on the overall medical status of the subjects. In a group of 179 middle-class males, 47 of whom were alcoholic inpatients, the consumption of alcohol was associated with a decrease in energy intake from other sources and a reduction in the nutrient density of the diet at both moderate and high levels of alcohol consumption (Hillers and Massey 1985).

A comparison of alcoholics of lower socioeconomic status with those of higher socioeconomic status showed small but clear differences in the ratio of height-to-weight, triceps skin fold, mid-arm muscle circumference, and hematocrit (Goldsmith, Iber, and Miller 1983). Only 8 percent of this middle-income group were moderately malnourished, compared with 24 percent of the low-income group. In the low-income group, 8 percent were severely malnourished. Thus, socioeconomic class is an important factor that often is not taken into full account in nutritional studies of alcoholics. Furthermore, very few studies have been conducted on middle-income alcoholics, although these indicate that the nutritional status of this group is

probably adequate for most purposes despite the occasional finding of selected nutritional deficiencies.

Effect of Alcohol on the Nutritional Status of Nonalcoholics

Few investigations have focused on the effects of alcohol on the nutritional status of nonalcoholic persons. In three groups of nonalcoholic individuals who kept a diary of what they ate over a period of 6 to 12 months, 79 percent reported drinking alcoholic beverages during the study (Bebb et al. 1971). Half of these reported consuming alcohol on half or more of the days recorded. For 22 percent of those who drank alcohol, alcohol contributed approximately 10 percent of average daily total calories; for another 23 percent, it contributed from 5 to 10 percent of daily calories. As the proportion of calories from alcohol increased, there was little change in protein intake but a decrease in carbohydrate and fat intake. The overall quality of the diet could not be related to the proportion of energy derived from alcohol.

In a recent representative sample of upper-middle-class persons in southern California, alcohol did not replace calories derived from other nutrients (Jones et al. 1982). Using the 24-hour recall method, the authors recorded that 51 percent of the subjects consumed an average of 30 g or more of alcohol per day. In a group of "moderate drinking" men, who consumed 25 to 49 g of alcohol per day, there was a significantly lower intake of protein, carbohydrate, and fat. Despite a higher energy intake, the drinkers were not more obese than the nondrinkers. Further studies are needed to define the possible effects of mild to moderate alcohol intake on nutrient intake in the general population. If these effects are negligible, as indicated by the two cited studies, public health efforts may be better focused on persons with alcohol abuse or alcoholism problems.

Role of Alcohol in Diseases of the Liver

Alcohol-related diseases include both the direct toxic effects of alcohol and the indirect effects caused by the nutritional deficiencies found in alcoholics. According to the DSM-III criteria, liver diseases that occur in chronic alcoholics may be found in periodic abusers as well (Task Force on Nomenclature and Statistics 1980).

Alcoholic Cirrhosis

Research into the etiology of alcoholic cirrhosis has produced many theories of causation, ranging from a strictly nutritional deficiency to a direct toxic effect of alcohol. Until about 20 years ago, it was believed that

maintaining normal protein synthesis would allow the liver tissue to return to normal despite continued alcohol ingestion (Leevy 1967), and protein- and vitamin-supplemented diets were recommended for prevention of alcoholic liver disease.

In the mid-1960's, a major change in the theory concerning the cause of alcoholic cirrhosis occurred (Lieber 1966). At that time, the calorie-for-calorie substitution of alcohol for carbohydrates in the diets of young nonalcoholic volunteers was shown to produce fatty liver and ultrastructural changes in the liver cells, even though the volunteers' blood alcohol concentration never exceeded 100 mg/100 ml and the subjects were not malnourished (Rubin and Lieber 1968). This result was consistent with the theory that alcohol produces a direct toxic effect on the liver.

The contention that alcohol itself is the primary offender in the development of cirrhosis was supported by epidemiologic data. The death rate from cirrhosis in the United States decreased in proportion to the reduction in the consumption of alcohol that occurred during Prohibition (Klatskin 1961), and a similar direct relationship between alcohol intake and cirrhosis was observed in France during World War II when wine was rationed and the per capita consumption of wine decreased (Pequignot and Cyralnik 1970). Further evidence to support this contention derives from the observation that countries with the highest per capita alcohol consumption have the highest rate of mortality from cirrhosis (Sherlock 1981). The death rate from cirrhosis in the United States has recently declined (Laforge et al. 1987).

The observation that the development of cirrhosis is partly a response to the long-term consumption of large quantities of alcohol (Lelbach 1975) does not explain why cirrhosis develops in only 12 to 15 percent of alcoholics. In addition to the dose of alcohol and duration of consumption, genetic factors or individual differences among people must be involved. The best evidence to date of the direct hepatic toxicity of alcohol has been shown in baboons, where alcoholic liver disease—including fatty liver and cirrhosis—can be produced in about one-third of the experimental animals even though they are consuming a nutritionally adequate diet (Lieber and DeCarli 1974). Despite these studies, the issue of malnutrition in the genesis of alcoholic cirrhosis continues to be raised, especially in the context of the hepatic pathology similar to alcoholic liver disease that occurs in patients who have undergone jejunoileal bypass surgery for obesity (Patek 1979).

Alcoholic Hepatitis

A relationship between nutritional status and alcoholic hepatitis (alcohol-induced liver inflammation) derives from the Veterans Administration cooperative study that found features of marasmus or kwashiorkor, the classic starvation diseases, among alcoholic men (Mendenhall et al. 1984). The extent of marasmus and kwashiorkor correlated closely with the severity of the liver disease.

Interest in the nutritional therapy of alcoholic hepatitis was elicited by the report that parenteral infusions of amino acids reduced the mortality of persons with severe alcoholic hepatitis (Nasrallah and Galambos 1980). Among a group of patients with biopsy-proven alcoholic hepatitis, improvement (as measured by clinical and biochemical markers) was more rapid in those receiving the amino acid infusion, although no apparent difference in liver pathology remained in the two groups at the end of 1 month of treatment (Diehl et al. 1985). The researchers concluded that the outcome of alcoholic hepatitis is strongly influenced by the metabolic consequences of alcohol consumption and that it is the resolution of these consequences that is most influenced by parenteral amino acid supplementation. The nutritional status of persons with alcoholic hepatitis needs to be recognized and addressed, but unfortunately at present, its role in the etiology and treatment of this condition remains uncertain.

Fatty Liver

Several mechanisms have been proposed to explain the fatty changes in the liver that occur as a result of alcohol consumption. Oxidation of alcohol results in the production of reducing equivalents, and the acetate from alcohol can be metabolized to acetyl-CoA. This combination results not only in reduced hepatic oxidation of fatty acids but also in increased production of alpha-glycerophosphate, which in turn favors conversion of fatty acids into long-chain fatty acids and triglycerides that can be deposited in the liver as fat. In addition, catecholamine release, in response to either intoxicating dosages of alcohol or alcohol withdrawal, can increase the mobilization of fatty acids from muscle and adipose tissue and, therefore, increase the delivery of fatty acids to the liver.

Role of Alcohol in Diseases of the Nervous System

Wernicke-Korsakoff's Syndrome

Wernicke's encephalopathy is characterized by weakness of eye movements, gait disturbance, and confusion, and Korsakoff's psychosis by

amnesia, a disordered sense of time, and confabulation. The two conditions probably represent a continuum, and they usually occur together as Wernicke-Korsakoff's syndrome. In approximately one-fourth of patients, the memory disturbance is completely reversible. In half of the cases, improvement ranges from slight to significant although the memory loss can be incapacitating, but in the remaining one-fourth of the patients, the memory disturbance is completely irreversible (Dreyfus 1979). If Wernicke's encephalopathy goes unrecognized, the chances of preventing its progression to Korsakoff's psychosis and resolving its manifestations are reduced.

In alcoholics, Wernicke-Korsakoff's syndrome is caused more by thiamin deficiency than by the direct toxic effect of alcohol. The eye manifestations of Wernicke's encephalopathy respond rapidly to thiamin administration, although the associated ataxia and confusion respond more slowly. Brain lesions similar to those found in patients with Wernicke-Korsakoff's syndrome are found in the brains of animals that are deficient in thiamin (Victor, Adams, and Collins 1971). Alcohol may directly or indirectly affect thiamin intake, absorption, storage, metabolism, and excretion (Hoyumpa 1983). Another possible mechanism includes altered cerebral energy metabolism resulting from deficiencies in the function of thiamin-dependent enzymes; these deficits can affect energy production, diminish acetylcholine neurotransmission, and impair DNA synthesis (Reuler, Girard, and Cooney 1985). Subclinical thiamin deficiency, as measured by the activity of the thiamin-dependent enzyme erythrocyte transketolase, may occur in as many as one-third of alcoholics suspected of having liver disease (Camilo, Morgan, and Sherlock 1981). Because alcohol inhibits active rather than passive transport of thiamin, supplementation of the vitamin in amounts larger than the Recommended Dietary Allowance can overcome the thiamin malabsorption caused by alcohol (Lieber 1983).

The variations in clinical presentation and the fact that most persons with thiamin deficiency do not have Wernicke-Korsakoff's syndrome raises the possibility that there may be genetic variants that predispose individuals to its development (Blass and Gibson 1977). For example, a variant of transketolase with a low affinity for the coenzyme thiamin pyrophosphate was found in all of four patients with Wernicke-Korsakoff's syndrome but in none of six control patients. There is considerable evidence that isoenzymes of human erythrocyte transketolase exist, but the significance of such heterogeneity and its relationship to differential susceptibility to Wernicke-Korsakoff's syndrome has not been determined (Nixon 1984).

Because the rate of long-term institutionalization for persons admitted for Korsakoff's psychosis is 30 to 40 percent, some experts have proposed that

thiamin be considered for addition to alcoholic beverages (Centerwall and Criqui 1978).

Alcoholic Peripheral Neuropathy

Alcoholic peripheral neuropathy, a distal mixed motor sensory neuropathy primarily affecting the lower extremities, is probably the most common neurologic complication of alcoholism, and it occurs in over 80 percent of persons with severe neurologic problems such as Wernicke's encephalopathy (Victor, Adams, and Collins 1971). The predominant pathologic abnormality is a "dying back" degeneration of nerve axons that affects distal segments of the longest nerve fibers (Behse and Buchthal 1977). Recovery from alcoholic peripheral neuropathy is slow and often incomplete.

