10th Special Report to the U.S. Congress on

Alcohol and Health

HIGHLIGHTS FROM CURRENT RESEARCH

From the Secretary of Health and Human Services

June 2000

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism

10th

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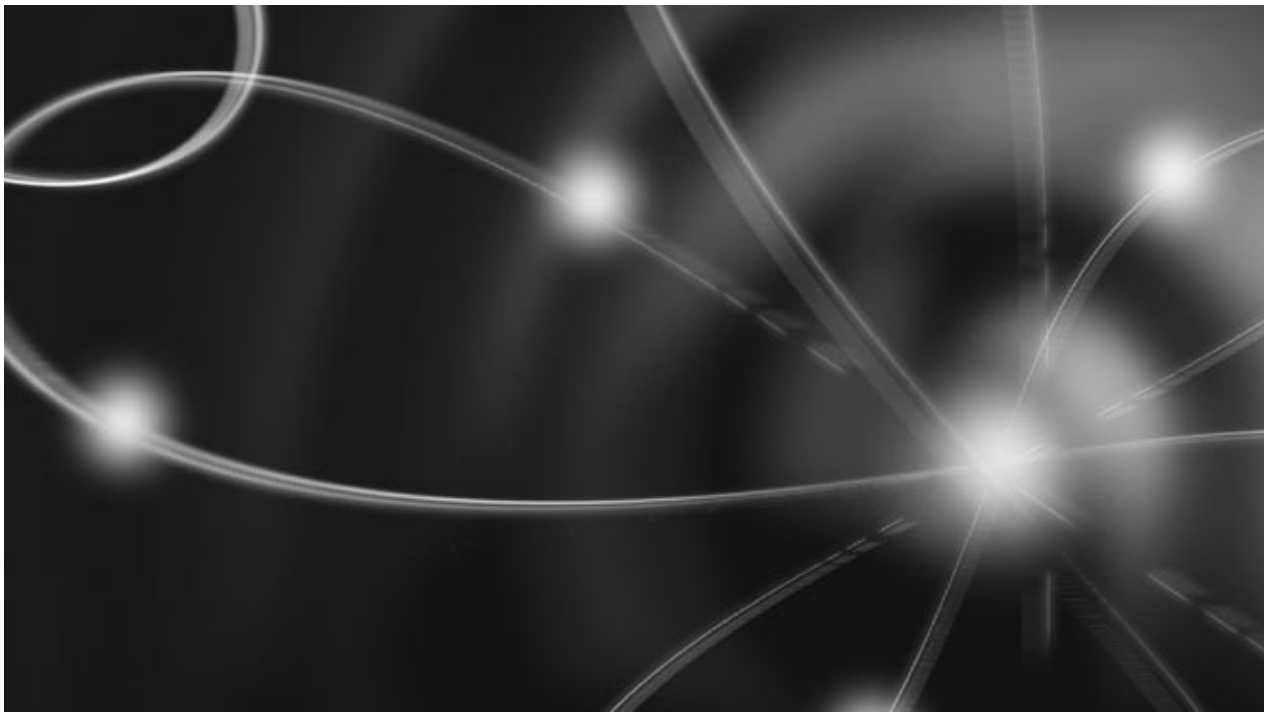

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Foreword

I am pleased to present the *Tenth Special Report on Alcohol and Health* to the U.S. Congress, and through them to the American people.

Alcohol problems, both those of individuals and those that affect society at large, continue to impose a staggering burden on our Nation. Domestic violence, child abuse, fires and other accidents, falls, rape, and other crimes against individuals such as robbery and assault—all are linked to alcohol misuse. Alcohol misuse also is implicated in diseases such as cancer, liver disease, and heart disease. Although often not aware of it, everyone shares a portion of this burden. For example, an estimated 20 to 40 percent of patients in large urban hospitals are there because of illnesses that have been caused or made worse by their drinking. This means that out of every 100 patients in such hospitals, *almost half* may be there because of their alcohol use. Each of us shares the price of these illnesses through rising health care costs. Because one in four children under the age of 18 lives in a household with one or more family members who are alcohol dependent or who abuse alcohol, our Nation will continue to be robbed of its future. As these children grow up, they too will be at risk for continuing the cycle of alcohol abuse and dependence that has plagued too many of our citizens for too long.

As overwhelming as these facts are, the real tragedy is that many people do not yet understand that alcohol problems can yield to scientific investigation and medical intervention in the same way as other health conditions, and in many cases more successfully.

The research findings presented in the *Tenth Special Report to the U.S. Congress on Alcohol and Health* clearly demonstrate that continued support for alcohol research, and the use of findings from research in prevention and clinical applications, offer the best hope for reducing the costs we all pay for alcohol problems. I commend it to your attention.

Donna E. Shalala
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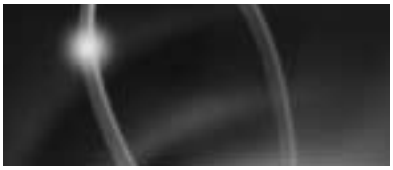
Preface



During the latter half of the twentieth century, we witnessed an unparalleled era of progress in medical science. Among other important scientific advances, we discovered the genetic code and are well on our way toward mapping the entire human genome, we began to explore how our brains work in concert with other body systems to promote or to impede health, and we developed increasingly sophisticated medical devices and technologies that allow us to look at the actual functioning of the myriad systems that make up human beings.

The *Tenth Special Report to the U.S. Congress on Alcohol and Health* presents significant new scientific findings about alcohol abuse and alcoholism since the last Special Report, issued in 1997. These findings clearly demonstrate that alcohol investigators working in fields as diverse as epidemiology, genetics, neuroscience, toxicology, prevention, and treatment are using the very latest tools and techniques of science to expand our knowledge of how to prevent, reduce, and treat alcohol problems. Because alcohol use problems exact such a personal, social, and economic toll on the American people—an estimated 100,000 lives and $184.6 billion annually—the scientific progress described in the *Tenth Special Report* is heartening.

As important as this progress is for those whose lives have been affected by alcohol use, I believe that the *Tenth Special Report* serves a greater purpose. Science does not happen in a vacuum. Rather, it is a cumulative process that builds upon the knowledge developed by many scientists working in many different areas of investigation. Therefore, what is discovered about one disease or health condition may very well provide important clues about other diseases and conditions, clues that will help in the development of medications, treatments, and preventive approaches that can be widely applied. Because alcohol affects virtually all body systems and because alcohol use problems affect all levels of human interaction, the alcohol research field represents, in many respects, a microcosm of science in its entirety. Thus, the findings described in the *Tenth Special Report* about genetics, neural circuitry, the effect of the environment on gene expression, fetal development, cognition, psychological therapies, prevention and education, and treatment contribute significantly to the knowledge we need to solve not only the problems associated with alcohol abuse and alcoholism, but also the problems of human biology and behavior in general.

I would like to commend the scientists who participated in the development of the *Tenth Special Report* and the staff of the National Institute on Alcohol Abuse and Alcoholism for their efforts to bring this important information to the attention of the U.S. Congress and the American people.

Ruth Kirschstein, M.D.
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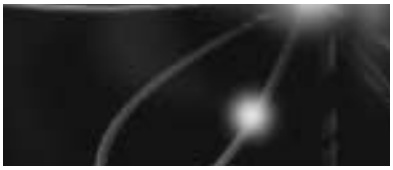
Introduction



The first *Special Report on Alcohol and Health* was presented to the U.S. Congress in 1971. In that report, and in each subsequent one, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) summarized for the Congress—and the American people—the cumulative body of alcohol research findings in each area of investigation. For this, our 10th edition of the Special Report, we found ourselves in a pleasant, if somewhat daunting, position. The breadth and scope of alcohol research has grown so tremendously that summarizing the total body of alcohol research in one document is no longer manageable; so we have chosen to present the findings from alcohol research in a new way—to summarize what is known in a particular area and to describe in greater detail significant research findings that have been reported since the *Ninth Special Report*. And, in the best tradition of the *Special Reports on Alcohol and Health*, this 10th edition continues to provide both extensive information on alcohol use problems and ample cause for hope that we are well on the way to preventing and effectively treating them.

Alcohol is widely used in our society. Most individuals who use alcohol drink in ways that do not increase risk for alcohol use problems. Some, however, drink in ways or at times during their life course that increase risk to themselves or others. Still others who use alcohol may derive a health benefit from its use. Defining precisely who is at risk for alcohol use problems and assessing the risks versus benefits of alcohol use are the first steps toward providing accurate public health information and designing effective interventions to reduce alcohol use problems. The *Tenth Special Report* presents important new findings about biological and behavioral factors that affect the risks and benefits of drinking over the life span.

Perhaps the single greatest influence on the scope and direction of alcohol research has been the finding that a portion of the vulnerability to alcoholism is genetic. This finding, more than any other, helped to establish the biological basis of alcoholism. It also provided the basis—and justification—for much of the progress in genetics, neuroscience, and neurobehavior described in the *Tenth Special Report*. Today we know that approximately 50 to 60 percent of the risk for developing alcoholism is genetic. Genes direct the synthesis of proteins, and it is the proteins that drive and regulate critical chemical reactions throughout the human body. Genetics, therefore, affects virtually every facet of alcohol research, from neuroscience to Fetal Alcohol Syndrome. It is clear from the findings presented in the *Tenth Special Report* that although much remains to be discovered, progress has been made toward understanding how genes are involved in the etiology of alcohol use problems, including how genes interact with other genes and with the environment to produce disease.

The progress made in the neurosciences over the last two decades has been spectacular. Alcohol investigators have taken full advantage of this progress by applying neuroscience techniques to the study of alcohol use problems. As a result, our understanding of the neural processes that underlie alcohol-seeking behavior and of how alcohol's actions in the brain are related to the phenomenon of addiction has grown dramatically. Recent progress in neuroscience research described in the *Tenth Special*

Report has yielded information critical to characterizing some of the cellular and molecular processes involved in alcohol use and has helped associate these processes with the behavioral and physiologic manifestations of alcohol use and abuse. One important tool used in both genetics and neurobehavioral research is the animal model. Alcohol scientists have applied molecular biology techniques to develop a number of important animal models that allow the study of the genes associated with traits that might influence alcohol-related behaviors. Findings from studies using both vertebrate and nonvertebrate animal models and other study results concerning the etiology of alcohol use problems are discussed in the *Tenth Special Report*.

Although the toxicology of alcohol—how alcohol damages the body—was one of the first areas in alcohol research to be studied, the acceptance of the biological foundations of alcoholism and the subsequent increase in alcohol-related biological research helped to focus scientific attention on the mechanisms by which this damage occurs. As described in several chapters of the *Tenth Special Report*, alcohol research scientists have uncovered new information about the kinds of damage that alcohol exposure can cause to the brain, both during prenatal development and later in life, and to other major body organs. More important, there is a very good accounting of the progress that alcohol scientists have made toward understanding how this damage occurs. It is knowing the "how" that has the potential to produce therapeutic interventions to limit or ameliorate many of the alcohol-related health consequences.

Limited in the past, research on prevention is coming into its own. The findings from prevention research applied to various public policies already have been shown to save lives. New approaches to school-based and community prevention are demonstrating that well-planned prevention programs based on rigorously studied and validated models can reduce the magnitude and extent of our Nation's alcohol-related problems. Prevention research is also examining the role that advertising plays with respect to alcohol use and abuse.

The main goal of alcoholism treatment is to help alcoholics maintain sobriety. The *Tenth Special Report* highlights the progress that has been made toward developing both behavioral strategies and medications to help achieve this goal. Some of the most compelling questions about treatment have to do with factors that help to make treatment services effective. Some studies have shown significant reductions in drinking following treatment with extensively tested and refined behavioral therapies. Other strategies, involving brief interventions in primary care settings, have proved to be effective in reducing alcohol consumption in persons drinking at levels associated with negative health consequences. Because many individuals continue to experience problems with alcohol after treatment, there is a need to further improve treatment efficacy.

One of the principal payoffs of biological research in genetics and neuroscience is the potential for developing medications to treat a variety of alcohol use problems. Neuroscience research already has provided the groundwork for new medications for treating alcoholism. Researchers now are looking for new medications that target the mechanisms of the addiction itself, such as drugs that interfere with the reward properties of alcohol or craving, which are thought to be major factors in relapse. It is likely that no one medication will be effective for everyone nor that there will be the proverbial "silver bullet" of pharmacotherapies for alcoholism. Just as there are different types of medications with different mechanisms of action to treat complex diseases like diabetes, it is likely that there will be a range of medications, coupled with verbal therapies, available to clinicians.

Last, like everyone else during this ending of one century and beginning of a new century, I would like to share my thoughts on where we are heading in alcohol research. Finding the genes for alcoholism is probably one of the most important goals in alcohol research. However, it is the

beginning of the story rather than the end. For this information to be of practical use, we must understand how biology and behavior interact to produce disease. There is a welcome trend in the alcohol field toward reciprocal work between the biological and behavioral sciences. The potential success of this type of collaboration has been well demonstrated by major research efforts such as the Collaborative Study on the Genetics of Alcoholism, which involved both biological and behavioral science and scientific principles. Other examples of this type of work can be found in research on the effects of alcohol on the fetus, where there are excellent behavioral studies of children with Fetal Alcohol Syndrome and other alcohol-related birth defects as well as detailed information from imaging studies about the tremendous structural changes in the brains of children exposed to alcohol in the womb. We also are learning about the proper connectivity among neurons. In this work it appears that alcohol actually prevents the appropriate expression of certain genes.

The trend toward studying the whole human animal, not just its genetic or neural parts, will continue to be advanced, I believe, by a rejection of the "reductionist" view, which seeks to define humankind in terms of its genes, and acceptance of the tenet that genes are not (or even mostly) destiny, just as humankind is not just the sum of its neurons and circuits.

That we are continuing to expand our knowledge of alcohol use problems is clear from the material presented in this Special Report. The scientists, and the NIAAA staff who have worked so diligently to present the *Tenth Special Report* to the Congress, have my thanks for their efforts. The task now for each of us who is concerned about the impact of alcohol abuse and alcoholism on our society is to accelerate the pace of research that has enabled us to come this far to ensure that the new millennium brings new successes.

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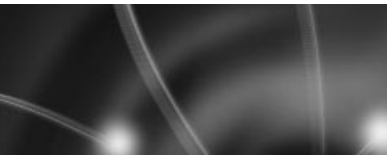
Drinking Over the Life Span: Issues of Biology, Behavior, and Risk



Forty-four percent of the adult U.S. population (aged 18 and over) are current drinkers who have consumed at least 12 drinks in the preceding year (Dawson et al. 1995). While most people who drink do so safely, the minority who consume alcohol heavily produce an impact that ripples outward to encompass their families, friends, and communities. The following statistics give a glimpse of the magnitude of problem drinking:

- *Approximately 14 million Americans—7.4 percent of the population—meet the diagnostic criteria for alcohol abuse or alcoholism (Grant et al. 1994).*
- *More than one-half of American adults have a close family member who has or has had alcoholism (Dawson and Grant 1998).*
- *Approximately one in four children younger than 18 years old in the United States is exposed to alcohol abuse or alcohol dependence in the family (Grant 2000).*
- *Of 11.1 million victims of violent crime each year, almost one in four, or 2.7 million, report that the offender had been drinking alcohol prior to committing the crime (Greenfeld 1998).*
- *Traffic crashes involving alcohol killed more than 16,000 people in 1997 alone (National Highway Traffic Safety Administration 1998).*
- *The estimated economic cost of alcohol abuse was $184.6 billion for 1998 alone, or roughly $638 for every man, woman, and child living in the United States that year (Harwood et al. 2000).*

Alcohol consumption has consequences for the health and well-being of those who drink and, by extension, the lives of those around them. The first section in this chapter, "Measuring the Health Risks and Benefits of Alcohol," surveys the health effects of alcohol, including the relationship between alcohol and cardiovascular risk. In addition, the section addresses some of the new approaches with which scientists are attempting to draw a more informative picture of how alcohol affects health. Investigators are, for example, analyzing alcohol-related mortality in terms of number of years lost as well as number of lives, measuring disability as well as illness and mortality, and looking at populations as well as individuals.

