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