In the early part of this century, thiamin deficiency was considered to be the cause of alcoholic peripheral neuropathy (Shattuck 1928). That a nutritional deficiency plays a role in its development is supported by many factors: the clinical and pathologic features are similar to those seen in beriberi, the classic thiamin deficiency disease; patients with alcoholic peripheral neuropathy have been shown to have deficiencies of thiamin, folic acid, and other B-complex vitamins; improvement may occur with vitamin supplementation; and thiamin deficiency alone can cause a similar type of peripheral neuropathy.

Some evidence suggests that the toxic effects of alcohol alone may cause peripheral nerve damage because some patients with alcoholic neuropathy show no evidence of any nutritional deficiency (Behse and Buchthal 1977). Other evidence suggests that both diet and alcohol toxicity are at fault. A heavy alcohol intake and a poor diet result in acute axonal degeneration; in persons with chronic neuropathy, a long history of alcohol intake, but a good diet, however, there is little evidence of axonal degeneration and, in fact, considerable evidence of nerve regeneration (Walsh and McLeod 1970). Supplementation with B-complex vitamins and an improvement in overall nutritional status are important in the treatment of this disease, but abstinence from alcohol may be the single most important factor.

Alcoholic Dementia

The toxic effects of alcohol on the brain have received greater attention since the development of computed tomography (CT). In young alcoholics, cerebral atrophy as measured by CT may be reversed with the cessation of excessive drinking (Ron et al. 1982), but the associated cognitive dysfunction, labeled as alcoholic dementia, may be due in part to nutritional deficiencies. In one study, pathologic examination of alcoholic persons

showed changes in the brain consistent with Wernicke's encephalopathy, although clinical signs of the disease were absent (Torvik, Lindboe, and Rogde 1982). The syndrome of alcoholic dementia is also probably due to a combination of thiamin deficiency and the direct toxic effects of alcohol on the brain (Nakada and Knight 1984).

Role of Alcohol in Cardiovascular Diseases

Alcoholic Cardiomyopathy

The adverse effects of alcohol on the heart muscle, or myocardium, have been known since the 1700's when William Withering observed that 10 percent of the patients to whom he administered foxglove (containing digitalis) for heart failure were excessive users of alcohol. Similar observations relating alcohol abuse to heart failure were made by other scientists, such as Steell in the late 1800's and Osler in the early 1900's, but these early observations were all but forgotten when beriberi heart disease was described in thiamin-deficient alcoholics (Weiss and Wilkins 1937). As with many other alcohol-associated conditions, nutritional deficiencies were presumed to be responsible for heart failure in alcoholics, and it was not until the early 1960's that alcohol was recognized to have a direct toxic effect on the myocardium (Brigden and Robinson 1964). Beriberi heart disease and the congestive cardiomyopathy of alcoholism are now known to be distinctly different entities.

The theory that alcoholic cardiomyopathy is caused by the direct toxic effect of alcohol on the myocardium has strong support. The ultrastructural changes seen in the myocardial cells of a person with alcoholic cardiomyopathy, such as fragmentation of myofibrils, clusters of giant mitochondria with distorted membrane folds, dilated sarcoplasmic reticulum, and increased glycogen and fat deposits, are similar to those seen in the livers of persons with alcoholic liver disease. Furthermore, thiamin administration and other nutritional therapies alone have produced no benefit in persons with alcoholic cardiomyopathy. The only factor shown to affect recovery significantly is abstinence from alcohol (Demakis et al. 1974).

The manner in which alcohol produces its direct toxic effect on cardiac muscle is unclear, although acetaldehyde, the first product of alcohol oxidation, may induce myocardial damage (Schreiber et al. 1972) and has been shown to diminish myocardial protein synthesis (Bing 1978). Changes in cardiac metabolism may also be involved. Alcohol inhibits mitochondrial respiration and the activity of mitochondrial enzymes in the tricarboxylic

acid cycle in addition to interfering with mitochondrial calcium binding and uptake. Alcoholics display blood levels of acetaldehyde high enough to inhibit the association of the muscle proteins actin and myosin *in vitro* and to interfere with mitochondrial protein synthesis (Rubin 1979).

Dysrhythmias

Another manifestation of the ability of alcohol to produce cardiac toxicity is seen in persons with alcohol-induced dysrhythmia, dubbed "the holiday heart syndrome" because it occurs more frequently around holidays such as New Year's Eve when alcohol intake is generally highest (Ettinger et al. 1978). Individuals with unexplained acute atrial fibrillation have been shown to have a significantly higher rate of heavy alcohol consumption than control persons (Rich, Siebold, and Campion 1985). Alcoholics with evidence of myocardial dysfunction are more sensitive to the depressant effects of alcohol on the heart and to atrial and ventricular dysrhythmias following the acute administration of alcohol. Serious dysrhythmias have been observed in patients consuming as little as 7 oz of vodka (Singer and Lundberg 1972).

Hemodynamic Effects

Acute alcohol ingestion produces complex changes in cardiovascular physiology, including dilation of peripheral blood vessels and diminished blood return to the heart. Recent studies have shown that acute alcohol ingestion in normal subjects has a depressant effect on heart muscle action (Lang et al. 1985), but in one group of patients with congestive heart failure, a single intoxicating dose of alcohol significantly reduced pumping efficiency without causing any significant deterioration in cardiac performance (Greenberg et al. 1982). It is well established from both animal and human studies that chronic alcohol use injures the heart muscle, depresses ventricular function, and impairs cardiac performance. Over time, alcohol abuse may lead to irreversible damage to the heart muscle and cause congestive heart failure or cardiac arrhythmias.

Hypertension

Most studies have indicated that a self-reported average consumption of three to four alcoholic drinks per day causes a measurable increase in both the systolic and diastolic blood pressures. These studies suggest that as much as 11 percent of hypertension in men may be attributable to consumption of alcohol at this level (MacMahon 1986).

Hypertriglyceridemia

The most common lipid abnormality associated with alcohol abuse and alcoholism is hypertriglyceridemia. In such persons, the very low density lipoprotein (VLDL) levels are high, corresponding to what would traditionally be classified as hyperlipidemia type IV. In more severely affected individuals, there may be an accompanying elevation of chylomicrons, which is consistent with hyperlipidemia type V. Because VLDL particles contain some cholesterol, the serum cholesterol may also be elevated as a result.

The effect of alcohol intake on triglyceride levels is often overlooked. Among patients referred to lipid clinics, only diabetes is more important as a secondary cause of hyperlipidemia. Typically, persons with alcohol-induced hyperlipidemia do not respond to dietary or drug intervention unless alcohol intake is limited (Janus and Lewis 1978).

Indeed, the alcohol intake of all persons with hypertriglyceridemia should be assessed. In a light to moderate drinker especially, awareness of this effect of alcohol may provide sufficient motivation to lower intake. In the alcoholic person, this awareness might lead to the identification and treatment of the alcoholism.

Severe hypertriglyceridemia may cause and/or result from pancreatitis (Geokas 1984). Because pancreatitis is more common in alcoholics than in nonalcoholics, all individuals presenting with pancreatitis or otherwise unexplained recurrent upper abdominal pain should be evaluated for hypertriglyceridemia and history of alcohol use.

In alcoholics, extreme forms of hyperlipidemia have been described in which excessive alcohol intakes were associated with jaundice, severe hyperlipidemia, and hemolytic anemia (Zieve 1958). Liver biopsies in such patients showed fatty infiltration with minimal to moderate portal cirrhosis. Fortunately, this syndrome appears to be rare.

Elevated Serum Cholesterol Levels

Several population studies have suggested that light to moderate drinkers (by self-report) have a lower risk for coronary artery disease than do nondrinkers (Yano, Rhoads, and Kagan 1977; Blackwelder et al. 1980). The observation that alcohol intake tends to increase high density lipoprotein (HDL) cholesterol was originally thought to be consistent with these epidemiologic findings, especially because HDL cholesterol appears to be inversely related to the risk for coronary artery disease. However, more

recent studies have shown that the HDL cholesterol can be subdivided into fractions. The HDL_2 fraction is thought to protect against coronary artery disease but is affected relatively little by moderate alcohol ingestion. Alcohol elevates the HDL_3 fraction, which appears to have no association with coronary artery disease. In alcoholics, however, the reports to date regarding HDL cholesterol level have been variable and appear to depend on a variety of factors such as level of alcohol intake, the degree of hepatic microsomal enzyme induction, and the severity of alcoholic liver disease (Hurt et al. 1986). Because of the association of reduced levels of apolipoproteins AI and AII (apo AI and AII) with coronary artery disease (Kottke et al. 1986), the effect of alcohol on apo AI and AII is also of interest and appears to parallel its effect on HDL cholesterol. In alcoholic men, however, the apo AI levels have been observed to be lower than in nonalcoholic controls (Hurt et al. 1986). The epidemiologic findings, therefore, await further confirmation as well as elucidation of a biologic mechanism to explain the apparent protective effect of alcohol.

Coronary Heart Disease

Some evidence suggests that the ingestion of two to three alcoholic drinks per day reduces the rate of nonfatal myocardial infarction and mortality from coronary heart disease (Yano, Rhoads, and Kagan 1977; Blackwelder et al. 1980). Whether these epidemiologic observations are mediated by effects of alcohol on HDL levels is unknown at present (Ernst et al. 1980). The effects at various levels of alcohol intake, the presence of liver disease, and effects of exercise on HDL cholesterol levels in alcoholics require further study. It appears that the benefits of consuming two to three drinks per day do not increase in persons who drink more. On the contrary, mortality from other diseases increases markedly when alcohol consumption exceeds those levels (Blackwelder et al. 1980; Marmet et al. 1981).

Role of Alcohol in Reproductive Disorders

The relationship between maternal alcoholism and adverse fetal effects has been known for centuries, but interest was revived after publication of a report on this relationship in the early 1970's (Jones et al. 1973). Fetal alcohol syndrome is characterized by a triad of features: (1) facial malformations, (2) prenatal and postnatal growth deficiencies, and (3) central nervous system disorders, including mental retardation, with the effect occurring as early as the time of conception (Ernhart 1987). Although the initial observations were made of the children of severe alcoholics with longstanding, high-volume alcohol use, fetal abnormalities have now been associated with lesser quantities of alcohol intake during pregnancy

(Streissguth et al. 1980), and there appears to be a dose-response relationship in which abnormalities increase in proportion to the dose of alcohol (AMA 1983; Ernhart 1987). The observation that the fetal alcohol syndrome occurs in disproportionately larger numbers of American Indians, in patients of lower socioeconomic background, and in children of older mothers might be explained on the basis that the rate of alcohol abuse and alcoholism is higher among these groups (Streissguth 1978).