Beginning in early childhood and continuing throughout life, many factors interact to affect a person's risk of developing alcohol-related problems. The second section in this chapter, "Alcohol Involvement Over the Life Course," describes research on the dynamic

interplay of social, psychological, and biological influences on the development of drinking behavior across the life span. Recent studies indicate, for example, that certain childhood traits are predictive of adult alcohol disorder. This research suggests that the process by which early risk leads to a clinical disorder involves biologically based vulnerability, psychosocial factors that support the vulnerability, and an environment that makes alcohol available for use. Developmental researchers seek to understand the causes of alcohol problems by examining interactions of multiple factors that emerge and change or remain stable over time and by identifying common underlying factors that place some subgroups at higher risk than others.

Studies show that alcohol is far more likely than other drugs to be involved in substance-related violence. As noted in the third section in this chapter, "Alcohol and Violence," in 25 percent of all incidents the offender used alcohol alone (20 percent) or in combination with other drugs (5 percent), whereas in only 5 percent of incidents did the offender use only drugs other than alcohol (Greenfeld 1998). Research has been advancing beyond confirmation of basic relationships between alcohol and violence toward an examination of the role of personality and situational factors that interact with both alcohol use and violence. Areas of research focus include youthful perpetrators, alcohol use by victims of violence, alcohol availability, and environments in which violence occurs. In addition, current research seeks to determine whether alcohol use is not merely associated with, but instead is perhaps a cause of, violence.

The research reviewed in this chapter represents a wide spectrum of approaches to understanding the causes and consequences of alcohol use and abuse. These research findings can help shape the efforts of communities to reduce the negative consequences of alcohol consumption, assist health practitioners in advising consumers, and help individuals make informed decisions about drinking.

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Measuring the Health Risks and Benefits of Alcohol

Over the years, scientists have documented the effects of alcohol on many of the body's organ systems and its role in the development of a variety of medical problems, including cardiovascular diseases, liver cirrhosis, and fetal abnormalities. Alcohol use and abuse contribute to injuries, automobile collisions, and violence. Alcohol can markedly affect worker productivity and absenteeism, family interactions, and school performance, and it can kill, directly or indirectly. On the strength of this evidence, the United States and other countries have expended considerable effort throughout this century to develop and refine effective strategies to limit the negative impact of alcohol (Bruun et al. 1975; Edwards et al. 1994).

In the past two decades, however, a growing number of epidemiologic studies have documented an association between alcohol consumption and lower risk for coronary heart disease (CHD), the leading cause of death in many developed countries (Chadwick and Goode 1998; Criqui 1996*a*,*b*; Zakhari 1997). Much remains to be learned about this association, the extent to which it is due specifically to alcohol and not to other associated lifestyle factors, and what the biological mechanisms of such an effect might be.

This section reviews information gained from epidemiologic studies on the health effects of alcohol use, with emphasis on new evidence. These studies focus on the extent to which alcohol consumption is associated with an increase or decrease in the risk of disease or death (Rothman and Greenland 1998). Many of the studies considered in this section use the traditional epidemiologic approach of relating average alcohol consumption to health outcomes (Rehm 1998). In light of recent research focusing on the patterns of alcohol consumption, such as daily drinking versus binge drinking, this section also discusses the impact of these patterns on health-related consequences (Rehm et al. 1996).

Definitions Related to Drinking

Studies investigating the health effects of alcohol vary in their definitions of "low," "moderate," and "heavy" drinking. According to the *Dietary Guidelines for Americans*, issued jointly by the U.S. Department of Agriculture and the U.S. Department of Health and Human Services, moderate drinking is no more than two standard drinks per day for men and no more than one per day for women (U.S. Department of Agriculture 1995). The National Institute on Alcohol Abuse and Alcoholism further recommends that people aged 65 and older limit their consumption of alcohol to one drink per day. Information on drinking levels as they are defined in the individual studies cited in this report can be found in the original references.

Finally, this overview addresses some of the approaches with which scientists are attempting to draw a more revealing and informative picture of how alcohol affects health, for example, by looking at mortality in terms of number of years lost as well as number of lives, measuring disability as well as illness and mortality, and looking at populations as well as individuals. Alcohol consumption has health consequences beyond the individual who is consuming alcohol, such as damage suffered by others as a result of alcohol-related motor vehicle collisions. Specific consequences for society are covered in the subsequent section on violence and in the chapters on economics and on prevention.

Topics not considered here include skeletal health and osteoporosis, diabetes, and cholelithiasis (gallstones). Definitive evidence has thus far not emerged from epidemiologic studies as to whether low to moderate alcohol consumption protects against, increases, or has no effect on the risk for these conditions. (The chapter on medical consequences provides more detailed discussions of individual health consequences of alcohol and of research aimed at revealing biological mechanisms for the alcohol-health connections suggested by epidemiologic studies.)

The information gained in the studies described here will be important not only to policy makers but also to health professionals and the individuals they advise with regard to alcohol's potential impact on health.

Risks and Benefits of Alcohol Consumption: Physical Health

Cardiovascular Diseases

Cardiovascular diseases account for more deaths among Americans than any other group of diseases. Of all causes of death, CHD is first, and stroke is third after cancer (U.S. Department of Health and Human Services [USDHHS] 1995). The role of alcohol as both a risk factor and a potential protective factor for cardiovascular diseases and the mechanisms that underlie the impact of alcohol on the cardiovascular system have been reviewed extensively in previous reports to Congress (see, for example, National Institute on Alcohol Abuse and Alcoholism [NIAAA] 1997) and in a comprehensive research monograph (Zakhari and Wassef 1996), and are considered as well in the chapter on medical consequences. The discussion below highlights recent findings concerning the role of alcohol in CHD, stroke, hypertension, and peripheral vascular disease.

Coronary Heart Disease. Several large prospective studies have reported a reduced risk of death from CHD across a wide range of alcohol consumption levels. (See the boxes "The Study of Risk" and "Does Abstaining Increase Risk?") These include studies among men in the United Kingdom (Doll et al. 1994), Germany (Keil et al. 1997), Japan (Kitamura et al. 1998), and among more than 85,000 U.S. women enrolled in the Nurses' Health Study (Fuchs et al. 1995). In research studies, definitions of moderate drinking vary.

How Much Is a Drink?

In the United States, a drink is considered to be 0.5 ounces (oz) or 15 grams of alcohol, which is equivalent to 12 oz (355 milliliters [mL]) of beer, 5 oz (148 mL) of wine, or 1.5 oz (44 mL) of 80-proof distilled spirits.

However, in these studies, most, if not all, of the apparent protective effect against CHD was realized at low to moderate levels of alcohol consumption. (In the last study cited above, for example, "light to moderate" drinking ranging from one to three drinks *per week* to one to two drinks *per day* was associated with a reduced risk of death from cardiovascular diseases.)

Similarly, a meta-analysis that pooled data from 19 cohort studies and 6 case-control studies found that although the risk of death from CHD was reduced at all levels of alcohol consumption, the maximum reduction in risk occurred at low levels (English et al. 1995). Other studies also have shown that drinking more is not associated with any additional reduction in risk (Maclure 1993).

An analysis of data from a 9-year follow-up of 490,000 Americans in the Cancer Prevention Study II (Thun et al. 1997) showed that, compared with abstainers, both men and women who consumed alcohol had a 30 to 40 percent lower risk of death from all cardiovascular diseases, with little relationship to the amount consumed. The reduced risk of death from CHD was especially marked among people at particular risk for cardiovascular diseases.

In addition to a reduced risk of heart disease death, several large studies have found a decreased incidence (number of new cases) of CHD in people consuming alcohol at low to moderate levels. For example, an analysis of data from the 1988 National Health Interview Survey indicated that both men and women had a reduced risk of heart disease at lower levels of drinking (the risk increased at drinking levels above five drinks per day for men and two drinks per day for women) (Hanna et al. 1997).

Follow-up of another large U.S. survey, the National Health and Nutrition Examination Survey I (Rehm et al. 1997*b*), found that, after an average of nearly 15 years of follow-up, the incidence of CHD in men who drank was lower across all levels of consumption than in nondrinkers. Incidence also was reduced among women, but only in those consuming low to

The Study of Risk

Epidemiologic research often uncovers evidence pointing to specific lifestyles, toxins, characteristics, or other factors that may make an individual or a population more or less likely to develop a given disease or to adopt a particular behavior. This likelihood is called risk, and the factors contributing to it are called risk factors. Factors that appear to reduce risk are called protective factors.

Researchers seek to identify, define, and study risk and risk factors for several reasons: to find out which individuals or groups are most likely to develop a disease; to gain an understanding of what may cause a disease; and, with that information, ultimately to be able to develop strategies to prevent or cure a disease.

Much of our understanding of how alcohol affects health and disease and society at large comes from epidemiologic studies, which compare various groups of persons who share common characteristics. Observations and data are collected at several levels: whole populations, groups representing a cross section of the general population, and special groups (for example, premenopausal women). Results of several different studies usually are compared to identify factors that contribute to health and disease and to evaluate the risk associated with those factors. However, estimates of risk arrived at from studying groups of people may not necessarily reflect the risk of a particular individual.

Defining Risk

Risk is the estimated likelihood of a certain outcome, such as the development of heart disease or colon cancer. Disease risk is related to certain characteristics, such as gender or age. For example, cancers of the breast and prostate are considered diseases of older age. Thus, the risk or likelihood of developing one of these cancers increases with age.

A multitude of factors can influence the risk of developing certain diseases. For example, smoking increases the risk for lung cancer, and high cholesterol is a risk factor for the development of heart disease. In contrast, regular physical activity or exercise lowers the risk for heart disease.

Types of Risk

Three types of risk are commonly used in studying health and disease: absolute risk, relative risk, and attributable risk. *Absolute risk* refers to the rate at which a disease (or mortality from that disease) occurs in the general population. Absolute risk is expressed as the number of cases in a specific group within a specific time period (for example, 50 cases of a given disease per 100,000 Americans occur annually) or as a cumulative risk up to a certain age. One well-known example of cumulative absolute risk is the often-cited statistic that breast cancer affects one in eight women in the United States. This number actually refers to the likelihood that a non-Hispanic white woman who lives to age 85 will develop breast cancer at some point during her lifetime.

A second type of risk, *relative risk*, is used to define the strength of a relationship between a risk factor, such as alcohol intake, and the occurrence of disease. A relative risk of 1.0 is the benchmark against which risk factors or protective effects are measured. A relative risk of 1.0 therefore reflects the rate of occurrence of disease in the absence of any risk factor (for example, the frequency of a disease among abstainers). (Another statistical term, *odds ratio*, is used to estimate relative risk under certain conditions.) Relative risks below 1.0 imply a protective effect in comparison with the reference category, often abstainers. A relative risk of, say, 0.5 for three alcoholic drinks per week and occurrence of a particular disease suggests that consuming that amount of alcohol halves the risk of developing that disease. In contrast, a relative risk of 2.0 suggests a doubling of risk. In general, the higher the relative risk, the stronger the evidence not only for increased risk but also for a causal relationship. Not all relative risks of equal value are equivalent in importance, however. For example, small relative risks may be of great importance to public health if large numbers of persons in the population are affected.

The third type of risk, *attributable risk*, considers the amount of disease in the population that could be prevented by changes in risk factors.

Epidemiologists also use other terms to describe the impact of alcohol on various aspects of society, such as health, disease, quality of life, mortality, and other factors. These measures are often very useful in developing health policy. Some of these terms include:

- **AAF—Alcohol-Attributable Factor:** AAF's are estimates of the fractions of deaths from disease and injuries that may be due to alcohol.
- **YPLL—Years of Potential Life Lost:** YPLL is an estimate of the extent to which alcohol contributes to premature death; the YPLL usually is calculated by subtracting from a standard age, such as the life expectancy in a particular region.
- **DALY—Disability-Adjusted Life Years:** DALY combines years of life lost and years lived with disability, in which each year lived with disability is adjusted according to the severity of the disability.

(continued on next page)

- **GBD—Global Burden of Disease:** GBD can be used to estimate the extent to which alcohol may account for occurrence of disease worldwide or regionally, or the percentage thereof.

Studying Risk

Researchers use a variety of approaches to study how alcohol and other factors affect health and disease. Sometimes they use *correlation studies*, which investigate alcohol intake and disease occurrence at the population level. In these studies, rates of particular diseases (or mortality) are compared with rates of consumption of alcohol at one point in time or over a period of time. Such comparisons help to identify trends in intake and disease incidence.

Another type of study used to examine the relationship between alcohol and disease risk is the case-control study. In *case-control studies*, individuals with a specific disease (the cases) are compared with a similar group of persons without that disease (the controls). Information about all study participants is then collected, often through interviews. Researchers analyze this information in an effort to find differences between the two groups with respect to alcohol intake. Failure to find such a difference would suggest that alcohol was not a cause of the disease being studied. Case-control studies also are called *retrospective studies* because they examine study participants' past lifestyle, activities, or characteristics with respect to the presence or absence of a disease.

In *prospective cohort studies*, the drinking habits of a large group, or cohort, of initially healthy individuals are examined. The cohort is then followed over time, often for more than 10 years. The relationship between drinking patterns and disease development (or absence) during the follow-up period is then analyzed and compared. Information in cohort studies is often collected using self-administered questionnaires.

Controlled trials are characterized by randomization, in which participants are randomly assigned to an experimental group or a control group. In a *double-blind* controlled trial, neither the volunteers nor the researchers know who belongs to which group. Trials examining the effects of alcohol may not be able to be "blinded," because the odor and taste of many alcoholic beverages are readily identified. Furthermore, because many of alcohol's deleterious effects are well defined, for ethical reasons controlled trials of alcohol in humans are restricted to short-term studies of limited scope (for example, an examination of alcohol's effect on circulating hormone levels within a few hours after administration of alcohol).

More recently, researchers have begun to pool data from several studies and perform what is known as a meta-analysis. *Meta-analyses* often allow modest but potentially important relationships between alcohol (or other factors) and disease to surface. Such relationships may be overlooked because of the relatively small size and inadequate statistical power of an individual study. The power to detect an effect from alcohol and other risk factors generally increases with larger data sets. Meta-analyses ideally include all relevant studies, preferably prospective studies or other studies judged to be well designed and conducted.

moderate levels of alcohol. In fact, an increased risk was observed in women consuming more than 28 drinks per week.

An association between moderate drinking and lower risk for CHD does not necessarily mean that alcohol itself is the cause of the lower risk. For example, a review of population studies indicates that the higher mortality risk among abstainers may be attributable to shared traits—socioeconomic and employment status, mental health, overall health, and health habits such as smoking—rather than participants' nonuse of alcohol (Fillmore 1998*a*).

It is also important to note that, as will be discussed later in this section, the apparent benefits of moderate drinking on CHD mortality are offset at higher drinking levels by increased risk of death from other types of heart disease, cancer, liver cirrhosis, and trauma (USDHHS 1999). The U.S. Department of Agriculture (USDA) and the USDHHS, in the *Dietary Guidelines for Americans*, have defined moderate drinking as one drink per day or less for women and two or fewer drinks per day for men (USDA 1995). In addition, the NIAAA further recommends that people aged 65 and older limit their consumption of alcohol to one drink per day.

Role of Type of Alcoholic Beverage. Some researchers have argued that wine confers special protection against CHD (Goldberg et al. 1995). Others have concluded that any benefit of

alcoholic beverages in protecting against CHD is derived mostly or wholly from alcohol itself rather than from components of particular beverages (Doll 1997; Rimm et al. 1996).

Laboratory studies as well as studies in humans have produced mixed results concerning the effects of wines in reducing the concentration of lipids, or fats, in the blood (for reviews, see Chadwick and Goode 1998; Goldberg et al. 1995) or in raising the blood levels of antioxidants—compounds that counter the effect of destructive by-products of metabolism (Puddey and Croft 1997). A study of Chinese men found no additional reduction in overall mortality associated with drinking rice-fermented wine (Yuan et al. 1997).