Although most authorities view the syndrome as a direct toxic effect of alcohol on the fetus, malnutrition may also play a role in its development. Acute and chronic alcohol consumption in the rat can significantly reduce the placental uptake of a variety of amino acids (Henderson et al. 1982). However, because of substantial structural differences in the placenta from species to species, extrapolation of these results to humans must be cautious. Animal studies, on the other hand, appear to support a direct causative effect of alcohol on fetal alcohol syndrome (Randall, Taylor, and Walker 1977). One additional study bears on this point. When pregnant women were separated into alcoholic and nonalcoholic groups by the use of the Michigan Alcoholism Screening Test and by an index of volume of alcohol consumed, pregnant alcoholics were found to have lower plasma zinc levels than nonalcoholic controls, and lower levels of zinc were observed in fetal cord blood (Flynn et al. 1981).

Although this last study undoubtedly brings attention to possible nutritional contributions to the fetal alcohol syndrome, the consensus at present is that the syndrome is due to toxic effects of alcohol and is not a nutritional deficiency syndrome. In addition, a recent study, after controlling for other risk factors, reported lower birth weights among infants born to mothers who consumed as little as one alcoholic drink per day during pregnancy (Mills et al. 1984). Until further information is available, the Surgeon General and the American Medical Association have recognized that complete abstinence at the time of conception and during pregnancy is the safest course (DHEW 1979; AMA 1983).

Implications for Public Health Policy

Dietary Guidance

General Public

Alcohol has been identified as a dietary factor that increases the risk for diseases of the liver, nervous system, and heart. It also contributes to the

development of certain cancers. Although consumption of up to one to two drinks per day has not been associated with disease among healthy male and nonpregnant female adults, evidence that 9 percent of the total population consumes two or more alcoholic drinks per day suggests that the risk for alcohol-related conditions could be reduced by an overall decrease in alcohol consumption among some segments of the general public.

Special Populations

Because studies in pregnant women have been unable to identify a threshold level of safety for alcohol intake during pregnancy, and because the risk for fetal abnormalities increases with increased alcohol intake during pregnancy, pregnant women—and women planning to become pregnant—should be advised to avoid drinking alcohol.

Persons with alcohol-related liver, nervous system, and cardiovascular conditions (e.g., elevated blood cholesterol and blood pressure levels) should receive advice from health professionals to reduce or eliminate alcohol intake to reverse or to prevent progression of these conditions. Persons with diabetes should also receive counseling on the effects of alcohol on caloric intake and blood glucose control.

Adolescents and young adults should be counseled in schools and through the media on the relationship between alcohol intake and motor vehicle and other accidents, suicides, and homicides. Older individuals should be counseled on the relationship between alcohol intake, nutritional deficiencies, and drug interactions.

Nutrition Programs and Services

Food Labels

Evidence related to the role of alcohol in health suggests that if alcoholic beverage containers are required to bear health warning labels, these labels should carry information warning of hazards to the developing fetus as well as of other health hazards associated with alcohol consumption abuse.

Food Services

Aside from the special populations noted below, evidence related to the role of alcohol currently holds no special implications for change in policies related to food service programs.

Food Products

There are no special implications for change in policy related to formulation of food products.

Special Populations

Pregnant women, including those served by the Special Supplemental Food Program for Women, Infants, and Children (WIC) and other maternal and child health programs, should be provided with counseling on avoidance of alcoholic beverages. Persons with alcohol-related conditions should be provided with counseling and referrals on the benefits of abstinence.

Research and Surveillance

Research and surveillance issues of special priority related to the role of alcohol and health include investigations into:

- The levels at which alcohol intake increases risk for chronic diseases and birth defects.
- The mechanisms by which alcohol induces fatty changes in the liver.
- The mechanisms by which alcohol increases blood pressure, blood cholesterol, blood glucose levels, and other risk factors for chronic disease.
- The mechanisms by which low levels of alcohol may reduce risk for coronary heart disease.
- The mechanisms by which alcohol increases cancer risk.
- The mechanisms by which alcohol damages the nervous system.
- The mechanisms by which alcohol intake interferes with nutritional status.
- Definition of the physiologic energy value of alcoholic beverages.
- The interaction of alcohol intake, nutritional status, socioeconomic status, and health.

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Chapter 18

Drug-Nutrient Interactions

. . . the suffering was caused by digestion
itself . . . vitiated by so long a use of opium.
Thomas De Quincey
Confessions of an Opium Eater (1821)

Introduction

Drugs are chemical agents used to prevent or treat disease. They interact with foods and nutrients in several ways. Drugs can interfere with appetite or with nutrient digestion, absorption, metabolism, or excretion. Similarly, both nutritional status and diet can affect the action of drugs by altering their metabolism and function, and various dietary components can have pharmacologic activity under certain circumstances. Such interactions raise concerns that drugs might impair nutritional status and induce nutritional deficiencies or that inappropriate dietary intake might impair or enhance drug activity. This chapter reviews these issues. More complete discussion of individual topics may be found in comprehensive reviews and monographs (Hathcock and Coon 1978; Young and Blass 1982; Smith and Bidlack 1982; Roe 1984; Roe 1985; Hathcock 1987a, 1987b).

Historical Perspective

Throughout history, treatments for injuries and diseases have often included manipulations of the diet and the use of remedies prepared from plants, animals, and minerals. The earliest surviving written records describe the ancient Sumerians' medicinal uses of laurel, caraway, and thyme. The first Chinese herb book, written in 2700 B.C., listed 365 medicinal plants and included ma-huang, the source of ephedrine. In 1000 B.C., the Egyptians were using garlic, opium, castor oil, coriander, mint, indigo, and other herbs as medicines, foods, and dyes (Young 1978). Hippocrates advocated the use of a few simple herbal drugs along with fresh air, rest, and proper diet to help the body's "life force" eliminate health problems (Lust 1974). Galen recommended large doses of drug mixtures to correct the

imbalances that he believed caused diseases. Descriptions of the properties and medicinal uses of about 500 plants in *De Materia Medica*, compiled in the first century A.D. by the Greek physician Dioscorides, remained an authoritative reference until the 17th century. Some of these plants from earlier writings are sources of modern drugs, including quinine from cinchona bark, morphine from the opium poppy, digitalis from foxglove, and reserpine from rauwolfia (Lust 1974).

In the 16th and 17th centuries, a school of scientists known as iatrochemists believed that chemistry's proper function was to assist physicians to improve health care (ACS 1977). Their teachings led in the 18th and 19th centuries to the use of minerals such as arsenic, iron, and sulfur to treat acute infections, a practice that may be said to be the beginning of chemotherapy. The purges and emetics of past medical practice usually were given as short courses of therapy and were unlikely to have a lasting effect on nutritional status. The chronic use of drugs such as opium or alcohol, however, was more likely to impair nutritional status through reduced nutrient intake or, in the case of alcohol, toxic effects on the digestive system (see chapter on alcohol).

As the sciences of medicine and nutrition developed, successful therapies tended to occur in areas associated directly or indirectly with the treatment of acute nutrient deficiency states, such as the use of limes to prevent or cure scurvy.

Eventually, the use of drugs evolved from an empirical art handed down through the centuries to a rigorous science of pharmacology in which known amounts of pure agents with specific physiologic effects are administered to treat particular conditions. The development of new drugs has the potential for introducing new drug-nutrient interactions, some of which may be beneficial to the patient while others may be deleterious. Thus, present interest in drug-nutrient interactions focuses on prevention of nutrient deficiencies in individuals who take drugs and on minimization of diet-induced impairments of drug function (Hathcock 1987a).

Significance for Public Health

Because of individual variations in dietary intake and in the use of and response to drug therapies, the effects of interactions between drugs and nutrients are difficult to measure, and no direct information is available on the incidence, prevalence, or health cost of such interactions. Drug-nutrient interactions are most likely to impair health or nutritional status in persons who take multiple drugs for prolonged time periods.

One indicator of the potential public health importance of drug-nutrient interactions may be found in the increasing level of use of medications by the general public. Population exposure to prescription drugs, defined as the average per capita number of prescription doses, increased 28 percent between 1971 and 1982. Males obtained 40 percent of the prescriptions, females 60 percent (Baum et al. 1985). In 1984, more than 1.5 billion prescriptions were dispensed from retail pharmacies, a 2 percent increase over 1983 levels. The cost of these prescriptions was $18.4 billion (Anonymous 1986a). New prescriptions accounted for 51 percent of the total, refills for 49 percent. The increase in prescriptions filled between 1984 and 1985 was 1.1 percent, largely as a result of increases in refills (Anonymous 1986b), and persons over 50 purchase prescriptions at about twice the rate of the rest of the population (Baum et al. 1985).

The proportionate share of prescription drugs taken by older persons increases with increasing age. Persons over age 65, for example, take about 25 percent of the national total of prescribed drugs and about an equal proportion of drugs sold over the counter although they constitute only about 10 percent of the population (Chen et al. 1985). Surveys show that the majority of elderly people take two to five different drugs daily and experience about two to three times more adverse drug effects than younger individuals (Rikans 1986). The medications most frequently used are drugs for cardiovascular disease, the central nervous system, and constipation, and most of the serious reactions are from cardiovascular and psychoactive agents (Chen et al. 1985). Older persons are thus at increased risk for deleterious drug-nutrient interactions because they take multiple drugs over long periods of time, are more susceptible to nutritional deficiencies (see chapter on aging), and have reduced ability to metabolize drugs (Rikans 1986).

Scientific Background: Methodological Issues

When interpreting the clinical significance of drug-nutrient interactions, it should be noted that recognized, frequent, serious interactions would result in unacceptable toxicity, and, consequently, in abandonment of the drug before marketing (Anonymous 1986c). Therefore, many drug-nutrient interactions will rarely be manifest clinically and can only be demonstrated in the laboratory. In most cases, excessive or abusive use of a drug is necessary before adverse effects become clinically apparent, and such effects are likely to occur only in vulnerable individuals who are chronically malnourished, elderly, or ill. Although it is possible that subclinical effects on health or nutritional status may occur at the usual levels of drug intake, especially when therapy is long term, such effects are difficult to

assess in individuals and are not yet possible to demonstrate in the population (Roe 1985).

The effects of drugs on human nutrition are complex and may not be recognized during routine preclinical toxicity testing in animals. Currently, the potential of a drug to affect adversely nutritional status is evaluated in animals by determination of food intake, body weight gain, and serum chemistry and hematology profiles. Although animal toxicology studies have often revealed adverse effects of drugs on food consumption and body weight gain, such effects are usually seen only at high drug doses and are not thought likely to affect nutritional status at doses typically prescribed (Gilchrist 1981). There are, however, occasions when a drug alters the nutritional status of animals at doses near the human therapeutic range. One such example is the inhibition of bile acids and fat-soluble vitamin absorption in both rats and humans by bile salt sequestrants such as cholestyramine (Harkins, Hagerman, and Sarett 1965; Hashim, Bergen, and Van Itallie 1961). The addition of cholestyramine to the diet of weanling rats at concentrations near those that are used in humans has been shown to reduce the normal body weight gain of these animals, perhaps because of vitamin A depletion; the inclusion of additional vitamin A in the diet was shown to prevent the weight loss, although liver stores of vitamin A remained low (Whiteside et al. 1965).

Many drugs have been shown to affect serum chemistries or hematologic parameters adversely during animal toxicity studies. In most cases, these changes are due to toxicities unrelated to nutrition. In general, the design of animal toxicology studies rarely allows for an adequate assessment of chronic drug effects on nutrition, but when a nutritional problem is identified in human clinical studies, animal studies can help clarify the mechanism of the interaction (Gilchrist 1981). Due to limitations in the doses used, in the number of subjects studied, and in the duration of drug administration, prospective (cohort) studies of drug safety can detect adverse effects on nutritional status only when they occur with high frequency in the study population. Depending on the intended use of the drug, populations at greatest risk for adverse nutritional effects—children, pregnant women, and older persons—may not be studied at all.

Key Scientific Issues

- Effects of Drugs on Nutritional Status
- Effects of Diet on Drug Metabolism

- Effects of Drug-Food Incompatibilities
- Effects of Drugs Used in Food Production
- Effects of Pharmacologic Doses of Nutrients

Effects of Drugs on Nutritional Status

Drugs can affect nutritional status by altering appetite, food digestion, and nutrient absorption, metabolism, utilization, or excretion.

Appetite and Food Intake

The regulation of food intake is exceedingly complex and involves the integration by the brain of chemical signals that convey visual, olfactory, and gustatory information as well as many internal signals regarding the quality, palatability, and need for food through multiple neurotransmitters and hormones (Morley et al. 1984; Sullivan and Gruen 1985). Appetite is stimulated, for example, by norepinephrine, opioid peptides, pancreatic polypeptides, growth hormone releasing factor, and gamma aminobutyric acid (GABA). Conversely, appetite is inhibited by factors such as dopamine, epinephrine, serotonin, neurotensin, calcitonin, and corticotropin releasing factor (Leibowitz 1986) and by intestinal hormones such as cholecystokinin, bombesin, somatostatin, and glucagon (Morely and Levine 1985; Sullivan and Gruen 1985).

The ways in which anorectic agents might affect appetite regulatory mechanisms are poorly understood. Amphetamines, fenfluramine, and the over-the-counter phenylpropanolamine (PPA) diet pills have been reported to exert their effects by causing the release from the central nervous system of neurotransmitters that increase feelings of satiety (Hoebel 1977). Other nutrition-related metabolic effects, such as lowering of body weight set points (Stunkard 1982), have been postulated but need confirmation. Although some drugs have been shown to induce weight loss in experimental animals, both the safety and efficacy of their use by humans is controversial. Certain studies suggest that they induce small but significant weight losses, but others have found them to be ineffective and possibly harmful (Friedman, Kindy, and Reinke 1982). PPA is an example of an amphetamine-like agent with no data on long-term benefits but well-documented side effects, including hypertension, seizures, strokes, headache, nausea, and behavioral disturbances (Pentel 1984).

Of considerable current research interest is exploration of the use of narcotic antagonists such as naloxone to block the appetite-stimulating

effects of endogenous opioid peptides in the brain. Naloxone has been shown to retard weight gain in experimental animals (Reid 1985). Although it also appears to reduce food intake in humans (Cohen et al. 1985), studies exploring its clinical use in weight reduction have been disappointing (Levine et al. 1985).

Digestion and Absorption

A variety of commonly used drugs impair the digestion and absorption of certain nutrients.

Laxatives decrease gastrointestinal transit time and reduce the absorption of glucose, calcium, protein, sodium, and potassium (Frier and Scott 1977). It has been suggested that mineral oil solubilizes and sequesters fat-soluble vitamins and prevents their absorption (Morgan 1941; Mahle and Patton 1947), but more recent data suggest this effect may be minimal. Cellulose can decrease absorption of calcium and magnesium (Berstad et al. 1975; Pak 1973).

Excessive consumption of aluminum-containing antacids can induce a phosphate depletion syndrome when dietary phosphate combines with aluminum hydroxide to form aluminum phosphate, which is insoluble and hence is completely excreted (Cooke, Teitelbaum, and Avioli 1978; Insogna et al. 1980). The risk of acute phosphate depletion is greatest when the diet is low in phosphate (Roe 1984). Antacids have been reported to have induced a severe copper deficiency in a patient with decreased gastric emptying time (Anonymous 1984a). Prolonged use of aluminum-containing antacids by patients with impaired renal or biliary excretion should be avoided, because the absorption and accumulation of aluminum under these conditions may impair calcium metabolism and lead to bone disease as is seen in kidney dialysis patients (Lemboke et al. 1982; Herzog et al. 1982).

Cholestyramine and colestipol prevent intestinal reabsorption of bile acids; they lower blood cholesterol levels by enhancing the conversion of cholesterol to bile acids. These drugs, however, also alter bile acid activity and may result in malabsorption of fat, vitamins A, D, K, and B_{12}, and folacin (Whiteside et al. 1965; West and Lloyd 1975). However, use of cholestyramine for 7 to 9 years in the Coronary Primary Prevention Trial by men with high blood cholesterol did not appear to cause nutrient deficiencies. Fat-soluble vitamins are frequently prescribed along with cholestyramine to eliminate any risk of deficiency.

Certain antibiotics, such as neomycin, may damage the intestinal mucosa and also precipitate bile acids, thus decreasing the absorption of vitamin K, carotene, and vitamin A, which are dependent on bile acid action for absorption (Levine 1967; Thompson et al. 1971; Barrowman, D'Mello, and Herxheimer 1973). Excessive amounts of broad-spectrum antibiotics can also destroy the natural vitamin K-producing bacterial population of the intestine, thus inducing bleeding conditions that can be reversed, if necessary, by vitamin K administration (Ansell, Kumar, and Deykin 1977; Anonymous 1984b).

The anti-inflammatory agent colchicine used to treat gout may alter intestinal transport mechanisms, leading to sodium, potassium, lipid, and nitrogen fecal loss (Race, Paes, and Faloon 1970; Webb et al. 1968).

Metabolism and Utilization

Oral Contraceptive Agents. Oral contraceptive agents are formulated from synthetic estrogens and progesterones that can affect metabolic processes involving essential vitamins and minerals. They are used by an estimated 10 million women in the United States (Ory, Forrest, and Lincoln 1983). Although numerous studies have reported laboratory evidence of marginal nutritional deficiencies among women taking these drugs, such evidence has been inconsistent and has only rarely been confirmed by clinical evidence. For example, blood levels of vitamin B_6 were found in some studies to be reduced among 20 percent or more of women using oral contraceptives, but other studies have failed to demonstrate such effects (Thorp 1980). The clinical significance of these observations is uncertain (Leklem 1986; Miller 1986). Circulating levels of zinc and release of zinc from tissues have also been reported to be reduced among users of oral contraceptives, but there is no evidence that such changes alter the dietary requirement for this mineral (King 1987). As with other interactions yielding minimal to moderate decreases in serum levels of micronutrients, clinical manifestations of deficiencies are likely to be detected only when nutritional status is below optimal levels before taking the drug.

Anticonvulsants. Various anticonvulsants accelerate the metabolism and elimination of vitamin D (Harvey 1985) and have been associated with clinical signs of rickets in children and osteomalacia in adults (Matheson et al. 1976). Also, the anticonvulsants phenytoin, phenobarbital, and primidone are capable of inducing a biochemical or clinical folate deficiency state (Chanarin 1979; Lambie and Johnson 1985; Edeh and Toone 1985). These drugs also interfere with metabolism of thiamin (Klein et al. 1977).

Newborn infants of mothers taking barbiturates or phenytoin are more likely to have coagulation defects because of reduced availability of vitamin K (Keith, Gundberg, and Gallop 1980; Keith et al. 1983). Osteomalacia secondary to phenytoin may require replenishment of vitamin K as well as vitamin D to restore the vitamin K-dependent proteins that are important for normal calcium metabolism in bone. Carnitine may be depleted by therapy with the anticonvulsant valproic acid, resulting in hepatic injury and a Reyes-like syndrome (Bohles et al. 1982; Coulter 1984; Murphy, Marquardt, and Shug 1985).

Vitamin Antagonists. Several drugs used as cancer chemotherapeutic agents (e.g., methotrexate), as diuretics (triamterene), or as antimalarial or antibacterial drugs (pyrimethamine) are antagonists of folic acid (Lambie and Johnson 1985). These drugs bind to the enzyme dihydrofolate reductase, preventing the conversion of folic acid to tetrahydrofolate, the vitamin form that is required for synthesis of purines. As a result, DNA synthesis is arrested and the cells die (Anderson, Smith, and Hutchinson 1966; Kahn, Fein, and Brodsky 1968; Lieberman and Bateman 1968; Myatt, Hernandez, and Coatney 1953). The drug sulfasalazine, used to treat ulcerative colitis, inhibits intestinal transport of folic acid and has been associated with the clinical signs of deficiency of this vitamin often seen in persons with inflammatory bowel disease (Halsted, Gandhi, and Tamura 1981).

The vitamin K antagonists—dicumarol, phenprocoumon, and warfarin—are used as anticoagulants; they block a specific carboxylation step in the activation of six vitamin K-dependent clotting factors (Wessler and Gitel 1984; O'Reilly 1985). Parkinsonian patients, whose tremors are controlled by L-dopa, may experience a precipitation of their symptoms if they ingest large doses of vitamin B_6 because of an interaction between L-dopa and pyridoxal-5 phosphate, the active form of this vitamin (Evered 1971; Mars 1974).

The antitubercular drug isoniazid binds and inactivates vitamin B_6, inducing pyridoxine deficiency and its resulting neuropathy (Biehl and Vilter 1954). Consequently, vitamin B_6 is often given to individuals receiving this therapy. One benefit of this interaction is that overdoses of isoniazid can be treated successfully by administration of vitamin B_6 (Wason, Lacouture, and Lovejoy 1981). A similar vitamin B_6-responsive neuropathy occurs in patients taking hydralazine, a hypotensive agent (Raskin and Fishman 1965). Cycloserine, another antitubercular drug, impairs niacin synthesis and absorption and may lead to a niacin deficiency (Heinivaara and Plava 1964).