Role of Drinking Patterns. The pattern of drinking, rather than the type of alcohol consumed, may help explain how drinking wine might protect against CHD. Researchers have suggested that in some studies the pattern of drinking for wine drinkers differed from the pattern for those consuming other alcoholic beverages (Doll 1997) and that this difference in pattern could explain differences in associated CHD risk (Grønbœk et al. 1995; Klatsky and Armstrong 1993). For example, people usually consume wine in small amounts on almost every day rather than in large amounts on only one or two days a week.

In a review, one researcher concluded that a pattern of frequent drinking may confer some protection against CHD and that large amounts are not needed to achieve a beneficial effect (Bondy 1996). Alcohol consumed with meals was found to reduce the high levels of blood lipids that occur after eating (Criqui and Ringel 1994; Veenstra et al. 1990). One study demonstrated that the positive effect on blood lipids conferred by moderate alcohol use was present only while alcohol was being consumed (Rubin and Rand 1994).

Other studies have reported a reduced risk of coronary death or acute myocardial infarction with moderate, regular drinking and an increased risk associated with binge drinking (McElduff and Dobson 1997; Kauhanen et al. 1997*a*,*b*).

In summary, current evidence suggests that drinking small to moderate amounts of alcohol is associated with reduced risk of CHD. Little, if any, additional benefit is derived from drinking larger amounts. Lowered CHD risk is most closely associated with a consistent pattern of drinking small amounts of alcohol. The apparent CHD benefit is largely, if not wholly, attributable to alcohol itself and not to specific beverages or to other constituents of particular beverages. The question of potential additional benefits of certain alcoholic beverages such as red wine is not fully settled; future research should help clarify this issue (Klatsky et al. 1997; Rimm et al. 1996).

Finally, because many of the epidemiologic studies from which much of the evidence is derived have involved middle-aged or older persons in stable social situations, the findings may not necessarily apply to younger drinkers (whose risk of CHD is low to begin with) or to other social groups.

Stroke and Hypertension. Cerebrovascular disease, in which arteries in the brain are blocked or narrowed, can lead to a sudden, severe disruption of blood supply to the brain, called a stroke. Ischemic stroke, which is by far the predominant type of stroke, results from a blockage of a blood vessel; hemorrhagic stroke is due to rupture of a blood vessel. Alcohol-related hypertension, or high blood pressure, may increase the risk of both forms of stroke. Yet, in people with normal blood pressure, the risk of ischemic stroke may be decreased due to the apparent ability of alcohol to lessen damage to blood vessels due to lipid deposits and to reduce blood clotting. Alcohol's anticlotting effects, while perhaps decreasing the risk of ischemic stroke, may increase the risk of hemorrhagic stroke (Hillbom and Juvela 1996). These studies are coming closer to providing a clear picture of the relationship between alcohol and risk of stroke.

Effects of Alcohol on Stroke Risk. The relationship between alcohol consumption and stroke risk has been examined in two recent overviews. In a meta-analysis, researchers compared the relationship between alcohol consumption and the risk of ischemic and hemorrhagic strokes

(English et al. 1995). They detected no differences in the risk patterns for the two types of stroke, but found clear evidence that heavy drinking was associated with increased stroke risk, particularly in women. At low levels of alcohol consumption, they found the evidence to be inconsistent regarding a protective effect against stroke. In the second overview, the author drew a similar conclusion from 12 case-control and 14 cohort studies, finding that although moderate drinking (defined in this review as usual consumption of fewer than two drinks daily for men and less than one drink daily for women) does not appear to increase the risk of ischemic stroke, it is not clear whether moderate drinking protects against this type of stroke (Camargo 1996). On the other hand, moderate drinking may increase the risk of hemorrhagic stroke, although the evidence is inconsistent. Other recent studies also fail to offer clear evidence that moderate drinking protects against stroke (Knuiman and Vu 1996; Yuan et al. 1997).

In contrast, the Cancer Prevention Study II found that, in men, all levels of drinking were associated with a significant decrease in the risk of stroke death, but in women, the decreased risk was significant only among those consuming one drink or less daily (Thun et al. 1997). A recent study reported that among male physicians in the Physicians' Health Study, those who consumed more than one drink a week had a reduced overall risk of stroke compared with participants who had less than one drink per week (Berger et al. 1999). The authors concluded that the benefit was apparent with as little as one drink per week.

Among young people, long-term heavy alcohol consumption has been identified as an important risk factor for stroke (You et al. 1997). Very recent alcohol drinking, particularly drinking to intoxication, has been found to be associated with a significant increase in the risk of ischemic stroke in both men and women aged 16 through 40 years (Hillbom et al. 1995). In another study, researchers reported that recent drinking of alcohol was associated with the onset of stroke in young people during weekends and holidays, possibly reflecting an association with heavy drinking (Haapaniemi et al. 1996).

Effects of Alcohol on Blood Pressure. The relationship between alcohol consumption and blood pressure is noteworthy because hypertension is a major risk factor for stroke as well as for CHD. A national consensus panel in Canada recently conducted an extensive review of the evidence concerning this relationship (Campbell et al. 1999), concluding that studies have consistently observed an association between heavy alcohol consumption and increased blood pressure in both men and women. Researchers analyzing data from middle-aged British men found an association between heavy drinking and an overall increased risk of stroke that was largely related to alcohol's effect on blood pressure (Wannamethee and Shaper 1996). However, in many studies comparing lower levels of alcohol use with abstention, findings are mixed. Some studies have found low alcohol consumption to have no effect on blood pressure or to result in a small reduction, while in other studies blood pressure levels increased as alcohol consumption increased.

Randomized controlled trials to determine the effect of reductions in alcohol consumption on blood pressure in people with both normal and high blood pressure have consistently found that reductions in alcohol consumption were associated with declining blood pressure levels, although not all of these reductions were statistically significant (Cushman et al. 1998). Drinking pattern—how often drinking occurs—may have as important an effect on blood pressure as how much a person drinks (Russell et al. 1991).

In summary, heavy drinking appears to increase the risk of hypertension and, although the evidence is not entirely consistent, also may increase the risk of stroke. It remains uncertain whether lower levels of alcohol can help prevent ischemic stroke. In addition to examining how much alcohol is consumed, it may be important to consider drinking pattern in determining stroke risk.

Peripheral Vascular Disease. The possibility that alcohol may protect against CHD has led researchers to hypothesize that alcohol may protect against peripheral vascular disease, a condition in which blood flow to the extremities is impaired due to narrowing of the blood vessels. In a 1985 analysis of data from the Framingham Heart Study, alcohol was not found to have a significant relationship, either harmful or protective, with peripheral vascular disease (Kannel and McGee 1985). Other studies also have failed to find a significant relationship between alcohol consumption and peripheral vascular disease, although a few have noted weak and inconsistent evidence of a protective association (Camargo et al. 1997).

However, an important recent study produced different results. In an analysis of the 11-year follow-up data from more than 22,000 men enrolled in the Physicians' Health Study, researchers found that daily drinkers who consumed seven or more drinks per week had a 26-percent reduction in risk of peripheral vascular disease (Camargo et al. 1997). This study took into account the effects of smoking, exercise, diabetes, and parental history of myocardial infarction.

Two other studies found inconsistent results with regard to gender. One study of middle-aged and older men and women in Scotland showed that as alcohol consumption increased, the prevalence of peripheral vascular disease declined in men but not in women (Jepson et al. 1995). In contrast, among people with non-insulin-dependent diabetes, alcohol was associated with a lower prevalence of peripheral vascular disease in women but not in men (Mingardi et al. 1997). Clearly, the relationship of alcohol consumption to peripheral vascular disease requires further study.

Liver Cirrhosis

There is no question that alcohol abuse contributes significantly to liver-related morbidity (illness) and mortality in the United States. The effects of alcohol on the liver include inflammation (alcoholic hepatitis) and cirrhosis (progressive liver scarring). As many as 900,000 people in the United States suffer from cirrhosis, and some 26,000 of these die each year. From 40 to 90 percent of people with cirrhosis are estimated to have a history of alcohol abuse (Dufour et al. 1993).

The risk for liver disease is related to how much a person drinks: the risk is low at low levels of alcohol consumption but increases steeply with higher levels of consumption (Edwards et al. 1994). This relationship has been confirmed in middle-aged and elderly adults enrolled in the Cancer Prevention Study II (Thun et al. 1997), in the 12-year follow-up study of more than 87,000 middle-aged women enrolled in the Nurses' Health Study (Fuchs et al. 1995), and among blacks and whites included in an analysis of the 1986 National Mortality Followback Survey (Parrish et al. 1993).

Gender also may play a role in the development of alcohol-induced liver damage. Some evidence indicates that women are more susceptible than men to the cumulative effects of alcohol on the liver (Becker et al. 1996; Gavaler and Arria 1995; Hisatomi et al. 1997; Naveau et al. 1997; NIAAA 1997).

Cancer

Alcohol has been linked to a number of cancers, including cancers of the head and neck (mouth, pharynx, larynx, and esophagus), digestive tract (stomach, colon, and rectum) and breast (World Cancer Research Fund/American Institute for Cancer Research [WCRF/AICR] 1997; Doll et al. 1993; International Agency for Research on Cancer [IARC] 1988).

Cancers of the Head and Neck. Alcohol is clearly established as a cause of cancer of various tissues in the airway and digestive tract, including the mouth, pharynx, larynx, and esophagus (Doll et al. 1993; IARC 1988; La Vecchia and Negri 1989; Seitz and Pöschl 1997; WCRF/AICR 1997). Research suggests that the risk of cancers of the upper digestive tract is associated with both the concentration of alcohol in beverages and the number of drinks consumed (Doll et al. 1993). Even users of mouthwash containing a high

alcohol concentration are at increased risk for cancers of the oral cavity and pharynx (Doll et al. 1993; Kato and Nomura 1994).

Alcohol acts synergistically with tobacco to dramatically increase the risk of cancers of the oral cavity, pharynx, larynx, and esophagus (Doll et al. 1993; Longnecker 1995), that is, above that for alcohol or tobacco use alone.

Stomach and Pancreatic Cancers. An increased risk of gastric or stomach cancer among alcohol drinkers has been identified in several, but not the majority, of case-control or cohort studies. In 1988, the IARC concluded that there was insufficient evidence of causation. There exist plausible mechanisms by which alcohol consumption might play a role in gastric cancer, particularly in cancers of gastric cardia, the uppermost portion of the stomach adjoining the esophagus. The link between alcohol use and chronic gastritis (stomach inflammation) is clear, although progression from chronic gastritis to neoplasia is less well understood and probably involves other factors in addition to alcohol (Bode and Bode 1992, 1997). A detailed review of the evidence concluded that a role for alcohol in stomach cancer cannot be ruled out completely, but there is insufficient evidence to demonstrate that alcohol plays a direct role (Doll et al. 1993).

A similar situation may exist for pancreatic cancer. Alcohol is a cause of chronic inflammation of the pancreas; thus, a link between alcohol and pancreatic cancer is conceivable, though unproven (Doll et al. 1993). Recently, researchers found alcohol use to be associated with one type of cancer of the esophagus—esophageal squamous cell carcinomas—but not adenocarcinomas of the esophagus or gastric carcinomas (Gammon et al. 1997).

Colorectal Cancer. Comprehensive reviews have found evidence of a weak, positive association between alcohol and colon and rectal cancers (Doll et al. 1993; Longnecker 1992; Longnecker et al. 1990; Seitz and Pöschl 1997). More recent studies indicating a weak association between alcohol and colon cancer suggest that smoking may serve as a trigger, or initiator, of this cancer (Yamada et al. 1997). In some cases of rectal cancer, the metabolite acetaldehyde may act in conjunction with alcohol, playing a role as a cocarcinogen (Seitz and Pöschl 1997).

Breast Cancer. An association between alcohol and breast cancer has been suspected for two decades, but a number of overviews have concluded that the evidence is not sufficiently compelling to report a causal relationship (English et al. 1995; IARC 1988; McPherson et al. 1993).

Recent meta-analyses have defined a modest, direct relationship between alcohol intake and risk of breast cancer (Longnecker 1992, 1994; Longnecker et al. 1988; Smith-Warner et al. 1998; WCRF/AICR 1997). At least one such study, however, found a stronger association with heavy drinking (Howe et al. 1991).

Epidemiologic evidence indicates that alcohol consumption may increase breast cancer risk in women using hormone replacement therapy following menopause (Zumoff 1997). The Women's Health Study indicated such an association (Colditz 1990), as did the Iowa Women's Health Study (Gapstur et al. 1992), but a third study did not (Friedenreich 1994). Whether alcohol is more strongly associated with pre- or postmenopausal breast cancers remains uncertain (Schatzkin and Longnecker 1994).

For a more detailed discussion of the role of alcohol in breast cancer, see the chapter on medical consequences.

Prostate and Endometrial Cancers. In general, studies examining whether alcohol use influences the development of prostate cancer have so far failed to find any consistent significant relationships, particularly at low and moderate levels of alcohol intake (Breslow and Weed 1998; Longnecker 1994; WCRF/AICR 1997). Similarly, no consistent relationship between alcohol consumption and risk for endometrial cancer has been observed (Newcomb et al. 1997).

Psychosocial Consequences and Cognitive Effects

Stress Reduction

Alcohol use plays a role in many social activities, from the "business lunch" to the parties to the special occasions, such as gift giving. The benefits to those who drink during social occasions are greatly influenced by culture, the setting in which drinking occurs, and people's expectations about alcohol's effects (Goldman et al. 1987; Heath 1987; Leigh 1989; Leigh and Stacy 1991).

In the few studies available of people who reported receiving psychological benefits from alcohol use, the number of benefits reported correlated with how much alcohol they drank as well as with how often they drank heavily (Hauge and Irgens-Jensen 1990; Mäkelä and Mustonen 1988). Stress reduction, mood elevation, increased sociability, and relaxation are the most commonly reported psychosocial benefits of drinking alcohol (Baum-Baicker 1985; Hauge and Irgens-Jensen 1990; Leigh and Stacy 1991; Mäkelä and Mustonen 1988). Alleviating psychological stress may be the most significant of these potential benefits, since stress reduction is reported to contribute to a lowered risk of cardiovascular disease and other health problems (Klatsky 1996; Pohorecky 1990; Poikolainen 1994; Zeichner et al. 1983). However, studies have not measured the effectiveness of alcohol use relative to other means for reducing stress-related diseases.

There is extensive evidence indicating that people who suffer psychological distress and rely on alcohol to relieve their stress are more likely to develop alcohol abuse and dependence (Castaneda and Cushman 1989; Kessler et al. 1996, 1997). Even moderate amounts of alcohol can be harmful to people with mood and anxiety disorders because their symptoms are likely to worsen, and they may experience adverse drug interactions if they are taking medication (Castaneda et al. 1996).

Alcohol Dependence and Abuse

One known risk of alcohol use is alcohol dependence and abuse. The National Longitudinal Alcohol Epidemiologic Survey (Grant et al. 1994), a U.S. household survey of more than 42,000 people, found that 7 percent of adults met the criteria for alcohol dependence, abuse, or both. Alcohol dependence means that a person continues to drink despite experiencing significant alcohol-related problems and cognitive, behavioral, and physiologic symptoms, such as physical withdrawal or the need to drink increasingly large amounts. Alcohol abuse is characterized by continued drinking despite adverse effects on family or work, trauma, or negative health consequences (American Psychiatric Association 1994; World Health Organization [WHO] 1992).

Because vulnerability to alcohol dependence varies greatly among individuals, it is difficult to assess the risk of dependence in relation to how much a person drinks. Two persons exposed to alcohol in exactly the same way may or may not have the same outcome for many reasons, including genetic differences, personality, behavioral features, and environment. Any of these differences may alter a person's level of risk in relation to any of the outcomes discussed in this overview (trauma, cancer, and cardiovascular disease for example), but individual variation is particularly important for alcohol dependence. It is unclear whether researchers can adequately quantify the risk of dependence arising from moderate drinking, in the absence of progression to heavy drinking or binge drinking, without taking individual differences into account.