Vitamin B_{12} metabolism is also affected by a variety of drugs. For example, the antitubercular drug paraminosalicyclic acid affects intestinal transport mechanisms for vitamin B_{12} (Toskes and Deren 1972), and prolonged exposure to nitrous oxide has been reported to produce a megaloblastosis (Chanarin 1982) and a myeloneuropathy similar to symptoms typical of vitamin B_{12} deficiency (Layzer 1978), perhaps because of binding and inactivation of the cobalt present in that vitamin.

Antihypertensive Drugs. These drugs produce disturbances of macronutrient metabolism, resulting in glucose intolerance and hyperlipidemia. Beta blockers increase blood levels of triglycerides but decrease levels of high density lipoprotein cholesterol (Helgeland 1984; Weinberger 1985). Thiazide diuretics decrease glucose tolerance (Amery et al. 1978; Murphy et al. 1982; Perez-Stable and Caralis 1983; Helderman et al. 1983; Ames 1984), increase serum levels of low density lipoprotein cholesterol (Goldman et al. 1980; Grimm et al. 1981; Weinberger 1985), and decrease losses of calcium in urine (McCarron 1985; Stier and Itskovitz 1986). Spironolactone lowers serum levels of high density lipoprotein cholesterol and increases serum levels of insulin (Falch and Schreiner 1983).

Excretion

Diuretics. Diuretics, such as the thiazides and furosemide, decrease the resorption of potassium and other minerals by the kidneys, thereby increasing their excretion (Dyckner and Webster 1979; Morgan, Murkinshaw, and Davidson 1978). Patients on long-term diuretic therapy are usually advised to consume foods rich in potassium.

In sum, drugs cause little nutrient-related difficulty for the great majority of individuals taking medications. Adverse effects are usually limited to persons who consume relatively high doses over prolonged periods, or to persons who have clinical conditions that interfere with normal drug metabolism and excretion or that make them unusually susceptible to drug-induced nutritional deficiencies (Smith and Bidlack 1982).

Effects of Diet on Drug Metabolism

Nutritional factors affect the activity of drugs by altering their rates of absorption, metabolism, or excretion.

Absorption

Dietary factors can decrease, delay, or enhance the absorption of drugs, primarily by altering their availability, their solubility, or the amount of time

they spend in the stomach or intestine (Hathcock 1985). Calcium, for example, can bind tetracycline antibiotics and form a complex that renders both the drug and nutrient unavailable (Roe 1985). Dietary fat enhances the absorption of fat-soluble drugs, but the absorption of drugs that bind to fiber is reduced by high-fiber diets. Drugs such as L-dopa and penicillin G that are metabolized or degraded in the stomach may be partially destroyed when gastric emptying is delayed. The bioavailability of certain drugs, such as the antibacterial nitrofurantoin, the cardiovascular drug propranolol, and the hypotensive drug hydralazine, is enhanced when gastric emptying is delayed and more of the agent can be dissolved in the gastric juice (Melander 1978; Toothaker and Welling 1980). Digitalis absorption is slowed by the presence of food in the gastrointestinal tract. Instructions to take drugs with or between meals, or the coating of drugs to prevent dissolution, attempt to take advantage of these gastric properties, although it is uncertain how well patients adhere to such instructions. The acidity of the gastrointestinal tract also affects drug disposition. A more acidic environment reduces the bioavailability of penicillin and isoniazid but increases the absorption of tetracyclines (Roe 1985).

Food decreases, delays, or enhances the absorption of certain antibiotics (Hathcock 1985). The complexity of the diet and of drug responses makes the clinical implications of such interactions difficult to predict.

Metabolism and Utilization

The effects of drugs are modulated by their rates of metabolism by the liver and other tissues. Drugs that are metabolized slowly do not need to be taken as frequently or in as high doses as those that are rapidly eliminated by the body. Drugs are metabolized by two basic processes. The first (Phase I) metabolic step is usually an oxidation reaction that alters a functional group in the drug. This alteration may either activate the drug or deactivate it. The most common example of this process involves the same mixed-function oxidase enzyme systems that metabolize many other endogenous or foreign (xenobiotic) compounds. These systems contain cytochrome P-450 and other cytochromes and employ reduced nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen in their reactions. A second step (Phase II) conjugates the oxidized drug to an inactive, water-soluble form that can be readily excreted (Bidlack 1982; Meydani 1987; Hathcock 1987a). Most effects of diet on drug metabolism affect the oxidation reactions, whereas relatively little is known about the ways in which nutritional factors affect conjugation reactions (Hathcock 1986).

The rate of drug metabolism by mixed-function oxidase systems can be accelerated (induced) by the drugs themselves as well as by a variety of dietary factors. Such factors include protein, cruciferous vegetables such as broccoli or cabbage, and charcoal-broiled meats (Bidlack 1982). Thiamin deficiency also increases drug metabolism—it has been shown to increase the demethylation of mestranol, for example (Hoyumpa and Schenker 1982).

On the other hand, low-protein, high-carbohydrate diets and deficiencies of several vitamins and minerals reduce levels of drug-metabolizing enzymes and, consequently, the rate of drug metabolism, so that drug concentrations may decline slowly. Thus, in many cases, the net effect of nutritional deficiency is to increase drug potency (Hathcock 1987a). In starved individuals, for example, the activities of the mixed-function oxidase enzymes are reduced and the clearance of drugs such as chloramphenicol and sulfadiazine is impaired. The metabolism of other drugs is unaffected by starvation (Bidlack 1982).

Excretion

High-fiber diets interfere with the enterohepatic circulation of drugs excreted in bile (Hathcock 1985). Urinary acidity, which can be affected by diet, also influences drug elimination. Aspirin, for example, is resorbed in acidic urine, whereas amphetamines are resorbed under more alkaline conditions (Welling and Tse 1983).

Effects of Drug-Food Incompatibilities

Certain drugs can interact with specific nutrients or non-nutrient components in foods to cause acute adverse reactions. Such reactions can be prevented by avoiding the foods when taking the medication. Examples include interactions between monoamine oxidase inhibitors and foods containing tyramine, and between alcohol and disulfiram, hypoglycemic agents, and many other drugs (Taylor 1987).

Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors are mood-elevating agents that were formerly used with great frequency to treat severe depression. Their nutrition-related problems stem from metabolism of the potentially toxic amine tyramine. Tyramine is formed when intestinal bacteria degrade the amino acid tyrosine; it is also found in fermented foods such as cheese, wine,

yogurt, some kinds of sausages, and beer. Under ordinary circumstances, the enzyme MAO converts tyramine to soluble products that can be excreted in urine. Inhibition of MAO in the presence of foods containing tyramine permits this toxic amine to increase in blood to the point where it causes severe—and occasionally fatal—hypertension (Asatoor, Levi, and Milne 1963). Because the use of MAO inhibitors by people who ingest foods containing tyramine can induce a severe hypertensive crisis, they are now prescribed less frequently (Roe 1984).

Alcohol

Acetaldehyde-induced nausea and vomiting can occur within 15 minutes after the consumption of alcohol by persons taking the drugs disulfiram (Antabuse), metronidazole (Flagyl), and chlorpropamide (Diabinese). Disulfiram inhibits the enzyme acetaldehyde dehydrogenase, which oxidizes acetaldehyde, a product derived from the metabolism of alcohol (Hald and Johnson 1948). This interaction, which is so unpleasant as to deter the use of alcohol, is the basis for the use of Antabuse in detoxification programs (for reviews see Roe 1984; Seitz and Simanowski 1987).

Alcohol consumption can cause hypoglycemia in persons with diabetes who are using agents such as the sulfonylureas to lower blood sugar levels (Harris 1971; Carulli, Manenti, and Gallo 1971). It also potentiates the prolongation of bleeding time induced by aspirin (Deykin, Janson, and McMahon 1982), an interaction that can have serious consequences in alcoholic patients who suffer from gastritis, esophageal varices, or peptic ulcers.

Acutely, alcohol inhibits the activity of drug-metabolizing enzymes by displacing other drugs bound to cytochrome P-450, by decreasing the availability of NADPH, or by disturbing the lipid bilayer membrane that provides the microenvironment for drug-metabolizing enzymes (Hoyumpa and Schenker 1982). Chronic alcohol consumption enhances oxidation and toxicity of many substances, for example, acetominophen (Seitz and Simanowski 1987). It increases the toxic side effects of analgesics, anesthetics, anticoagulants, anticonvulsants, antihistamines, antimicrobials, tranquilizers, and narcotics (Anonymous 1979). Meprobamate, chloral hydrate, and barbiturates are also metabolized and excreted more slowly when alcohol is taken simultaneously (Hoyumpa and Schenker 1982). Ingestion of benzodiazepines and alcohol together results in higher plasma concentration of the drugs and enhanced sedative effects due to decreased hepatic clearance. The postural hypotension produced by organic nitrates for angina is accentuated by alcohol (Needleman, Corr, and Johnson 1985).

As a general rule, any toxic side effect of a medication will be potentiated if alcohol is consumed along with it (Anonymous 1979; Seitz and Simanowski 1987).

Effects of Drugs Used in Food Production

Antibiotics such as tetracycline and penicillin are fed to livestock to prevent infections and to promote growth. Because the genetic information that controls some kinds of resistance to antibiotics is carried on transposable genetic elements (plasmids) that can be transferred from one organism to another, questions have been raised as to whether subtherapeutic doses of livestock with antibiotics (a procedure that enhances growth and feed utilization) might encourage the proliferation of antibiotic-resistant microorganisms that are human pathogens or are capable of transferring antibiotic resistance to human pathogens (Stallones 1982).

In 1980, a National Academy of Sciences (NAS) report concluded that the research necessary to establish and to measure potential risks of antibiotic use in animals had not yet been conducted (NAS 1980). Since then, human infections with drug-resistant *Salmonella* have been documented, both as a result of eating hamburger originating from cattle that had been fed subtherapeutic doses of tetracyclines (Holmberg et al. 1984) and from drinking raw cow milk infected with *Salmonella* resistant to chloramphenicol and several other antimicrobial agents (Tacket et al. 1985). As a result of these studies, the Center for Veterinary Medicine of the Food and Drug Administration, with the counsel of a new NAS committee, is reviewing the available research findings on the hazards and benefits of this use of drugs. At issue is whether to institute procedures to suspend low-level uses of penicillins and tetracyclines in animal feeds (Goodman-Malamuth 1986).

Effects of Pharmacologic Doses of Nutrients

Nutrients are sometimes used in unusually high doses for their pharmacologic effect. Niacin, for example, is used pharmacologically to reduce blood cholesterol levels (Grundy et al. 1981; Blankenhorn et al. 1987). Retinoid derivatives of vitamin A have been used successfully to treat severe acne and other conditions (Bollag 1983). All pharmacologic therapies induce side effects (pharmacology has been described as "applied toxicology" because even the desirable effects of drugs are obtained by altering—poisoning—normal metabolic function), and high-dose nutritional therapies are no exception. Although excess water-soluble vitamins are excreted and usually cause little difficulty, side effects have been

reported in cases of excessively high doses (Miller and Hayes 1982). High-dose niacin induces flushing, and neurologic symptoms have been reported from excessive intake of vitamin B_6 (Schaumburg et al. 1983). Excessive intake of fat-soluble vitamins or their derivatives is well known to induce toxic symptoms. Excess vitamin A, for example, causes birth defects in animals, and, possibly, in humans; caution has been urged in its use for women who are pregnant or likely to become pregnant (Teratology Society 1987).

Individuals born without the genes to produce key functional enzymes may require amounts of certain nutrients greatly in excess of those required by most people. Such inborn metabolic errors have been identified for enzymes necessary for absorption, metabolism, or storage of nearly all of the vitamins (Stanbury et al. 1985). In some cases, higher-than-normal intake of the vitamin will restore activity. A classic example of such a vitamin-responsive syndrome is pernicious anemia, a condition of impaired absorption of vitamin B_{12}. Patients with this condition must have exceedingly high doses of the vitamin from food or supplements, or lower doses by injection. Another example is homocystinuria, a condition that results from a deficiency of the enzyme cystathione beta synthetase. Lack of this enzyme leads to the accumulation of methionine, the appearance of homocystine in urine, and clinical symptoms ranging from thromboses and osteoporosis to mental retardation. About 40 percent of individuals with this condition respond favorably to doses of vitamin B_6 that are 50 to 500 times higher than levels defined by Recommended Dietary Allowances (Mudd and Levy 1983).

Acrodermatitis enteropathica, a severe skin and gastrointestinal disorder, is caused by a deficiency in zinc absorption, but it can be overcome by zinc administration at levels greatly in excess of those normally required (Prasad 1983). An inborn error of metabolism resulting in systemic carnitine deficiency, with clinical manifestations of excessive ketone production, has been treated successfully with supplemental carnitine (Wolff et al. 1986).

In other conditions, certain metabolic products cannot be degraded and, therefore, accumulate to toxic levels. In some cases, such disorders can be treated with carefully designed dietary preparations having a very low content of the poorly metabolized nutrient. An example of this type of condition is phenylketonuria, a genetic lack of the enzyme that converts the amino acid phenylalanine to tyrosine. Patients with phenylketonuria accumulate phenylalanine and other metabolites that, at high levels, are toxic and cause mental retardation and other neurologic damage (Anony-

mous 1986d). Dietary treatment is designed to reduce the phenylalanine content of the diet to levels below those that cause symptoms. The special infant formula product Lofenelac, for example, contains sufficient quantities of all of the essential amino acids with the exception of phenylalanine (Tourian and Sidbury 1983).

Implications for Public Health Policy

Dietary Guidance

General Public

Although drugs interact with dietary factors in many ways that impair nutrient availability, evidence about the public health significance of such interactions is insufficient to recommend general shifts in the pattern of use of any particular drug on the basis of its adverse effects on nutritional status. Nor may any implications be drawn at this time for the general public on intake of specific nutrients with relation to nonprescription drug interactions.

Special Populations

Studies of patients consuming multiple drugs for prolonged time periods, especially those patients who are older, suggest that dietary intakes may need to be adjusted to compensate for adverse interactions of specific nutrients with medications and that information should be provided to such patients by qualified health professionals on appropriate use of such diets. Patients taking drugs that induce acute reactions in the presence of dietary factors such as tyramines or alcohol should be instructed on appropriate means to avoid those factors.

Persons with inborn metabolic errors that respond to pharmacologic doses of nutrients or to special products designed to minimize toxic symptoms should be advised on the safe and effective use of such therapies. Health professionals should receive instruction about drug-nutrient interactions to understand how best to maximize drug efficacy and minimize adverse reactions.

Nutrition Programs and Services

Food Labels

Evidence related to the role of diet in drug interactions currently holds no special implications for change in policy related to food labeling.

Drug Labels

Evidence related to the role of diet in drug interactions suggests that drug manufacturers should provide information in the package insert on the potential effects of the medication on nutritional status, and vice versa.

Food Services

Evidence related to the role of diet in drug interactions currently holds no special implications for change in policy related to food service programs.

Food Products

Evidence related to the role of diet in drug interactions currently holds no special implications for change in policy related to packaged food products. Preliminary evidence relating human infections to antibiotic-resistant micro-organisms derived from animals treated with subtherapeutic doses of antibiotics suggests the need for close scrutiny of this practice.

Special Populations

Persons—especially older persons—who consume drugs should be provided with counseling and assistance on dietary methods to avoid adverse drug-nutrient interactions. Persons with inborn metabolic errors requiring therapy with pharmacologic doses of nutrients should be provided with counseling and assistance on appropriate and safe use of such supplements.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in drug interactions should include investigations into:

- The extent of drug taking (prescription, over the counter, and illegal) among the population.
- The extent of adverse drug-nutrient interactions in the population and their clinical significance.
- Age-related changes in nutrient metabolism with special implications for pharmaceutical use.
- Effects of medications on the nutritional status of older persons.
- Drug effects on nutrient intake, absorption, metabolism, and excretion.
- Effects of diet, including alcohol, on drug absorption, metabolism, and excretion.

- The effects of antibiotics, hormones, or other drugs in animal feeds on human health.
- The levels of intake of essential nutrients that induce toxic symptoms.
- The most effective means to educate health professionals and the general public about drug-nutrient interactions.

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Chapter 19

Dietary Fads and Frauds

The advertising quack . . . is the black wolf, aye, the Bengal tiger of the profession. . . . He is full of shrewdness and cunning, and knows the poor weak human nature like a book.
Dr. Willis P. King, 1882
Quacks and Quackery in Missouri

Introduction

Historical Perspective

Food, an indispensable ingredient of life, has long been endowed with metaphysical, moral, and theological meanings. The folklore and superstitions of cultures throughout history have attributed healing or harmful properties to certain foods. This tendency has not disappeared with the advent of the sciences of nutrition and medicine. Food folklore continues today, although in many instances it is inconsistent with scientific evidence (Young 1978).

Contemporary food fads often make one or more of the following claims, none of which are substantiated by available scientific evidence (Bitensky 1973; Darby 1974; Shifflett 1976; Deutsch 1977; Stare 1980; Miller 1980; Jarvis 1983, 1984b):

- Some foods have magical, life-promoting properties.
- Modern foods are grown on depleted soil, are overprocessed, and, therefore, cannot provide good nutrition.
- Food supplements are always necessary to ensure good nutrition, and megadoses of nutrients provide "supernutrition."

Definitions

Nutrition fraud is a comprehensive term used by the U.S. Food and Drug Administration (FDA) to describe the abuses that occur as the result of the misleading claims for traditional foods, dietary supplements, and dietary

products and of the deceptive promotion of other food substances, processes, and devices (Nightingale 1984). Nutrition fraud has long been recognized as the leading example of health fraud (Larrick 1963). Food faddism and quackery describe two types of nutrition fraud commonly purveyed to the public (Huenemann 1956; Todhunter 1973; Jarvis 1984a).

Food faddism is a dietary practice based upon an exaggerated belief in the effects of food or nutrition on health and disease. Food fads derive from three beliefs: (1) that special attributes of a particular food may cure disease, (2) that certain foods should be eliminated from the diet because they are harmful, and (3) that certain foods convey special health benefits (McBean and Speckmann 1974). Unlike more transitory fads, many key concepts associated with food faddism persist or reappear periodically. Food faddists are those who follow a particular nutritional practice with excessive zeal and whose claims for its benefits are substantially more than science has substantiated. In most instances, foods praised as beneficial, such as special products or vitamin supplements, are not as good as faddists claim, and those foods condemned as harmful, such as white flour or sugar, are not as bad (Jarvis 1983).

Food quackery, which involves the exploitive, entrepreneurial aspects of food faddism, is the promotion for profit of special foods, products, processes, or appliances with false or misleading health or therapeutic claims. A food quack is one who pretends to have medical or nutritional knowledge and who promotes special foods, products, processes, or appliances with false or misleading claims, usually for personal financial gain.

Factors Contributing to Nutrition Fraud

Nutrition fraud flourishes in the United States today because of the diversity of cultures, the historical tradition of concern for health and the use of natural remedies, and the introduction of advanced communication technologies. Some frauds derive from traditional folklore inherited from the many cultures populating this country, while others are uniquely American (Young 1978; Deutsch 1977).

Food faddism in America had its roots in Great Britain, where patent medicines were advertised and sold by everyone from hairdressers to goldsmiths. In the colonies, legal protection of consumers against fraudulent claims was first recorded in Massachusetts Bay in 1630. A citizen, Nicholas Knopp, was whipped and fined five pounds for selling a cure for scurvy that had "no worth nor value" and was "solde att a very deare rate" (Young 1961).

Food faddism was very common in 19th-century America, perhaps as a result of the high literacy rate and the proliferation of newspapers that provided a medium for advertising. Claims for health benefits were an integral part of the promotion of foods and food components sold by patent medicine men and women and popular health reformers (Whorton 1982). One of the earliest nutrition faddists was Sylvester Graham, a "back to nature" reformer who was suspicious of any food, such as white flour, altered from its "natural" condition (Young 1978; Whorton 1982). His legacy continues among those who question whether processed food of any type can provide adequate nutrition (Deutsch 1977; Stare 1980; Miller 1980).

Popular interest in nutrition, coupled with concern about food shortages during World War I, was fostered by the increasing promotion of the health properties of foods in the early 20th century (Young 1967). Vitamins, by the very nature of their discovery, became associated with the prevention or cure of disease (Todhunter 1973) and were soon promoted as curative agents (Young 1967). George P. Larrick (1959), then Commissioner of Food and Drugs, explained this trend:

> In the wake of scientific advances there often follows a host of persons who misinterpret them and exploit them for private gain. That has been true in the field of nutrition. The nutritionist studies the long-range benefits to the public health from new scientific findings, withholds premature endorsement, and has confidence that future research holds great promise. . . . The promoter . . . does not wait for the facts or the possibility of different findings in the future. He hastens to cash in before all the facts are known. Those interested only in profit employ clever copywriters to promote products by pseudoscientific statements, using half-truths and gross exaggeration to build up a scare psychology. . . .