Psychiatric Comorbidity. Most mental disorders occur much more often than expected by chance among people who are abusing alcohol or are alcohol dependent (Kessler et al. 1996). Of these individuals, those who are alcohol dependent are more likely than alcohol abusers to have mental disorders. In fact, alcohol dependence elevates the risk for all types of affective and anxiety disorders (Kessler et al. 1996).

One recent study found that alcohol consumption is related to the lifetime prevalence of mental disorders (Ross et al. 1997). In this study, current at-risk drinkers, defined as individuals who had consumed at least 29 alcoholic drinks in the

previous week, had approximately twice the risk of mental disorder as lifetime abstainers (Ross et al. 1997). The likelihood of having an antisocial personality disorder was very high for current at-risk drinkers compared with lifetime abstainers. In addition, current at-risk drinkers were two to three times as likely as lifetime abstainers to have mood disorders and between one-and-a-half and two times as likely to have anxiety disorders. Unlike in previous studies (Leifman et al. 1995; Lipton 1994; Vaillant 1995), Ross and colleagues found no protective effect for any kind of drinking pattern (Ross et al. 1997).

A detailed review of the literature in this research area can be found elsewhere (National Institute on Alcohol Abuse and Alcoholism).

Cognitive Performance

Although the relationship between heavy alcohol consumption and cognitive impairment is well established, the effects of moderate drinking on the ability to perform cognitive tasks, including remembering, reasoning, and thinking, are largely unexplored.

Most studies of the relationship between alcohol consumption and dementia, notably Alzheimer's disease (Tyas 1996), have failed to find statistically significant associations. However, several recent studies suggest that moderate alcohol consumption may have a positive effect on cognitive function. In an analysis of baseline data (data collected at the beginning of a study) for persons aged 59 through 71 who were enrolled in the Epidemiology of Vascular Aging Study in France, moderate alcohol consumption was associated with higher cognitive functioning among women but not men after a number of possible confounding variables were controlled for (Dufouil et al. 1997).

Another study, which followed 3,777 community residents in France who drank primarily wine, found a markedly reduced risk of the incidence of dementia among moderate drinkers relative to abstainers (Orgogozo et al. 1997). This analysis controlled for age, gender, education, occupation, and baseline cognitive functioning. Observations from at least one study showed that the relationship between higher cognitive functioning and moderate drinking was confined to men with cardiovascular disease or diabetes, both of which are associated with impaired circulation (Launer et al. 1996). An understanding of the mechanisms by which alcohol may affect the brain will enable researchers to clarify the relationship between alcohol consumption and cognitive performance.

Effects on Society of Alcohol Use: Injuries and Violence

Researchers have identified and classified a wide variety of adverse consequences for people who drink and their families, friends, co-workers, and others they encounter (Edwards et al. 1994; Harford et al. 1991; Hilton 1991*b*,*c*). Alcohol-related problems include economic losses resulting from time off work owing to alcohol-related illness and injury, disruption of family and social relationships, emotional problems, impact on perceived health, violence and aggression, and legal problems.

The risk of such consequences for the individual varies widely and depends on the situation. However, researchers have found a general trend toward an increased risk of adverse effects on society as the average alcohol intake among individuals increases (Mäkelä and Mustonen 1988; Mäkelä and Simpura 1985). The pattern of drinking also is important in determining the risk of alcohol-related problems. Variables such as the frequency of heavier drinking occasions (Midanik 1995; Midanik et al. 1996; Room et al. 1995) and the frequency of drinking to intoxication (Harford et al. 1991; Hilton 1991*a*; Knupfer 1984; Midanik 1995) help to predict potential problems related to alcohol, even after average volume of intake is controlled for.

Injuries

Alcohol use is associated with increased risk of injury in a wide variety of circumstances, including automobile crashes, falls, and fires (Cherpitel 1992; Freedland et al. 1993; Hingson and Howland 1993; Hurst et al. 1994). The

increased risk of injury stems primarily from reduced cognitive function, impaired physical coordination and performance, and increased risk-taking behavior (Koelega 1995). In addition, alcohol increases the likelihood of more serious injury and lowers the probability of survival because of its effects on the heart and circulatory system (Fuller 1995; Li et al. 1997). Culture and drinking environment also influence the relationship between alcohol and various types of injury (Cherpitel 1997*a,b*).

Research shows that as people drink increasing quantities of alcohol, their risk of injury increases steadily and the risk begins to rise at relatively low levels of consumption (Cherpitel et al. 1995). An analysis of risk in relation to alcohol use in the hours leading up to an injury has suggested that the amount of alcohol consumed during the 6 hours prior to injury is related directly to the likelihood of injury occurrence (Vinson et al. 1995). The evidence showed a dose-response relationship between intake and injury risk—the more a person drank, the greater the risk—and found no level of drinking to be without risk.

In contrast, two studies of injury among older adults reported a U-shaped relationship between alcohol use and occupational injury (Zwerling et al. 1996) and between alcohol use and traumatic deaths (Ross et al. 1990). In these studies, abstaining was associated with a higher risk of injury than were low to moderate levels of alcohol intake. However, abstinence among the elderly may be related to existing health or cognitive problems, which, in turn, are related to risk of injury (Zwerling et al. 1996).

The pattern of drinking, such as binge drinking, clearly relates to the relative risk of injury, with risk increasing markedly as blood alcohol concentration rises (Hurst et al. 1994). Tolerance to the effects of alcohol may mediate the risk and severity of injury (Li et al. 1997), but the degree of protection is limited. Both frequent heavy drinking and frequent drunkenness are associated with injury, particularly that resulting from violence (Cherpitel 1996). Variation in the amount a person drinks on different occasions appears to have the strongest relationship with a high risk of injury; in contrast, consistently drinking small amounts of alcohol across occasions is associated with a lower risk of injury (Gruenewald et al. 1996*a,b*; Treno et al. 1996).

Violence

Patterns of alcohol consumption also increase the risk of violence and the likelihood that aggressive behavior will escalate (Cherpitel 1994; Martin 1992; Martin and Bachman 1997; Norton and Morgan 1989; Zhang et al. 1997). Alcohol appears to interact with personality characteristics, such as impulsiveness and other factors related to a personal propensity for violence (Lang 1993; Zhang et al. 1997). Violence-related trauma also appears to be more closely linked to alcohol dependence symptoms than to other types of alcohol-related injury (Cherpitel 1997*b*). See the section "Alcohol and Violence" later in this chapter for a more detailed discussion.

Assessing Risks and Benefits: Mortality, Morbidity, and Disability

The relationships and studies described in this section reflect the current state of knowledge and take into account concerns about the methodological rigor of epidemiologic studies in the field of alcohol and health. Many of these relationships have proven to be stable across studies, settings, and research designs. Research on the biological underpinnings of the most important relationships, such as between alcohol and CHD or alcohol and some cancers, has identified possible mechanisms through which alcohol can have an impact on these diseases.

Research findings continue to confirm an association between moderate drinking and lower CHD risk. Research is now in progress to clarify the extent to which alcohol itself, or other factors or surrogates such as lifestyle, diet, exercise, or additives to alcoholic beverages, may be responsible for the lower risk. Broader means of quantifying the relationships between relative risks and specific consumption levels and patterns are needed to more clearly and simply describe epidemiologic findings and translate them into improved public health strategies.

Overall Mortality

The overall impact of alcohol consumption on mortality can be assessed in two ways (Rehm and Bondy 1998): (1) by conducting meta-analyses using epidemiologic studies that examine all factors contributing to mortality, or (2) by combining risk for various alcohol-caused diseases with a weighted prevalence or incidence of each respective disease.

The meta-analysis approach to assessing overall mortality was used by researchers to examine the results of 16 studies, 10 of which were conducted in the United States (English et al. 1995). In this overview, researchers found the relationship between alcohol intake and mortality for both men and women to be J-shaped curves: the lowest observed risk for overall mortality was associated with an average of 10 grams of alcohol (less than one drink) per day for men and less for women. An average intake of 20 grams (between one and two drinks) per day for women was associated with a significantly increased risk of death compared with abstainers. The risk for women continued to rise with increased consumption and was 50 percent higher among those consuming an average of 40 grams of alcohol (between three and four drinks) per day than among abstainers. Men who averaged 30 grams of alcohol (two drinks) per day had the same mortality as abstainers, whereas a significant increase in mortality was found for those consuming at least 40 grams of alcohol per day.

The effect found in this evaluation—that, in industrialized countries, low to moderate drinking is associated with reduced overall mortality—holds true in more recent research in which epidemiologists adjusted statistically for the "unhealthy abstainer" effect. Including former drinkers in abstainer groups also can influence, and confound, the shape of the curve used to describe the relationship between alcohol intake and mortality (Fillmore et al. 1998*a*,*b*; Leino et al. 1998). (See the box "Does Abstaining Increase Risk?" For a discussion of the unhealthy abstainer effect, see Shaper 1990*a*,*b*; Shaper et al. 1988; Fillmore et al. 1998*a*,*b*; Leino et al. 1998. For examples of statistical control of this effect, see Fuchs et al. 1995; Rehm and Sempos 1995*b*.)

The proposed J-shaped relationship between alcohol intake and mortality does not apply in all cases, however. For example, because most of the physiologic benefit of moderate drinking is confined to ischemic cardiovascular conditions, such as CHD, in areas of the world where there is little mortality from cardiovascular diseases, alcohol provides little or no reduction in overall mortality. Rather, the relationship between intake and all-cause mortality assumes more of a direct, linear shape (Murray and Lopez 1996*c*), with increasing consumption associated with higher overall mortality. The same holds true for people under age 45, who have little ischemic cardiovascular mortality (Andréasson et al. 1988, 1991; Rehm and Sempos 1995*a*).

The impact of alcohol on all-cause mortality also changes with the measure used. For example, although studies have found that more deaths are prevented than are caused by alcohol in some countries, such as Australia (English et al. 1995) and Canada (Single et al. 1996, 1999), this relationship is reversed if years of life lost are considered. In other words, alcohol consumption causes more years of life lost than gained in these and other industrialized countries (Murray and Lopez 1996, 1997*a*) because even with the assumption that alcohol protects against ischemic heart disease, CHD tends to occur later in life, whereas harm resulting from injuries or other diseases tends to occur more often at younger ages. This is likely to be the case for the United States as well. (When interpreting these findings, it is important to keep in mind that the evaluations are based on the hypothesis that any level of alcohol consumption is beneficial with respect to CHD [English et al. 1995; Murray and Lopez 1996*c*; Single et al. 1996]. At least one recent study found an upturn in risk for CHD among women who were heavier drinkers [Rehm et al. 1997*a*], but these data have not yet been replicated.)

Researchers have examined the overall relationship between alcohol consumption and mortality

Does Abstaining Increase Risk?

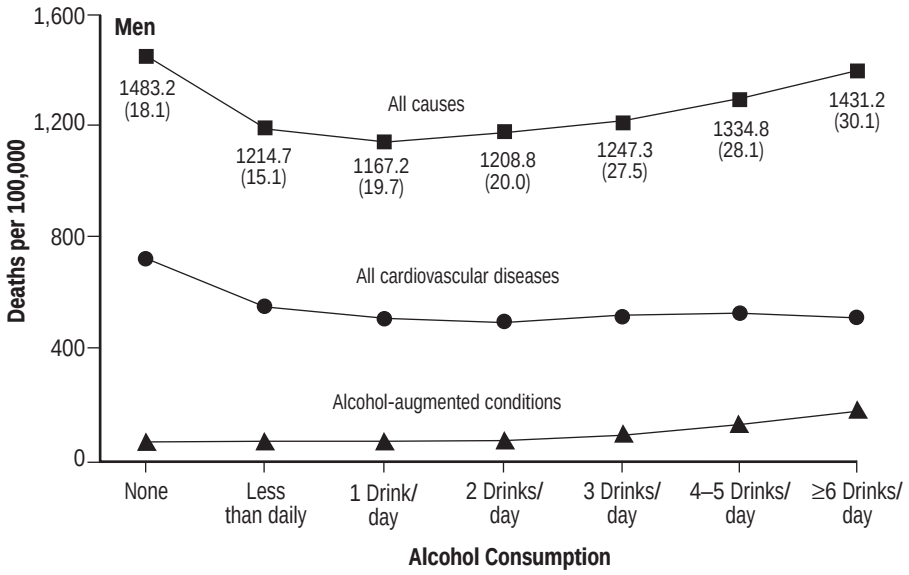
Epidemiologic evidence has shown that people who drink alcohol heavily are at increased risk for a number of health problems. But some studies described in this section suggest that individuals who abstain from using alcohol also may be at greater risk for a variety of conditions or outcomes, particularly coronary heart disease, than persons who consume small to moderate amounts of alcohol.

This type of relationship may be expressed as a *J-shaped* or *U-shaped curve*, which means that the risk of a disease outcome from low to moderate drinking is less than the risk for either abstinence or heavier drinking, producing a curve in the shape of the letter J or U (figure 1).

By examining the lifestyle characteristics of people who consume either no alcohol or varying amounts of alcohol, researchers may uncover other factors that might account for different health outcomes. For example, gender, age, education, diet, and social involvement are among the factors that may be taken into account in determining relative risk of disease.

Similarly, people may quit drinking because of health problems, or even if that is not the case, former drinkers may have characteristics that contribute to their higher mortality risk, such as smoking, drug use, and lower socioeconomic status. If former drinkers are included in the abstainers group, they may make alcohol appear to be more beneficial than it is. Therefore the best research studies will distinguish between former drinkers and those who have never used alcohol.

Figure 1: Rates of death from all causes, all cardiovascular diseases, and alcohol-augmented conditions from 1982 to 1991, according to base-line alcohol consumption



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through conducting studies called time-series analyses, in which changes in overall mortality are related to changes in alcohol consumption. A recent study of 1982–90 data from 25 European countries estimated that increases or decreases of 1 liter in per capita consumption of pure alcohol were associated with corresponding increases or decreases of about 1 percent in all-cause mortality rates (Her and Rehm 1998). A recent analysis of European data from the turn

of the century (Norström 1996) indicated similar findings. Results from this type of analysis on the aggregate level contrast with results based on individual-level studies. Since aggregate-level analyses are quite scarce, more such studies would help to determine if these types of results can be replicated in different regions and time periods.

Morbidity and Disability

Quantifying the level of disability and morbidity related to alcohol can be difficult, in large part because few standardized measures exist. Both nationally and internationally, there is less information available on morbidity and disability than on mortality. In addition, the morbidity data are less reliable (Murray and Lopez 1996*a*), and existing measures for health-related disabilities are not standardized, often varying from country to country (Goerdt at al. 1996) because the current international classification, the *International Classification of Impairments, Disabilities and Handicaps* (ICIDH) (WHO 1980), is not used routinely in health service delivery in most countries, including the United States. This lack of standardization may change with the use of the new revision of the ICIDH, which will include a standardized assessment instrument (WHO 1997).

The most stable indicator of morbidity in industrialized countries appears to be hospitalizations. The risks of alcohol consumption clearly outweighed the benefits with regard to hospitalizations in Australia (English et al. 1995) and Canada (Single et al. 1999).

On the basis of measures of well-being or symptoms of depression or stress, several studies have found that both abstainers and heavily drinking persons report poorer subjective health than low to moderate drinkers (Fillmore et al. 1998*a*,*b*; Lipton 1994; Neff and Husaini 1982; Poikolainen et al. 1996). Moderate drinkers also may be more likely to have attributes that contribute to good mental and physical health (Kunz, 1997; Lipton 1994; Poikolainen et al. 1996). In one study, however, the J- or U-shaped association between alcohol use and poor subjective health was observed even after a number of such attributes were controlled for (Poikolainen et al. 1996). As with estimates of morbidity, measures that accurately and reliably capture the relationship between alcohol and disability are clearly needed.

Disability-Adjusted Life Years

One way to quantify the relationship between alcohol and health-related consequences is to use a measure called the disability-adjusted life year (DALY), which may prove useful in summarizing the effects of alcohol on the full spectrum of health outcomes (Murray and Lopez 1996*b*; see also the discussion of the Global Burden of Disease Study below). In addition to serving as a descriptive measure, the DALY provides a potentially useful tool for health policy purposes. Use of the DALY may assist policy makers in allocating resources for health care (WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options 1996) and may allow for better measurement of specific policies or interventions designed to reduce harm or improve health. This measure does have its shortcomings, however, and must be considered together with other, more conventional approaches to balancing the risks and benefits of alcohol consumption on health and social well-being.

In the Global Burden of Disease Study (Murray and Lopez, 1996, 1997*b*), the researchers combined years of life lost and years lived with disability into a single indicator, DALY, in which each year lived with a disability was adjusted according to the severity of the disability (Murray and Lopez 1997*b*,*c*). Within this framework, the researchers identified three effects of alcohol: harmful effects in relation to injuries, harmful effects in relation to disease, and the protective effect in relation to ischemic heart disease (Murray and Lopez 1996*c*). Overall, the research team found that alcohol accounted for 3.5 percent of the global burden of disease (that is, mortality and disability together), 1.5 percent of all deaths, 2.1 percent of all life years lost, and 6 percent of all the years lived with disability (Murray and Lopez 1997*c*). In other words, the relative effect of alcohol on disability was considerably larger than its effect on mortality.

The Global Burden of Disease Study found tremendous differences in alcohol's impact on disability across different regions of the world. The most pronounced overall effect was observed in established market economies (mainly high-income as opposed to developing regions—10.3 percent of all DALY's in these regions were attributable to alcohol), Latin America and the Caribbean (9.7 percent), and the former socialist economies of Europe (8.3 percent). The researchers found the smallest effect of alcohol in the middle eastern crescent, which is not surprising given the region's high proportion of abstinent Islamic populations (Murray and Lopez 1997*a*).

Of course, these calculations can be only as precise as the underlying data. As mentioned above, there is a lack of data sources for alcohol-related morbidity and disability in all regions of the world, including the United States. Since the findings of the Global Burden of Disease Study indicate that alcohol may have a greater effect on nonfatal than fatal health consequences (for example, researchers have estimated 15.6 percent of all life years lost to disability in established market economies were due to alcohol, compared with 5.1 percent of all life years lost due to mortality) (Murray and Lopez 1996*b*, 1997*b*), more intense research efforts in this area will be important because of the high public health relevance.

In Closing

Epidemiologic studies have long provided evidence of the harm alcohol can cause to individual health and to society as a whole. Newer studies have identified an association between low to moderate alcohol consumption and reduced CHD risk and overall mortality. The most significant association with lower CHD risk is largely confined to middle-aged and older individuals in industrialized countries with high rates of cardiovascular diseases. Elucidation of the mechanisms by which alcohol affects CHD risk will clarify the relationship and may enable scientists to develop pharmacologic agents that could mimic or facilitate the positive effect of alcohol on health (Hennekens 1996), perhaps by augmenting the effects of other health-improving behaviors such as engaging in physical activity, eating a low-fat diet, and not smoking.

Guidelines to low-risk drinking exist in many countries (Bondy et al. in press; Hawks 1994; UK Inter-Departmental Working Group 1995; USDA 1995). At this point, research clearly indicates that no pattern of drinking is without risks. However, for individuals who continue to consume alcohol, certain drinking patterns may help reduce these risks considerably.

Among teenagers and young adults in particular, the risks of alcohol use outweigh any benefits that may accrue later in life, since alcohol abuse and dependence and alcohol-related violent behavior and injuries are all too common in young people and are not easily predicted. To determine the likely net outcome of alcohol consumption, the probable risks and benefits for each drinker must be weighed. These assessments are based on the individual drinker's consumption levels, his or her personal characteristics (such as age or preexisting risk factors for CHD), and subjective values, as well as on social considerations (Dufour 1996). Overall, within the entire picture of costs and consequences, the benefits of limited alcohol use will need to be weighed carefully against its significant costs to individuals and to society.

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Alcohol Involvement Over the Life Course

Alcohol is the world's most commonly used drug. In all drinking societies, patterns of alcohol use and abuse are superimposed on the structure of a person's life activities. For this reason, indicators of variation between people's lives, such as age and gender differences, socioeconomic status, and ethnocultural group membership, have all been useful as markers in understanding variation in alcohol use and abuse.

Social scientists interested in describing this variation use explanatory models that have focused on the differences between subgroups in norms about alcohol use and abuse and on differences in the availability of alcohol (Edwards 1994; Greenfield and Room 1997). Underlying reasons for variation in alcohol use include social controls and availability. If the larger social group frowns on use, then people are less likely to drink, or to drink heavily. Similarly, when alcohol is not readily available, fewer cues prompt people to drink (out of sight, out of mind). Also, if alcohol is harder to obtain, consumption rates tend to be lower.

These explanations are sometimes referred to as "top-down" factors because they focus on the effects of societal and group-level influences on an individual's behavior. However, the impact of social and cultural influences on drinking behavior is not the same for all members of a culture. Families and peer groups create smaller spheres of influence within the larger culture. In addition, differences in each person's neurobiology create unique personal vulnerabilities and protections. Thus, each individual can be seen as a host environment upon which social and cultural factors act. Influences at the level of the individual person are sometimes referred to as "bottom-up" factors. From the bottom up, a person's drinking behavior can be seen to begin with molecular genetics, and behavior follows a causal path from molecules, to cells, to brain systems and structures, to behavior (Anderson 1998).

At the same time, not all drinking behavior is explainable by either top-down or bottom-up factors. Some of the variation results from interaction of these factors and occurs at the level of the drinking behavior itself. Learning is one such interactive influence, since drinking is a learned behavior. Children begin to learn about alcohol and its effects long before they have had their first drinking experience. They continue to learn about it as a function of where and how they obtain their first drink, who introduces it, how much the environment allows or even encourages a progression of drinking, and their own subjective experience of the drug's pharmacologic effects. Thus, alcohol involvement occurs over time and progresses—or not—according to an intricate process that involves the larger sociocultural system; the individual's age, life stage, and social role within that system; the demands and opportunities of the individual's more immediate social environment; and the unique pattern of neurobiological vulnerability and protection that his or her genetic endowment provides.

These ideas are central to developmental theory, a conceptual framework that has enhanced understanding of the factors regulating gene expression in animals (Gottlieb 1991) and in humans (Sing et al. 1992, 1996), the changes in risk factors for physical and mental disorders from early childhood to adulthood (Wierson and Forehand 1994; Windle and Tubman 1998), and the top-down social forces that dampen or increase the expression of individual psychopathology from one historical era to another (Elder and Caspi 1989). Within the field of alcohol research, the body of work based on this view has become known as the developmental perspective on alcohol use, abuse, and dependence. This perspective has fostered a line of research that has gained momentum in the last two decades because of compelling evidence (1) that individuals and groups demonstrate great variability in their drinking patterns, (2) that

variability in drinking patterns is not constant across the life span, and (3) that pressures to drink—or not to drink—are concentrated at certain stages in the course of a person's life.

Like all researchers on alcoholism, developmental scientists seek to understand the causes of alcoholism. They examine the interplay of multiple factors—sociocultural, psychological, and neurobiological—that influence drinking behavior and that create a variety of pathways leading to or away from different subtypes of alcoholism. The developmental perspective, with its emphasis on maturational processes, life course variation, and the interplay of environment and individual vulnerability, is of central importance to the field because findings from this research have demonstrated that, for the majority of individuals, risk is fluid over the course of life. As each person moves through his or her life, a variety of risk and protective factors come into and move out of play. Not all are present at the same time, and their sequencing is regulated not just by the individual's unique vulnerability, but also by the person's history of exposure to alcohol and the immediate presence (or absence) of an environment that enhances risk in some instances and dampens it in others.

The developmental perspective has enriched our understanding of the timing and mechanisms involved in these "in and out of play" sequences (for example, Caspi and Bem 1990; Schulenberg et al. in press). It has also stimulated researchers to include indicators of the larger social context—the top-down factors—in their explorations of individual vulnerabilities in more recent models of risk development. The work has demonstrated that developmental clocks set in different eras lead to different long-term experiences (Elder 1997). For example, when investigating drinking behavior, it is important to understand that a person who came of age during World War II has very different norms and expectations about substance use than a person who came of age in the Vietnam War era. Similarly, a woman from a Hispanic-American culture has a different pattern of alcohol use than a man in her culture and than women in other cultures. Further, to understand her risk factors, it is important to know whether she is a first-, second-, or third-generation American and whether she is a grandmother, a young mother, or a teenager.

One way that developmental researchers convey the variability in drinking behavior that occurs over the span of a person's lifetime is by using the term "drinking trajectory," a concept that embraces the ideas of time, course, and progression. A trajectory is different in subtle but important ways from a "drinking pattern," which suggests unchangingness and persistence over time. When viewed over the short term, some trajectories describe patterns of problem drinking that appear stable. However, some trajectories shift when researchers extend the span of time observed. Other trajectories describe a steady progression that reflects a gradual accumulation of risk factors.

From the developmental perspective, it is also important to understand that the accumulation of risk factors, no matter how heavy, does not lead inevitably from heavy risk burden to alcoholism. Intervening factors, both internal and environmental, play a role in sustaining some trajectories and shifting others. By examining variability in alcohol use and abuse across the life span and by simultaneously tracking the interplay of other internal and environmental factors, developmental scientists seek to isolate and describe the different drinking trajectories of individuals and of important subgroups, such as ethnic and gender groups.

This section is based on life course theory, which explores processes by which multiple factors, at multiple levels, interact over time. These interactions have the potential to produce varying patterns of drinking and drinking consequences at each stage of an individual's life. Understanding the multiple and varied influences on an individual's drinking trajectory is a complex problem. However, developmental scientists have been able to "deconstruct" the process into its component parts to allow focused analysis and

refined understanding. A clearer understanding of the course of drinking behavior and its variability is important for developing prevention and treatment methods effective with specific subgroups.

This section summarizes recent research, with special focus on two phenomena: developmental variations in drinking behavior over the life course, and developmental differences in patterns of drinking behavior among subgroups. Specifically, this section first reviews the well-documented age progression in alcohol use and related problems in adolescence and discusses how age serves as a basic indicator of critical developmental experiences. Within this framework, early-childhood influences on alcohol use are considered, and findings are reviewed from studies about how a child's learning leads to his or her initial understandings about alcohol. The section then reviews the substantial evidence that very early behavioral differences are markers of a high-risk trajectory into alcohol-related problems and dependence in adolescence and young adulthood. The section then moves from a focus on variation across an individual's life span to evidence about the role that social contexts play in the development of drinking behavior. Like age, membership in certain social groups, such as gender and ethnic groups, is an indicator of important underlying social processes. Recent evidence on the interaction of demographic factors and variations in alcohol use among the elderly is also reviewed.

Understanding the Age Progression of Alcohol Involvement in Childhood and Later Life

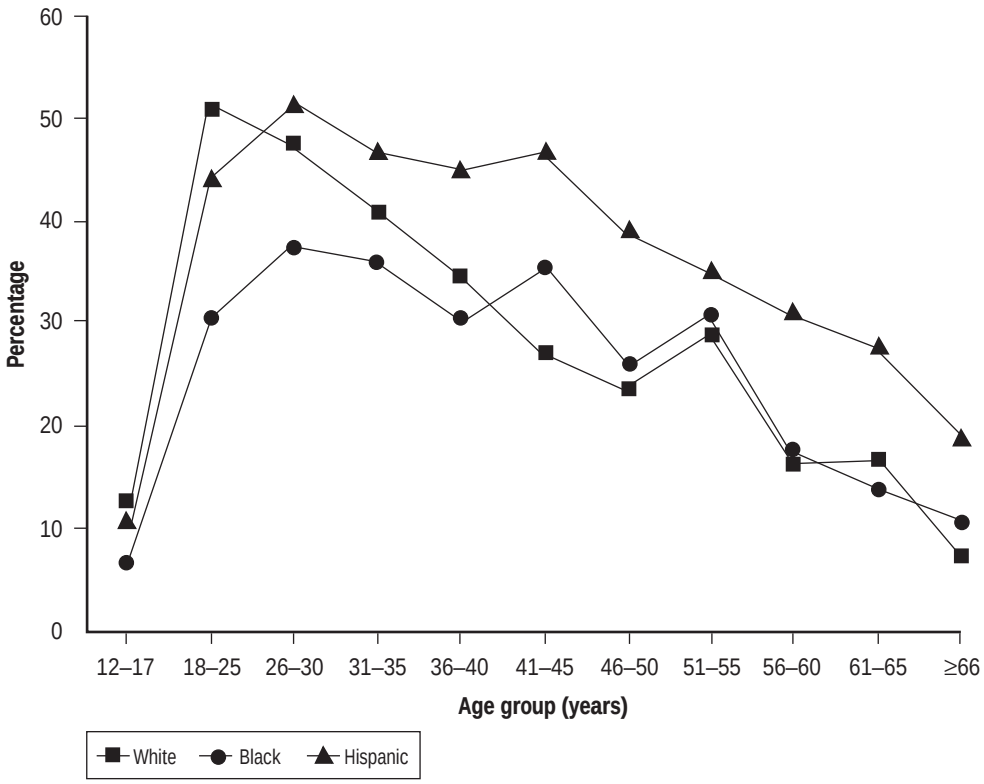
Most research on age-related variation in early drinking behavior has focused on adolescence because alcohol use and associated problems typically begin during the teenage years. In 1999, for example, 52 percent of 8th graders (that is, 14-year-olds) and 80 percent of 12th graders (18-year-olds) reported having used alcohol at least once (Johnston et al. 1999). Also, more problematic drinking patterns usually begin during the teen years, in a parallel age-related progression that involves fewer individuals. Thus, 15 percent of 8th graders and 31 percent of 12th graders reported bingeing (taking five or more drinks in a row at least once in the past 2 weeks), and 9 percent of 8th graders and 33 percent of 12th graders reported being drunk in the past 30 days (Johnston et al. 1999). The problem indicators continue to move upward until the early 20's, and then start to drop off (Jackson et al. 1998) (figures 1 and 2).

In describing these age-related changes in alcohol use, life course theory emphasizes that age progression, in and of itself, does not explain the process. Rather, age serves as a marker for a large number of experiences related to being familiar with alcohol, using it over time, seeing others use it or refuse to use it, and receiving encouragement—or discouragement—to drink. It is the accumulation of experiences that leads to the change in behavior, not increasing age itself. The technical term that researchers use is that these experiences "mediate" the age-related variation.

Developmental Patterns

From the perspective of the child's accumulating experience, neither the first drink nor the first experience of heavier drinking marks the beginning of alcohol involvement. The developmental problem for researchers is to specify the factors (the mediators) that establish a person's early drinking experience. What circumstances move the individual from lighter to heavier and more problematic drinking? An important area for investigation is the thought processes that shape a person's decisions about whether or not to drink (Fischhoff and Quadrel 1995). As individuals develop, they acquire information on which their knowledge, beliefs, and attitudes are based. Information about alcohol can be acquired directly and indirectly, through experience and observation, via thoughts and emotions, and from obvious and subtle events. Knowledge, beliefs, and attitudes about alcohol, which serve to motivate behavior, are organized into frameworks known as cognitive models or schemas (Zucker et al. 1995*b*).