Today, the traveling patent medicine man has been largely replaced by the highly skilled and organized use of electronic means to promote fraudulent marketing—computers, customized mailing lists, national advertisements, WATS banks of telephone lines, and other mass media. The medium and the details have changed, but the message and the goals remain. It is difficult for consumers to evaluate the validity of the health claims perpetrated by quacks and faddists (Tierney 1984).

Background

Regulation of Nutrition Fraud

The need for public protection from fraud was recognized over a century ago, when Congress enacted statutes to combat mail fraud (Nelson 1984).

The first Federal legislation, the Pure Food and Drug Act of 1906, made it unlawful to manufacture or introduce into interstate commerce adulterated or misbranded food or drug products (Anderson 1964). This Act was passed in response to an intensive campaign against patent medicines and food abuses stimulated by the work of Dr. Harvey Washington Wiley, chief chemist at the U.S. Department of Agriculture. Because of this, it soon became known as "Dr. Wiley's Law."

The Federal Trade Commission Act of 1914 established Federal authority for regulation of false advertising in interstate commerce, including advertising of foods for human consumption. The 1938 Federal Food, Drug, and Cosmetic (FD&C) Act gave the FDA new and more effective authority over health food claims. Under the FD&C Act, a food is considered a drug if therapeutic claims are made for it, and the burden of proving claims fraudulent is less demanding than under the earlier law (Young 1967).

Currently, numerous Government, medical, and consumer-oriented organizations are responsible for preventing and controlling fraud (U.S. Congress 1984b). At the Federal level, the FDA, the U.S. Postal Service (USPS), and the Federal Trade Commission (FTC) have authority to act against various kinds of illicit food and health-related practices. These agencies work cooperatively, and their antifraud activities have become more visible in recent years (Barrett 1985). The regulatory roles of these various Federal agencies are reviewed below.

State enforcement activities against fraud are largely the responsibility of the State attorneys general and offices of consumer affairs and aging. County consumer affairs offices and metropolitan police may also become involved in regulation.

Private agencies and organizations such as the Better Business Bureau, the American Dietetic Association, the American Heart Association, the Arthritis Foundation, the American Cancer Society, the American Medical Association, the National Council Against Health Fraud, and other health professional groups are also active against food fraud. These organizations often maintain informal liaison with each other and actively cooperate with Federal regulatory agencies.

Despite these efforts, misleading claims about foods and nutrients are difficult to regulate. As noted by the 1969 White House Conference on Food, Nutrition, and Health, "No other area of the national health probably is as abused by deception and misinformation as nutrition. Many travesties

cheat the public of enormous sums of money, and of good health as well. Yet the American people falsely believe they are well-protected, both by Government and by the ethics of commerce" (White House Conference 1969).

Not only is regulation difficult because of the complexity of the science base, the ease of exploiting the mails, and the special vulnerabilities of people with health concerns, but in the United States, governments at all levels are limited in what they can do about fraudulent nutrition practices by an obligation to observe the constitutional rights to free speech and a free press. Nutrition information, whether supported scientifically or not, is guaranteed the same protection under the first amendment as any other information (Stephenson 1978; Young 1967). The right to say, write, or publish anything one chooses is protected, as long as it is done without intentional malice (Barrett 1977; Pennington 1984).

Regulatory Roles of Federal Agencies

Food and Drug Administration Authority. The FD&C Act empowers the FDA to prohibit the introduction of any food, drug, device, or cosmetic that is adulterated or misbranded. The Act does not include explicit authority to address health fraud, but many of its general provisions enable actions in these areas. Sections 702–704 authorize the gathering of information about health fraud products and practices through inspections, collection of samples and records of interstate shipments, and gathering of evidence such as photographs and copies of labeling. Many fraud cases are based on misbranding charges resulting from false or misleading labeling of products. Only factual and nonmisleading information is allowed on food labels. Most false promotional claims, therefore, are not made on labels. Instead, they appear in books, lectures, and mass media that are protected by constitutional rights.

The FDA has the authority to use its food additive and drug approval processes to control food products allowed on the market and to remove fraudulent products. Although food products do not need to receive premarket approval as safe for human consumption, some food components need either to be classified as "Generally Recognized As Safe" (GRAS) or to have undergone the required FDA approval process for a food additive. If one or more of a food product's ingredients are subject to these provisions but is neither GRAS nor an approved additive, the product is considered adulterated and therefore illegal.

The FD&C Act defines drugs as articles that are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in hu-

mans. Most fraudulent food products are classified as foods, but when therapeutic claims are made for them, they are also considered to be drugs. The Act's provisions require drug products to have (1) an approved New Drug Application that demonstrates both safety and efficacy for its intended uses and (2) adequate directions for use. If a food product is also classified as a drug and is considered by the FDA to be ineffective for its claimed use, it will not have an approved New Drug Application. For example, if it is promoted for treating a disease that is not amenable to lay diagnosis, it cannot have adequate directions for use and will not be approved. Recently, the FDA proposed a new policy on the appropriate use of health-related messages on food labels (FDA 1987).

Educating the public on health fraud is complementary to the FDA's regulatory activities. The Agency's magazine, *FDA Consumer*, devotes editorial space to health fraud and includes major articles on the subject. In addition, FDA consumer affairs officials across the country conduct a health fraud consumer education program covering foods as well as medical devices and drugs. The objectives of this program are to increase public knowledge and understanding of the FDA's statutory responsibilities and the limitations of the FDA's authority in protecting consumers from misinformation about foods, dietary supplements, nutrition, and other FDA concerns. The program provides guidance to enable consumers to recognize fraud, evaluate product claims, make informed decisions, and register complaints and concerns about fraudulent products.

U.S. Postal Service Authority. The authority of the USPS to control health fraud is based on a general congressional mandate to protect the public from marketing schemes conducted by mail. The purchaser is particularly vulnerable to fraudulent inducements by mail because of the inability to observe the product before payment (U.S. Congress 1984b). Specific authority to protect the mail order consumer is vested in the criminal fraud statute (18 U.S.C. 1341), the administrative false representation statute (39 U.S.C. 3005), and the supporting injunctive statute (39 U.S.C. 3007).

The mail fraud statute provides that any use of the mails in furtherance of an intentional scheme to defraud is punishable by a fine of $1,000 and imprisonment of up to 5 years. Many nutrition-related schemes are prosecuted under the mail fraud statute; they typically involve cure-alls, instant weight reduction techniques, and a variety of substances falsely described as having the ability to cure diseases or disabilities.

The false representation statute mandates that persons offering goods or services for sale through the mail refrain from misrepresenting their prod-

ucts in any material respect. The Mail Order Consumer Protection Amendments of 1983 enhance the effectiveness of the false representation statute and are designed to address the problems of repeat offenders and "fly by night" promoters who advertise a product, take orders, receive payments, and change addresses without delivering any merchandise (Nelson 1984). This new legislation gives the USPS authority to purchase and test without delay any products or services sold through the mail. The 1983 amendments also authorize the USPS to issue cease-and-desist orders. Such actions, however, are limited by the validity of the address given by the manufacturer. A growing number of promoters are advertising toll-free telephone numbers and then delivering products using private parcel delivery services that are not under the USPS jurisdiction (Debrosse 1984).

Upon showing probable cause that a scheme violates the false representation statute, Federal district courts can order the Postal Service to detain mail. Apparent violations of the postal fraud and misrepresentation statutes are investigated by the Postal Inspection Service. Suspected criminal violations are referred to the appropriate U.S. attorney.

Federal Trade Commission Authority. The FTC's authority to act against deceptive food, drug, or other health claims derives from sections 5 and 12 of the Federal Trade Commission Act. Section 5 of the Act identifies unlawful, unfair, and deceptive acts and practices in or affecting commerce. Section 12 of the Act specifically prohibits the use of false advertisements regarding food, drugs, devices, or cosmetics. The Commission can act under one or both sections to halt certain food, drug, or other health care acts or practices.

Deceptive as well as fraudulent food, drug, and health care advertising claims that induce people to purchase ineffective cures and nostrums are important areas of FTC enforcement activity (Crawford 1984). A special effort has been instituted to monitor claims for health care products, many of which may fit into the fraud category. The FTC has implemented special programs to monitor the advertising of some types of fraudulent products in tabloid publications and health magazines directed toward nontraditional disease treatments. The FTC also monitors radio and television networks and major newspapers and magazines to identify targets for Commission action. Such targets are also identified through ongoing contacts with other State and Federal officials and private groups.

Key Issues

- Health Consequences of Fraud
- Economic Consequences of Fraud

Purveyors of nutrition fraud capitalize on people's desire to be healthy and on the lack of certainty in many areas of nutrition and health. Although the public may be injured by deceptive food claims, there are no reliable statistics on the extent of health and nutrition fraud in this country (Young 1984).

Health Consequences of Fraud

Nutrition fraud may lead to deleterious health consequences, caused by the failure to seek legitimate medical care, by potentially toxic components of foods and products, by nutrient toxicities and deficiencies, by diversion of monies from essential treatments, and by interference with sound nutrition education.

Failure to Seek Legitimate Medical Care

Public health and safety can be jeopardized by false promises that divert or deter individuals from pursuing sound forms of medical treatment or that encourage them to abandon beneficial therapy for a disease (McBean and Speckmann 1974). Fraud may encourage people to reject legitimate medical advice and to practice inappropriate self-medication that is less likely to be helpful, and more likely to be directly harmful, than medical technology based on a sound understanding of human biology and nutrition.

The FDA's annual reports document numerous instances of fraud-induced failure to obtain appropriate health care (Young 1985). Because early detection and treatment improve the prognosis for many illnesses, unproven "nutritional" therapies may unnecessarily delay beneficial intervention (Brown 1984). Some diet regimens recommended by health faddists to treat cancer, for example, are so nutritionally deficient or toxic that adherence to them has caused death or serious illness (U.S. Congress 1984b). Although evidence is increasing that a proper diet may reduce the risk of developing some forms of cancer, no diet or supplement can yet be guaranteed to protect against—or to treat—these conditions.