Figure 1: Percentage of males reporting having four or more drinks on any single day in past 30 days, by age group and race/ethnicity, United States



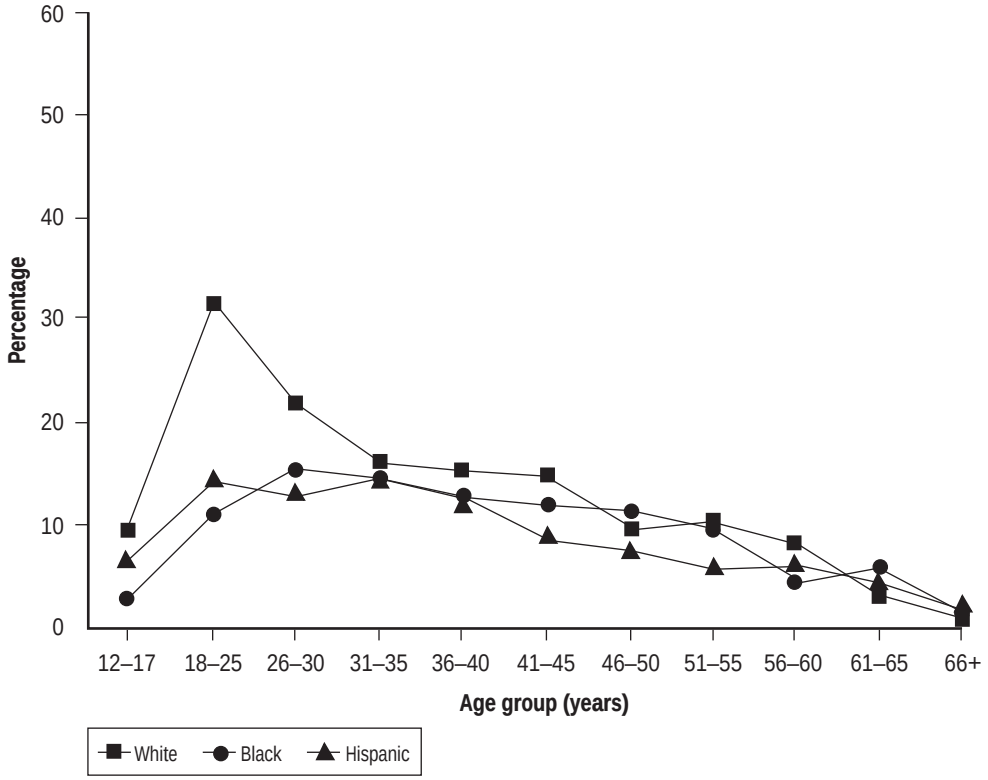
Source: Jackson et al. 1998.

For regular and intentional drinking to occur, a person must first understand that there is a class of substances known as alcoholic beverages and that certain effects are connected with drinking them. Further, the effects must be perceived by the person as desirable enough to motivate alcohol-seeking or alcohol-accepting behavior (Zucker et al. 1995*b*). These awarenesses and perceptions (or schemas) operate on both conscious and unconscious levels. Thus, people form conscious and explicit expectations about the anticipated effects of alcohol (Goldman et al. 1991; Rather et al. 1992), as well as unconscious memories, called implicit cognitions, that influence behavior (Stacy et al. 1996). Both explicit and implicit cognitions have been found to predict alcohol use (Smith et al. 1995; Stacy 1997; Stacy et al. 1996).

Early Understandings About Alcohol

Alcohol involvement has its roots in early childhood, when youngsters first learn about alcohol and its use. Because alcohol has a place in the ritual practices of many religions, some children have limited experience with alcohol consumption well before they have made a conscious decision to drink (Glassner 1991; Heath 1991). In addition, media exposure virtually assures some knowledge of alcoholic beverages long before the opportunity for drinking arises (Atkin 1995; Wyllie et al. 1989). Children also learn by more direct experience. Research has shown that young children, even at age 3 through 5, attribute alcoholic beverage consumption more to adults than to children, and more to adult males than to adult females (Noll et al. 1990). Further, the ability to identify alcoholic beverages by smell, indicating personal

Figure 2: Percentage of females reporting having four or more drinks on any single day in past 30 days, by age group and race/ethnicity, United States



Source: Jackson et al. 1998.

rather than media exposure, has also been seen in preschool children, with older children more successful than younger ones at identifying alcoholic beverages (Noll et al. 1990). This ability to recognize alcoholic beverages was directly related to the amount of alcohol consumed by the child's parents and the degree to which parents reported drinking for "escape" reasons.

On the basis of this research, one might expect that children of alcoholics would develop alcohol schemas earlier than other children, and one would want to focus on early identification of "risky cognitions" about alcohol because of their long-term significance in the development of problem drinking. When researchers explored cognitions in 3- to 6-year-olds, they found that early alcohol understandings were more common in children of alcoholics than in children of nonalcoholics (Zucker et al. 1995*b*). When photographs of alcoholic beverages were shown to children of alcoholics and children of nonalcoholics, the children of alcoholics were more likely to identify at least one alcoholic beverage, and they were better able to identify specific alcoholic beverages. Further, children whose parents drank more were more likely to attribute alcoholic beverage use to adults. Thus, children's schemas about both knowledge and use of alcohol were more common in alcoholic families. Other recent research indicates that these processes may begin even before formal language is present. Six- to 13-month-old infants whose parents reported higher alcohol consumption and who had some indicators of alcoholism responded differently to toys that were scented with alcohol than did infants from families in which parents drank less (Mennella and Beauchamp 1998). This work indicates that the child's learning and recognition of alcohol begins at a very young age.

Although research has yet to reveal how early understandings about alcohol relate to the actual onset of drinking behavior, studies on the thought processes of second through fifth graders (aged 8 through 11) showed that children's expectations about the effects of using alcohol were similar to those of adults (Dunn and Goldman 1996). Further research among 3rd through 12th graders indicated that younger children had mostly negative alcohol-related associations, describing drinkers with words such as "dizzy" and "goofy," while the older children had more positive associations, using words such as "outgoing," "relaxed," and "funny" (Dunn and Goldman 1998).

Taken as a group, these findings from early to middle childhood indicate a developmental progression in understandings about alcohol, including expectations about alcohol's effects, that takes place much earlier than regular use of alcohol begins. The progression varies with age, but in part also reflects differences in exposure to consumption in the family, with precocious development of understandings about alcohol being more common in alcoholic homes.

Early Behavioral Indicators of Risk for Alcohol Problems

Not all of the factors that play a role in early alcohol use and the development of alcohol problems are related to alcohol-specific processes, such as childhood exposure to alcohol. An important and much-repeated finding of past research has been the link between aggressive behavior, delinquent activity (that is, behavior that deviates from social norms), and earlier onset of alcohol use and problematic use (Donovan and Jessor 1985; Donovan et al. 1998; Jessor and Jessor 1977; Kandel et al. 1978; White et al. 1999). Alcohol use is only one part of a broader syndrome of adolescent problem behavior that includes other drug use, earlier sexual activity, and delinquent and aggressive conduct. Extensive research has shown that these problem behaviors cooccur and emerge from a common matrix of personality structure, attitudes, and parental socialization practices that encourage the development of independent and rebellious behavior (Kandel et al. 1978; Zucker et al. 1995*a*). Adolescents with these risk characteristics become more involved in relationships with like-minded peers, which, in turn, fuels the emergence of earlier and more problematic alcohol use.

A parallel line of research has focused on individual differences in temperament as early links in the chain of risk for the development of alcohol problems in later childhood and adolescence and for the subsequent development of alcoholism in adulthood. A person's temperament is evident in early childhood and even in infancy and is believed to be heavily under genetic control, regulated by neurobiological mechanisms. Alcohol researchers have looked at such dimensions of temperament as elevated activity level, low attention span and persistence, and high emotionality as predictors of problem alcohol use (for example, Tarter and Vanyukov 1994*a*; Tarter et al. 1985).

Developmental researchers pursuing this line of inquiry have been interested in a sequential hypothesis. Simply stated, the sequence is that the child's underlying "risky temperament," coupled with a difficult family environment that exacerbates the temperamental characteristics, leads the child to heightened antisocial behavior and to more frequent associations with delinquent peers. These attributes in turn drive early alcohol use, the transition into early problem use, and ultimately, the emergence of a diagnosable disorder (Tarter and Vanyukov 1994*b*; Zucker et al. 1995*b*). Until very recently, only the preadolescent and adolescent versions of this model had been tested, and the tests involved cross-sectional rather than longitudinal data. Even so, investigators have found support for a model of risk for alcohol use in preadolescents and adolescents that involves difficult temperament plus risk factors in the family-rearing environment and peer group (Blackson 1997; Blackson and Tarter 1994; Blackson et al. 1994).

The first long-term tests of the connections between early childhood and adulthood have been reported. In a New Zealand study, more than

1,000 children born between 1972 and 1973 were followed up by researchers over a 20-year period (Caspi et al. 1996). Among males, the researchers found a direct link between "behavioral undercontrol" at age 3 and alcohol dependence at age 21. Behavioral undercontrol was characterized as irritable, impulsive, impersistent, and rough behavior and an unstable emotional response. Boys having these traits were significantly more likely than boys without them to be diagnosed 20 years later with alcohol dependence. No differences in later alcohol dependence were found for undercontrolled girls. In the same study, another childhood temperamental factor—behavioral inhibition—was found to be linked to later development of alcohol problems at age 21 among males. Behavioral inhibition included social reticence, concentration difficulties, and being upset by strangers. Girls who were inhibited at age 3 did not display more alcohol-related problems at age 21.

These findings from New Zealand are similar to observations of 3- to 5-year-old boys from alcoholic families and matched nonalcoholic control families being followed in a longitudinal study of high-risk children in Michigan. This work, as well as three studies of older children that also yielded findings similar to the New Zealand study, is described below.

Early results from the Michigan study indicated that 3-year-old sons of alcoholics were more impulsive than comparison children, and a greater proportion of them were rated in the upper clinical range of behavior problems (Fitzgerald et al. 1993). Later work found that boys with clinically diagnosed behavior problems also displayed more difficult temperaments (Jansen et al. 1995). These troubled children were also more likely than comparison children to come from families in which the fathers were of lower socioeconomic status, had more severe and long-standing alcohol problems, and displayed higher levels of antisocial behavior. Thus, multiple factors converged to heighten these children's risk for later alcohol problems (Jansen et al. 1995; Zucker et al. 1996*a*).

More recent longitudinal findings over the interval from 3 to 8 years of age, and involving girls as well as boys, continue to support the earlier cross-sectional observations (Wong et al. 1999). They also support the sequential hypothesis described above. The typical maturational pattern of childhood involves decreases in aggression and undercontrolled behavior (also known as "externalizing" behavior) from early to middle childhood. However, for children in the study who were from the highest risk families—families that were more antisocial and alcoholic—aggressive and undercontrolled behaviors decreased at a slower rate than for children from lower risk families. In addition, the link between risky child temperament and externalizing behavior in the highest risk families was mediated by the parents' behavior. Parents who reported more negative experience (more sadness and "bad mood") and who reported spanking their children more often were more likely to have children with higher levels of undercontrolled behavior (Wong et al. 1999). In other words, the most damaging child outcomes were being sustained in families where the children had risky temperament characteristics *and the families acted in ways to exacerbate those attributes*. As noted in the introduction to this section, the concept of risk burden or risk load, in which multiple risk factors interact with and exacerbate one another, is important for understanding the development and maintenance of problem behavior over time.

Three other studies have provided information about developmental variation after the preschool years by focusing on middle childhood and early adolescence. One investigation of Swedish adoptees found that personality patterns at age 11 predicted alcohol abuse and dependence at age 27 (Cloninger et al. 1988). These results are similar to the New Zealand findings in that two quite different types of temperament noted in childhood—behavioral undercontrol and behavioral inhibition—led to problems with alcohol. Swedish boys who were high in novelty seeking and low in harm avoidance (dimensions akin to behavioral undercontrol), as well as boys high in

harm avoidance and low in novelty seeking (akin to overcontrol, fearfulness, and inhibition), were more likely to have alcohol problems at age 27.

In a second study (Masse and Tremblay 1997), teacher's ratings of certain traits of children at ages 6 and 10 were predictive of the onset of drunkenness during the age range of 11 to 15 years. The ratings used by the teachers involved "fearfulness" and "hyperactivity"; however, the authors interpreted these ratings as measuring the same behaviors rated in the Swedish study. They equated fearfulness with the Swedish measure of harm avoidance, and they equated low fearfulness and hyperactivity with the Swedish measure of novelty seeking. Teacher's ratings indicating hyperactivity and low levels of fearfulness at ages 6 and 10 were significant predictors of drunkenness between ages 11 and 15. Among 6-year-olds, the high fearfulness rating was a better predictor of later problems, and hyperactivity was a better predictor for the 10-year-olds.

A third study investigated long-term correlates of aggressive behavior in more than 600 subjects followed from age 8 to 30 (Eron et al. 1987). Results revealed that children who were rated as aggressive by their peers were more likely than other children to have records for driving while intoxicated some 22 years later. Taken altogether, these studies provide major evidence that features of temperament observed from early childhood are predictive of alcohol problems and alcoholism in adulthood.

Varying Developmental Trajectories Over the Life Span

Risk factors for problematic alcohol involvement such as those described above do not inevitably result in alcohol-related problems. Other influences that may foster problems or protect against them come into play as the individual develops (Sher and Gotham 1999; Zucker et al. 1996*a*). Moreover, one factor alone may not be sufficient to cause problems. Rather, multiple factors acting in concert increase the likelihood that alcohol problems will develop by increasing the risk load. Researchers explore these intricate patterns of influence and their gradual emergence by charting developmental trajectories to describe the various pathways that, over time, may lead to or away from an outcome.

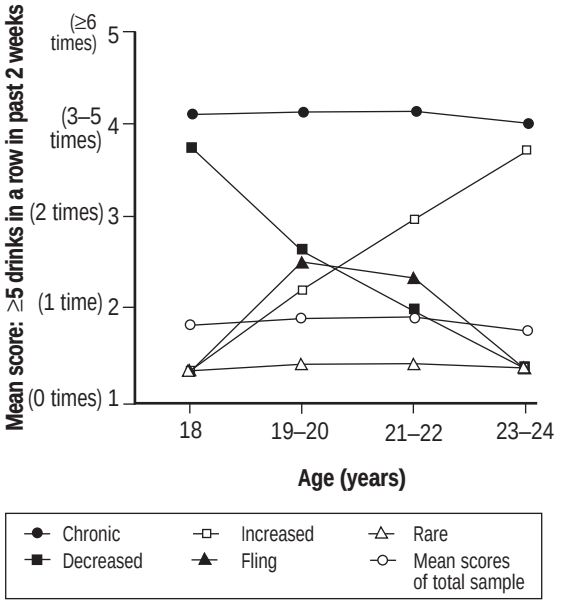
Longitudinal projects like the New Zealand study point toward the existence of quite different developmental pathways that begin in early childhood and involve behavioral forerunners of alcohol use. Among the children studied, two very different traits, behavioral undercontrol and behavioral inhibition, were associated with development of alcohol abuse and dependence in early adulthood (Caspi et al. 1996). Because high-risk children began with two different behavioral traits and moved to a common endpoint, some other influences, either in the intervening time period or in baseline characteristics of the two groups, or both, had to be operating (Patterson et al. 1998).

Developmental trajectories can be used to describe the big picture from early childhood through adulthood or to clarify details of a smaller part of the picture. Recent work based on nationally representative longitudinal data from the Monitoring the Future Study has focused on developmental processes using biennial assessments (Schulenberg et al. 1996*a,b*). This research charted pathways of alcohol involvement for the interval between late adolescence and early adulthood, examining patterns of stability and change in frequent binge drinking between ages 18 and 24. This age group spans the important developmental period of transition from adolescence to adulthood. It is also the life stage with the heaviest concentration of alcohol problems. Frequent binge drinking was defined as taking five or more drinks in a row on at least two occasions during the past 2 weeks. Patterns of binge drinking were explored in terms of behaviors, attitudes, personality traits, and characteristics of the social context that either shifted or remained stable along with the drinking.