Promotions of foods designed to treat various disorders are often targeted to vulnerable populations (U.S. Congress 1984a). The use of these food

products accomplishes little besides increasing the market share of the company making the fraudulent claims.

Potentially Toxic Food Components

Public injury can occur when foods and unproven remedies are toxic. Just because a substance occurs naturally in food does not mean that it is necessarily safe (Herbert and Barrett 1981). Many of the chemicals known to be present in herbs, for example, have never been tested for safety (Larkin 1983). Some plant foods contain potentially unsafe, pharmacologically active ingredients such as aflatoxin, one of the most potent carcinogens known. Few buyers are aware of the harmful components in these products (Anonymous 1979).

There has been a substantial increase in the use of herbal products (Siegel 1976) that may contain pharmacologically active ingredients that can possibly produce undesirable effects such as an increase in blood pressure (Brody 1978). Occasional poisonings and clinical intoxications are reported after the use of herbal tea products (Huxtable 1980; Siegel 1976; Larkin 1983). Ginseng, one of the most popular herbs in the United States, has been reported to produce estrogen-like effects in some people (Siegel 1979; Greenspan 1983). From present evidence, it cannot be concluded that all herbal products can be consumed safely over extended periods of time (Larkin 1983).

Potentially harmful ingredients have been identified in samples of other food supplements, such as an estrogenic hormone in commercial alfalfa tablets (Elakovich and Hampton 1984), arsenic in kelp tablets (Walkiw and Douglas 1975), and cadmium in dolomite (Boulos et al. 1983). Potentially toxic amounts of lead in bonemeal and dolomite have caused the FDA to caution against use of these products, particularly by pregnant women and young children (FDA 1982).

Nutrient Toxicities and Deficiencies

Frauds and fads may induce nutrient toxicities or deficiencies (Henderson 1974). Many people take vitamins as self-medication for the prevention or treatment of health problems (Levy and Schucker 1987). An estimated 40 percent of U.S. adults consume vitamins, minerals, and/or miscellaneous dietary components as supplements. The use of these products varies with such demographic factors as geographic region, education, income, and race. Women are more frequent consumers than men. Intake ranges widely, extending up to 10 to 50 times the Recommended Dietary Allowance

(RDA) for individual nutrients (Stewart et al. 1985). Data from the National Health and Nutrition Examination Survey suggest that individuals with better nutritional intake patterns are the predominant users of supplements. Thus, supplement users may not be the individuals most in need of them (Shank and Wilkening 1986).

Nutrient supplements are usually safe in amounts corresponding to the RDA, but the RDA's are already set to provide maximum benefit consistent with safety. Thus, there is no reason to think that larger doses will improve health in already healthy people, and excess intake can be harmful. Megadose intakes (often defined as 10 or more times recommended levels) can have seriously harmful effects (Rudman and Williams 1983; Herbert 1980; Dubick and Rucker 1983a). The toxicity of high dosages of vitamins A and D is well established (DiPalma and Ritchie 1977). Although water-soluble vitamins are relatively nontoxic, some of them also are reported to produce toxic effects at high doses (Alhadeff, Gualtieri, and Lipton 1984). Because the margin is narrow between a safe and a toxic dose of most trace elements, excessive supplementation with these substances may be particularly hazardous.

Excessively restrictive dietary practices can also induce serious medical problems or even death. Popular weight reduction products, for example, provide very low daily calorie intakes (Newmark and Williamson 1983b). Because such products have been associated with the deaths of some young women, the FDA now requires warnings on labels to alert consumers of the potential of such products (FDA 1984).

Many popular diets are potentially harmful because they eliminate food groups or severely limit food variety (Council on Foods and Nutrition 1973; Barrett 1981; Willis 1982). Examples include the Atkins, Stillman, and other weight reduction diets that drastically reduce carbohydrate intake and the Beverly Hills Diet, which advocates excessive fruit consumption. Fad diets seldom produce long-lasting weight control (Newmark and Williamson 1983a). Highly restricted diets, such as the more extreme forms of Zen macrobiotics, have led to nutritional deficiencies, starvation, and even death in a few individuals (Council on Foods and Nutrition 1971; Newmark and Williamson 1983a). Such diets also have been associated with retarded fetal development and childhood growth or other nutritional problems in young children (Dwyer et al. 1983).

Interference With Sound Nutrition Education

Commercial interests have capitalized on a heightened public awareness of nutrition and health issues, but much of the public cannot evaluate the validity of available weight reduction schemes, supplements, and services (White and Selvey 1982). Self-appointed health and nutrition advisors have expressed distrust of proven public health measures such as fluoridation and pasteurization and, instead, have promoted treatment alternatives that are not supported by accepted medical practice (Jarvis 1983). The public also may be misled by extravagant claims of health benefits from the use of certain foods or nutrient supplements (Council on Scientific Affairs 1979; White and Selvey 1982).

Economic Consequences of Fraud

Impact on Consumers

People experience economic injury when purported remedies and cures do not work, are untrue, or are greatly exaggerated or when purchased products are not needed. Fraudulent products are known to be extremely profitable for those who sell them. A 1984 report by the Subcommittee on Health and Long-Term Care of the Select Committee on Aging, for example, stated:

> . . . the practice of quackery . . . now invades nearly every aspect of our lives, and, at points, attracts adherents with . . . a keen sense of the vulnerability of potential customers, the limitations of the law and the profitability of exploiting both. Quackery has become big business. Twenty-five years ago, quackery was said to cost $1–2 billion a year. Today, it probably totals at least $10 billion (U.S. Congress 1984b).

This estimate is probably conservative because it does not include the sales of weight reduction pills and diet cures, which alone are estimated to cost $5 to $6 billion yearly (Halamandaris 1984).

Many fraudulent products and services can be very costly yet are promoted as having nutritional or health benefits that have not been substantiated in the scientific literature (Meister 1984; Dubick and Rucker 1983a, 1983b; Herbert 1980; Larkin 1984; Anonymous 1985). Examples include:

- Superoxide dismutase (SOD) and nucleic acids (RNA and DNA) as antiaging remedies.
- Bee pollen as a source of youth and health and as an energy pill for athletes.

- Lecithin in combination with vinegar, kelp, and vitamin B_6 for the prevention and cure of heart disease and as a diet aid.
- Spirulina and glucomannan as diet aids.
- Ginseng as a panacea for many ailments.
- Alfalfa tablets for treatment of arthritis.
- Aloe vera for treatment of an array of unrelated medical conditions.
- Para-aminobenzoic acid (PABA) as an essential or curative nutrient.
- Pangamic acid, the so-called vitamin B_{15}, as an essential nutrient.
- Hair analysis for determination of nutritional status.
- Oral chelation products as treatment for heart disease.

The public incurs other costs because many products labeled as "natural" or "organic" sell for higher prices than their "regular" counterparts, although their special benefits are not generally demonstrable (Gourdine, Traiger, and Cohen 1983). "Natural" vitamins, for example, often sell at twice the price of synthetic products even though they are chemically identical. In some such products labeled as "natural," only a minor fraction of the vitamin is actually derived from natural sources (Seneker 1979; FDA 1979).

Although many food supplements are of unproven benefit, the food supplement industry has expanded rapidly over the past several years (Stewart et al. 1985). Consumer spending for the entire nutritional supplement market—which includes nonprescription vitamins, minerals, and other products—was estimated to approach $2.7 billion for 1983, an increase of 5.3 percent over the 1982 sales volume (Ehrlich 1985).

Impact on Responsible Industry

Nutrition fraud can also have an adverse economic impact on responsible members of the food industry. The false claims made by food faddists and promoters of fraudulent products cause confusion in the minds of consumers and may result in a distrust of the regular food supply and its products—a distrust that may paradoxically increase the frequency and severity of poor nutritional practices and food quackery. Although regulatory agencies are responsible for maintaining a fair marketing environment, the cost of combatting fraudulent activities often exceeds the available regulatory resources.

Summary

In summary, nutrition fraud in its various forms is prevalent in this country. Health professionals and other authorities consider it to be a significant public health problem, as well as one that can affect economic well-being. Furthermore, the use of sophisticated communication marketing techniques has substantially increased public exposure to nutrition fraud.

Implications for Public Health Policy

Dietary Guidance

General Public

Running counter to—and sometimes capitalizing on—legitimate gains in scientific understanding of the relationships between diet and health, food faddism and nutrition fraud are increasingly prevalent in the United States. Although most of the adverse consequences of this trend are economic, fraud can cause significant health consequences to individuals as a result of direct toxicity and as a result of failure to seek appropriate medical care or to engage in genuinely healthful dietary practices. Cooperative educational efforts by Government, health professionals, and the private sector, including the news media, are needed to expose emerging fads and frauds before they are widely accepted. One approach to this end is general public education to reinforce the basic principles of sound nutrition as stated in the *Dietary Guidelines for Americans*. Another approach is to direct the public to responsible sources of nutrition information.

Special Populations

Special efforts should be directed toward older persons, who are the target of much nutrition fraud. Cooperative educational efforts by Government and the private sector, such as current collaborations of the FDA with the Pharmaceutical Advertising Council and the Council of Better Business Bureaus, can provide effective support for Government enforcement programs. People with chronic debilitating illnesses—such as cancer, coronary heart disease, arthritis, or Alzheimer's disease—may be especially susceptible to fads and frauds, and health providers should be informed about the most common schemes in each area and should be involved in the effort to forewarn patients.

Nutrition Programs and Services

Food Labels

Food labels should contain information about nutrient content that is provided in a straightforward, effective, and efficient way. Should a health-claims-approved program be implemented, claims for a particular product should be presented in a manner that is most informative, scientifically sound, and not misleading to consumers.

Food Services

Education provided in the context of food services should emphasize general principles of sound nutrition for the general public and inform people about the nature of and problems associated with common nutritional frauds and fads.

Food Products

The FDA is charged with ensuring that misleading claims about foods are not presented to the public and that specific foods are not promoted as therapeutic or preventive agents unless there is adequate documentation to support such claims. Continued support for, and vigilence by, the FDA is important in this regard. A cornerstone of this effort is close coordination of regulation and enforcement activities of the various agencies at the Federal, State, and local levels through coalitions developed against nutrition fraud.

Research and Surveillance

Research and surveillance issues of special priority related to the issue of food fads and frauds should include investigations into:

- Frequency and type of fraudulent claims and harmful effects.
- Establishment of safe levels of essential nutrients as well as other components in food.
- The personal and behavioral factors that enhance response to certain unscientific claims and ways to counter them.
- The level of use of vitamin, mineral, and food components that may induce nutrient toxicities or deficiencies by the general public.

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