The researchers found that six distinct trajectories described the binge drinking of over 90 percent of

the sample (figure 3) (Schulenberg et al. 1996*a*). Three patterns were stable—Never, Rare, and Chronic—and three patterns varied across time—Decreased, Increased, and Fling (the Fling group had no frequent binge drinking at the first and last measurement points and frequent binge drinking at the midpoints). People with different binge trajectories showed differences in the problems alcohol caused them, in their attitudes about heavy drinking, in the amount of time they spent with heavily drinking peers, and in the extent of their involvement with illicit drugs. Gender differences were also evident. Women dominated the Never group, but appeared less frequently than men in the Chronic and Increased groups. Personality also played a role (Schulenberg et al. 1996*b*). People who had lower scores at age 18 on both conventionality and belief in one's own effectiveness in accomplishing an objective (self-efficacy), as well as those who said they drank to get drunk, were more likely to be in the Increased binge drinking group. On the other hand, higher self-efficacy and lower motivation to get drunk were protective factors among initially frequent binge drinkers who decreased their drinking.

Figure 3: Mean scores for five or more drinks in a row in the past 2 weeks by binge drinking trajectory



Source: Schulenberg et al. 1996*a*. Reprinted with permission from *Journal of Alcohol Studies*, Vol. 57, pp. 289–304, 1996. Copyright 1996, Alcohol Research Documentation, Inc., Rutgers Center of Alcohol Studies, Piscataway, NJ.

These findings demonstrate considerable variation in pathways to drinking patterns once regular drinking has begun and reflect developmental differences in the success with which adolescents make the transition to adulthood. A very important approach for future studies, from both a theoretical and a prevention perspective, will be to identify, before people begin regular drinking, the characteristics associated with specific trajectories that they would later follow. The studies reviewed in the previous section indicate that this process of identification is already possible for a subset of the population. This knowledge base needs to be expanded.

An implicit acknowledgment that developmental pathways exist can also be seen in work attempting to classify different subtypes of alcoholism, a body of work with a long history (Cloninger 1987; McCord 1988; Zucker 1994, 1987; Zucker et al. 1996*a*). Investigators who have focused on differences in family history of alcoholism, parental criminality, alcohol use, and other psychopathology, as well as timing of initial symptom onset, all have worked under the assumption that different trajectories of alcohol problems and dependence follow from these background characteristics. Research has focused on identifying alcoholic subtypes in which people with common characteristics develop similar alcoholism patterns. For example, typologies classify alcoholism according to age of onset, family history of alcoholism, and presence or absence of antisocial behavior (Babor et al. 1992; Hesselbrock et al. 1984; McGue et al. 1997; Zucker et al. 1995*a*). Studies investigating childhood personality predictors of adult alcohol use disorder represent efforts to describe early developmental trajectories (see Chassin et al. 1999; Cloninger et al. 1988; Martin and Sher 1994; Vaillant 1995; Wong et al. 1999; Zucker and Gomberg 1986; Zucker et al. 1996*a,b*).

Relatively little is known about developmental pathways that bring about change in a person's diagnosis of alcoholism over the adult life course. However, research has shown that the progression of alcoholism is not uniform for all individuals, whether or not they are treated. That is, not all alcoholics remain actively alcoholic after the onset

of the disorder. A general population study investigated stability and change in measures of alcohol abuse and dependence over 4 years among male drinkers (Hasin et al. 1990). Of those originally classified as alcohol dependent, 46 percent still reported indicators of dependence 4 years later, 15 percent had moved to the abuse only category, and 39 percent no longer reported any indicators of alcohol abuse or dependence. Of those originally classified as alcohol abusers, 24 percent remained in the abuse only category, 30 percent reported indicators of alcohol dependence with or without indicators of abuse, and 46 percent no longer reported any indicators of alcohol abuse or dependence. Similarly, a recent review summarizing eight long-term studies found that individuals originally classified as alcohol dependent became abstinent at a rate of about 2 percent per year (Vaillant 1995).

Whether remission is spontaneous or results from treatment efforts, little is known about developmental pathways leading to changes in drinking status over time. As noted in the *Ninth Special Report to the U.S. Congress on Alcohol and Health* (National Institute on Alcohol Abuse and Alcoholism [NIAAA] 1997), factors contributing to successful recovery during treatment have been identified, including increased self-efficacy, fewer coexisting psychiatric problems, a supportive social network, experience with the negative consequences of drinking, and readiness to change. Developmental research on earlier phases of drinking careers suggests that risk factors do not act independently of each other but rather cluster together (Babor and Dolinsky 1988; Donovan and Jessor 1985; McGee and Newcomb 1992; Murphy and O'Farrell 1994, 1996). Conversely, the degree to which context and personality factors interact in contributing to remission is not well understood.

The epidemiologic evidence clearly indicates that problem use drops off with increasing age and with the restriction of consumption that comes with the increased responsibilities of marriage, a regular job, and other adult responsibilities (Bachman et al. 1997; Gotham et al. 1997). Conversely, the presence of the "problem behavior syndrome" predicts continuity of heavier drinking into young adulthood (Baer et al. 1995; Bennett et al. 1999). Other research suggests that "protective" factors (for example, the absence of problem behaviors such as criminal activity) predict a successful return to nonproblematic drinking for alcohol-abusing and alcohol-dependent individuals (Sobell et al. 1993; Tucker et al. 1994), but the degree to which protective factors cluster together is not clear. Unfortunately, the range of opportunity for problem drinkers to benefit from protective factors is often restricted by their drinking behavior and its consequences, including having poorer jobs and lower income, living in a more disadvantaged neighborhood, and choosing to marry a more troubled partner (Jacob and Bremer 1986; Kandel et al. 1986; Zucker et al. 1996*b*, in press). Thus, any contact with a more supportive environment may initially take place piecemeal.

A more complete understanding of how these factors operate, either separately or in concert, is critical to understanding stability and change in alcohol dependence over time. In addition, the role played by environmental risk factors in fostering individual stability or change at other points in the life cycle after adolescence needs to be addressed. The contribution of factors, such as chronic health, marital stresses, spousal and other peer approval of drinking, and factors related to the settings in which drinking occurs need to be better understood (Brennan and Moos 1996; Sher and Gotham 1999). It is important to note that what patients and clinicians regard as "recovery" is called that only because a formal diagnosis has been made. From a developmental perspective, the more general phenomenon that needs to be understood is the natural history of use and problem use over time, which involves both increases (clinically termed "relapse") and decreases (clinically called "recovery").

Social Contexts and Drinking Behavior

Variability in Drinking Behavior Among Societies and Subcultures

In the effort to document the damaging effects of alcohol use, abuse, and dependence at the individual level, overarching social factors that

also influence use and problem drinking behavior are sometimes ignored. One of the factors consistently identified in the epidemiologic literature is that the overall level of consumption in a society (that is, its relative "wetness" or "dryness") is related to the rate of alcohol problems (Edwards 1994; Hilton 1988; Skog 1985). In cultures and historical epochs where consumption is high, rates of alcoholism are higher, and in cultures or epochs where consumption is lower, alcoholism rates are lower (Reich et al. 1988). At the same time, research has shown that among drinkers in drier regions, there is a higher rate of alcohol-related problems, such as accidents, problems with spouses and friends, and difficulties with the police (Hilton 1988).

These data underscore the principle that both drinking and problem drinking are regulated by social structures (rules, role expectations, norms, and values) and by the social behavior of the drinker's peers (Clark 1991; Greenfield and Room 1997; Hilton 1988). Because of the importance of these factors, developmental scientists have worked to understand the role that social context and group membership play in maintaining or changing developmental pathways (Bronfenbrenner 1979; Ford and Lerner 1992).

Demographic Variables as Proxy Indicators for Social Behavior

Racial/ethnic group membership and membership in an age group are identifying characteristics of individuals, but they are simultaneously indicators of the differences in attitudes, values, beliefs, and practices of social subgroups. As discussed above, memberships in and of themselves do not explain how alcohol use and more problematic drinking patterns come about. Aside from providing an identity, the label of group membership is also a proxy for differences in the way the group acts, how available it makes alcohol and other drugs, its regulatory structure for alcohol and other drug use, and other social behaviors. This underlying social structure defines and shapes the relationship between group membership and alcohol involvement (Heath 1988). One of the core aims of developmental research has been to identify the common underlying factors that place some groups and social contexts at higher risk than others and then to develop prevention and intervention strategies to eliminate or neutralize their effects.

When the research question is framed this way, it highlights an interesting observation, namely, that many of these markers are cooccurring and therefore are potentially related indicators of a more basic set of influences. For example, both low overall rates of alcohol use and high rates of problem drinking among current drinkers have been observed among people with a lower educational level, rural residence, and Southern location (Dawson et al. 1995). These characteristics also happen to be markers of a subculture with strong abstinence values, which influence both the individual drinking patterns and the overall level of alcohol consumption of the society (Edwards 1994; Hilton 1988; Skog 1985).

The more general point is that variations in demographic characteristics indicate differences in lifestyle that relate to norms about alcohol use and misuse (Greenfield and Room 1997), including the valuing of alcohol as a sought-after beverage (Laflin et al. 1994) and the accompanying presence of a social network that provides pressure to use or not to use, or to engage in more or less problematic drinking behavior when using (Oostveen et al. 1996).

Demographic Factors as Life Course Identifiers

Age-related variations in alcohol use exist for virtually all indicators of alcohol involvement. In addition, at least among men, differences between racial/ethnic groups are more the rule than the exception. Indeed, cross-sectional data from a number of surveys show that within racial/ethnic groups, levels of both alcohol consumption and alcohol abuse vary significantly with gender (Caetano and Clark 1998; Caetano and Kaskutas 1995; Gerstein et al. 1994; Grant 1997; Grant et al. 1992). From a life course perspective, these variations suggest that people in different racial/ethnic and gender groups should be looked at in terms of their different life cycle tasks and patterns of alcohol use.

With respect to gender differences alone, more than a decade ago, a longitudinal study showed that problematic drinking patterns emerge later in life for women than men (Fillmore 1987). In addition, for women, less time elapses from the initial emergence of the problem to full-blown problem development. In other words, the shapes of their trajectories differ from those of men. However, more recent data, discussed later in this section, suggest that this gap is closing (Grant 1997).

With respect to racial/ethnic distinctions alone, analyses of shifts in national drinking patterns between 1984 and 1992 indicate that decreases in heavy drinking observed among whites were not present among either blacks or Hispanics (Caetano and Clark 1998; Caetano and Kaskutas 1995). Thus, these subpopulations are operating differently with regard to patterns of alcohol abuse.

Variation across ages according to race/ethnicity and gender is illustrated in figures 1 and 2, which show the percentage of subgroups in the U.S. population that reported having four or more drinks on any single day during the prior 30 days. These data derive from the Substance Abuse and Mental Health Services Administration National Household Survey (Gerstein et al. 1994; Jackson et al. 1998). At all ages, females in each racial/ethnic group exhibited lower levels than comparable males. Within each gender, however, racial/ethnic groups displayed different age-related patterns. These age-related racial/ethnic patterns were most marked in males. Among white men, the proportion of heavy drinkers peaked between ages 18 and 25 and then declined with increasing age. In Hispanic men, the peak occurred between ages 26 and 30, and the age-related decline was less marked than in whites. In black men, the peak also occurred between ages 26 and 30, but the proportion was consistently lower at each age in blacks than in Hispanic men.

Researchers in the last decade have been attempting to look beneath these surface demographic data and develop theories about the common social forces that regulate variations in drinking behavior among these racial/ethnic and gender subgroups. Using a life course framework, some researchers have focused on racial/ethnic subgroup variations. For example, differences between blacks and whites in the age trajectory of alcohol use and problems (see figures 1 and 2) have been related to a combination of factors, including urban migration, declining heath status of middle-aged black Americans, less access of blacks to the opportunities among blacks of the larger society, and the cumulative effects of adverse living conditions and restricted socio-economic opportunities among blacks (Geronimus 1992; Jackson et al. 1998).

A related idea is that culture-specific social forces might affect alcohol problem rates reported by black and white women. Research suggests that black women experience more tolerant attitudes toward their drinking than white women do and that blacks historically demonstrate greater equality in gender roles than whites do (Herd 1997). These factors may influence the amount of negative reaction to heavy drinking encountered by black and white women, and may thereby indirectly affect their self-ratings of alcohol dependence (Herd 1997). Similarly, one researcher has proposed that both trajectory effects and life course-related role differences between older and younger members of the Hispanic community account for the stability of heavy drinking among elder Hispanic men (Caetano 1991). The social networks of these drinkers tend to insulate them from outside pressures to change; because of their status, older men are less likely to be challenged by younger members of the community. Thus, patterns of heavy drinking that the elder men established at an earlier life stage are not as likely to become disrupted.

Finally, although differences clearly exist in drinking patterns from one culture to another, cross-cultural similarities have also been observed. Evidence for both the differences and similarities can be derived from a review and synthesis of data from more than 20 international longitudinal surveys of drinking behavior (Fillmore et al. 1991; Johnstone et al. 1996). National origin of the research, an indicator of the culture of each sample, was the most influential factor in

predicting drinking patterning. Evidence supports the view that within a given culture, each gender develops a pattern of alcohol consumption in youth and early adulthood and the pattern is largely set for a person's lifetime. The evidence also points to a "maturational hypothesis" that can be seen in all cultures. This cross-cultural pattern involves rapid rises in drinking behavior in early adulthood followed by declines in frequency of use with increasing age (Johnstone et al. 1996).

Changes in Patterns of Drinking Behavior as a Function of Social Change

Cohort and Subgroup Differences

As noted, it is a common epidemiologic observation that the problems of alcohol involvement are most heavily the problems of youth. This observation is as true for the United States as it is for the rest of the world (Dawson et al. 1995). Here also, as part of the normal life cycle, alcohol consumption and problem use decline with advancing age (Adams et al. 1990; Bachman et al. 1997; Blane 1979). However, changes in individual drinking behavior over time are not solely a function of age-graded life cycle changes. As discussed above, individuals' different developmental pathways, such as those related to temperament, are superimposed on life stage changes, as are influences of the larger society (Zucker et al. 1995*a*). Thus, if the society's patterns of use and attitudes about use change, one can anticipate that such a change will either suppress or enhance the emergence of individual drinking behavior.

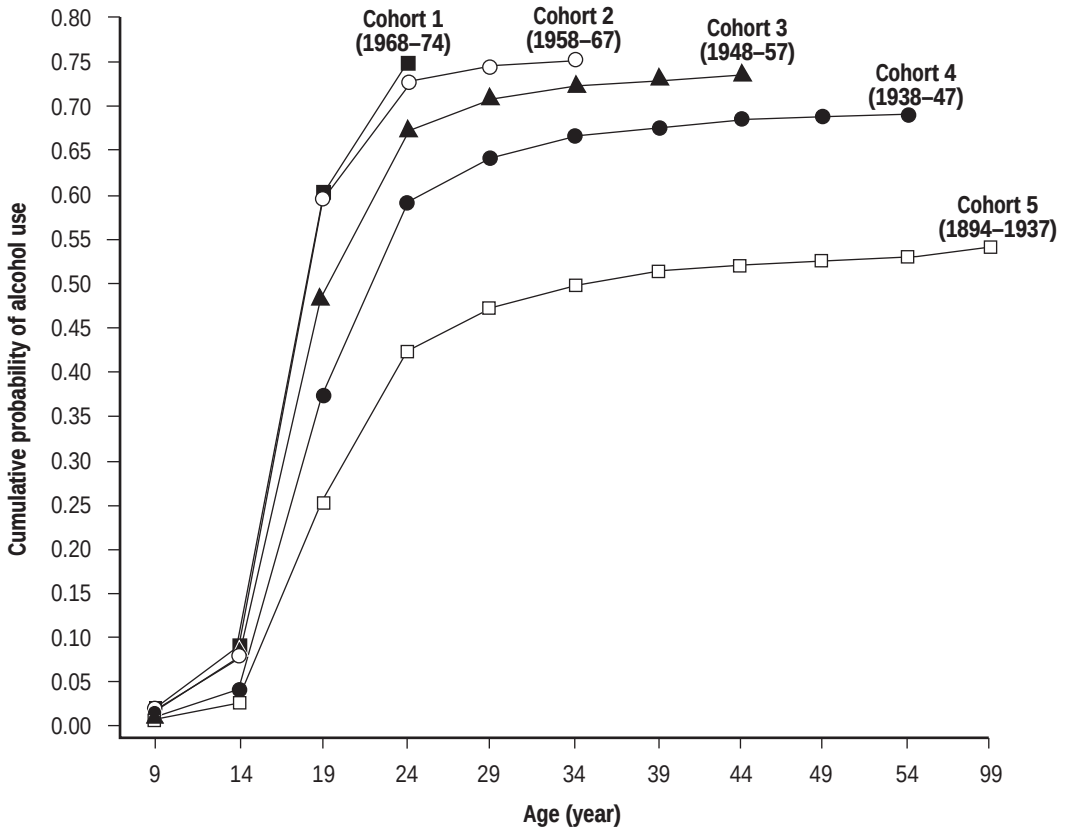
Recent analyses from the first wave of the National Longitudinal Alcohol Epidemiologic Study (NLAES) (Grant 1997) suggest that considerable social change in drinking has occurred over the past century. This change has been characterized by increasingly earlier ages for the onset of alcohol use (figure 4) and increased likelihood of alcohol dependence among cohorts of drinkers (figure 5). For example, a shift was observed in the probability of alcohol use in early adulthood (ages 20 through 24). In the group born before World War II (between 1894 and 1937), drinking was confined to less than half of the young adult population. However, in the group born in the Vietnam era (between 1968 and 1974), alcohol use involved approximately three-fourths of young adults. Both genders displayed this trend, although levels among females were consistently lower than levels among males. A major upward shift was also observed in the likelihood that a drinker would be diagnosed with alcohol dependence at some point in his or her lifetime. Although these findings are quite consistent, caution should be used in their interpretation, since the data were derived using methods in which individuals were surveyed at a single point in time. In addition, participants were asked to remember the age at which various alcohol-related problems became manifest. Thus, methodological problems, such as recall difficulties, especially for events from the distant past and for relatively transitory events (as well as cohort-specific differences in willingness to reveal alcohol problems), may have affected the results.

Gender-specific data indicate the appearance of another major social change: increasing similarity of drinking patterns of men and women (Grant 1997). For persons in early adulthood (ages 20 through 24), males born before World War II were 2.4 times as likely as females to use alcohol. The ratio is much smaller for those born in the Vietnam era: males were only 1.2 times as likely as females to use alcohol. For lifetime diagnosis of alcohol dependence, findings are equally striking: males born before World War II were 4.9 times as likely as females to receive such a

Cohorts

Cohorts are groups of persons born during a given time span (such as Baby Boomers) who experience a common set of historical, social, and economic influences that tend to shape the behavior of group members in similar ways. Central to the concept of a cohort is the idea that those who share a culture acquire a body of common experiences, and in so doing create a unique subculture, with shared norms and values and commonalities in behavioral repertoire.

Figure 4: Cumulative probability of alcohol use, by cohort



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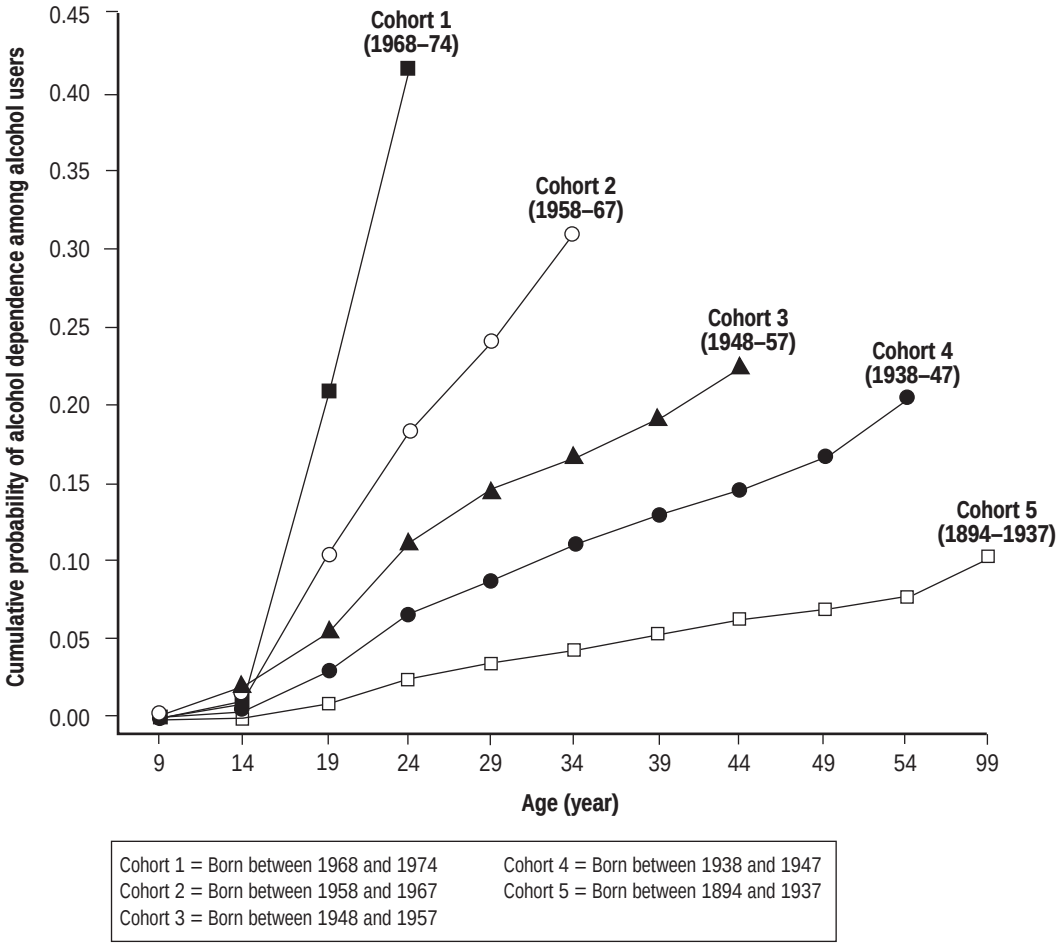
diagnosis, but for those born in the Vietnam era, the male-to-female ratio was only 1.4. A similar pattern of converging rates of alcohol dependence in men and women has also been noted in the National Comorbidity Study (Nelson et al. 1998).

NLAES data highlight yet another phenomenon of developmental interest: diagnostic stability into later life (Grant 1997). Men were more likely to sustain a diagnosis of alcohol dependence over time than were women, and this persistence was most evident in the youngest cohort (that is, those born between 1968 and 1974), the group that also showed the earliest onset of both alcohol use and dependence. These findings also lend support to a long-held view in the field of alcohol and other drug abuse that differences in the timing of onset of use can change the structure and trajectory of the disorder (Robins and Pryzbeck 1985). Stronger support comes from recent data (Grant and Dawson 1998) indicating that the younger the age of drinking onset, the greater the likelihood that an individual will develop an alcohol use disorder at some point in life.

From a developmental-contextual perspective (Ford and Lerner 1992), the individuals in each cohort have been moving through the life course surrounded by a different social structure of attitudes and expectancies about alcohol use and other social behavior and about alcohol dependence. On these grounds, the effects of the social change on individual drinking behavior

Figure 5: Cumulative probability of alcohol dependence among alcohol users, by cohort



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should vary according to the individual's stage in life, or "life course location" at the time the change is occurring. This proposition has been labeled the "life stage principle" (Elder and Caspi 1989). It specifies that the influence of a historical event on the life course depends on the stage at which an individual experiences the event. The effects of social change and individual response to such change will vary in type and relative influence across the life course (Elder and Caspi 1989). The analytic usefulness of the life stage principle in alcohol research lies in its potential to help the field organize and understand the significant changes in patterns of use and dependence that occur at both the younger and the older ends of the age spectrum.

Variations in Alcohol Use Among the Elderly

Patterns of drinking among those over age 60 provide another illustration of the interaction of a person's location in the life course, the subgroup to which he or she belongs, and the level of alcohol involvement. The elderly population is an important and interesting subgroup because it is rapidly increasing in size, as it has throughout U.S. history, and its composition is changing (Day 1996; Hobbs and Damon 1996). Between 2010 and 2030—when the Baby Boom cohort moves into the ranks of the elderly—this population will swell to more than 55 million people (some estimates range as high as 75 million), from about 33 million in 1994. The

proportion of the population over age 65 will increase by 73 percent during this 20-year interval, while the segment under age 18 will decrease by 3 percent. Whereas about one in eight Americans were over age 65 in 1994, by 2030 that figure will be one in five (Day 1996; Hobbs and Damon 1996). These data suggest that in the coming years the Nation will become more focused on the processes and outcomes of aging, and that the needs of older citizens will become an even more central concern (Zucker 1998).

Along with demographic and social changes, patterns of alcohol consumption among the elderly are also changing. Sales data for alcoholic beverages and results from a national survey show a significant decline in the 1980's in the level of alcohol use in the U.S. population as a whole (Midanik and Clark 1994). Results from 1984 and 1990 national surveys on alcohol use show that 70 percent of the population reported current drinking in 1984, but only 65 percent did so in 1990. (Current drinking was defined as consuming alcohol at least one time in the year preceding the survey.) However, these overall population figures obscure significant variation in certain subgroups, especially age and gender groups. For example, 59 percent of men aged 60 and older were current drinkers in 1984, but the figure increased to 66 percent in 1990 (Midanik and Clark 1994). For women aged 60 and older, the trend was reversed: 49 percent were current drinkers in 1984, and 37 percent in 1990. Thus, elderly men displayed a larger increase and elderly women exhibited a larger decline in current drinking than the overall population did.

This age-by-gender variation, on the one hand moving in opposition to overall population trends and on the other hand consistent with them, underscores another developmental principle that has special relevance for the elderly, namely, that there is very large subgroup heterogeneity (Hertzman et al. 1994; Ruchlin 1997). Thus, although population statistics indicate that drinking generally declines as people age, this decline does not translate to low levels of drinking and low levels of problems for all elderly individuals. For example, when the elderly population is examined in terms of racial/ethnic group membership (see figures 1 and 2), the heterogeneity of drinking patterns is clear. The relatively greater use of alcohol and the higher prevalence of alcohol dependence in the Baby Boomer cohort compared with the previous cohort (Grant 1997) are also important factors, particularly because this group will be the next generation of elderly Americans.

In general, drinking among the elderly produces problems not seen in younger groups because of changes in health and social support that often accompany aging. Thus, for older individuals, even relatively modest alcohol use may cause significant problems because of chronic illnesses, the interactions of alcohol with medications, grief brought on by the death of loved ones, and isolation due to the loss of social support networks (Dufour et al. 1992; Gomberg et al. 1998).

In addition to increased numbers of older individuals in the population, other changes can be expected to produce substantially greater problem use among the elderly than in past generations (Zucker 1998). One change will be the substantial increase in the total number of white Americans in the elderly population (Hobbs and Damon 1996). In absolute numbers, the subpopulation of Caucasian older Americans will increase by 45 percent, which may have ramifications for the future because white males who drink have historically continued to use alcohol into older age (Caetano and Kaskutas 1995; Substance Abuse and Mental Health Services Administration 1997). In addition, this subpopulation, which will remain the largest subgroup of the elderly population over the next two decades (Hobbs and Damon 1996), will have a higher educational level and greater financial resources than earlier generations, resulting in a lifestyle of sustained leisure-time activity in which moderate alcohol use is the norm. As noted above, even moderate use can create significant problems as people age.

Another change likely to lead to increased problem alcohol use in the elderly will be the growth of the Hispanic population, which is expected to show the largest rate of increase of any racial/ethnic elderly subgroup over the coming decades (Hobbs and Damon 1996). Results from a 1992 survey show that Hispanic males have the highest incidence of frequent heavy drinking among all racial/ethnic groups (Caetano and Kaskutas 1995). In addition, when 1992 results were compared with 1984 findings, the heavy-drinking patterns of Hispanic men were more likely than those of white men to remain stable over time (Caetano and Kaskutas 1995). Yet another change that will likely increase problem drinking is the projected doubling of the number of elderly persons from socio-economically disadvantaged groups. These groups already have higher rates of drinking problems and appear to be sustaining a higher level of problem use into older age than existed in earlier cohorts of the elderly (Caetano and Kaskutas 1995).

Finally, the elderly population will experience increased longevity—the oldest-old population (those aged 85 and older) is expected to double to 7 million persons by 2020 (Hobbs and Damon 1996). As older people live longer, complications from interactions of alcohol with medications and medical disorders are likely to increase sharply. Little is currently known about the relationship between patterns of alcohol use, especially higher levels of drinking, and the physical and health conditions unique to persons in this group (NIAAA 1997), or about differing medical consequences of alcohol intake within different age groups of the elderly population (Smith and Baltes 1997). What is known, however, foreshadows difficulties as changes occur in the makeup of the elderly population. Alcohol-related hospitalizations among the elderly are common, with rates similar to those for heart attack (Adams et al. 1993). Injuries and deaths in alcohol-related accidents are a serious problem among the elderly: 11 percent of drivers aged 65 through 74 in fatal crashes in 1994 tested positive for alcohol (National Highway Traffic Safety Administration 1995). In addition, in nonfatal crashes, the extent of injury sustained by an older person is likely to be greater than that sustained by a younger person for a crash of equal force (Waller 1998).

Development and Drinking Behavior: Dynamic Models of Stability and Change

The usefulness of the developmental perspective is shown by its recent emergence as a tool for understanding the development of risk for a variety of health behaviors and chronic diseases (for example, see Blane 1995; Kuh and Ben-Schlomo 1997; Mann et al. 1992). A recent extensive review of the relationship between socioeconomic status and health outcomes noted that the course of adult health and disease risk is influenced by multiple sets of life course factors (Kuh et al. 1997). One set involves exposure to long-term biological chains of risk, another involves exposure to social chains of risk. Both chains continue to operate throughout the life course via learning experiences (a third chain) that lead to adult outcomes, which in turn affect disease risk through behavioral style and through heightened exposure to causal factors later in life.

In the same manner, a multilevel set of factors produces life course variation in alcohol use and alcohol dependence. Patterns of use are regulated by cognitive and motivational networks, which are determined by the user's subjective experience of the drug, knowledge of the rule structure for appropriate use, and belief about whether it is more or less desirable to drink at a given point in time (Fischhoff and Quadrel 1995). The immediate encouragement and availability offered by peers also regulate onset and course. The timing of when initial use takes place and the development of problem use are heavily influenced by patterns of alcohol use among peers. Peers whose behavior involves risk taking and antisocial behavior are also more likely to encourage early problem drinking, and their continued presence increases the likelihood that drinking problems will emerge and be sustained.

At the same time, alcohol-related disorders are brain disorders, involving the brain's mechanisms

for appetite, craving, reward (Koob et al. 1994), planning and forethought, affective states such as depression and anxiety, and behavioral control. Relative sensitivity to alcohol's effects (Schuckit 1994) and the ability to control drinking (Pihl and Bruce 1995; Pihl and Peterson 1991) also play a role.

Developmental theory reminds us that the two domains of influence—one psychosocial, the other neurobiological—operate within the confines of a larger, less visible system that surrounds its members. Nonetheless, the rule, availability, and activity structure of the larger society plays a highly significant role in regulating drinking behavior. This larger social system restrains heavy consumption in some eras and in some community settings and allows it to flourish in others. Legal restriction and social policy affect the use of alcohol. Prohibition and wartime rationing are examples of a phenomenon that continues to change as lawmakers and policy makers restrict or increase the availability of alcohol and change the penalty structure for its use. Finally, societal context and neurobiology interact from the time of an individual's conception. Thus, the individual becomes a dynamic organism functioning in a social, psychological, and biological context (Gottlieb 1991; Nesse and Berridge 1997; Wiers et al. 1998). This multilevel explanatory structure is the causal puzzle that scientists are currently working to piece together. The developmental framework allows the pieces to begin to be fit together.

In Closing

A complex set of factors introduces individuals to alcohol and produces variations in alcohol use and abuse over the life course. Factors include psychosocial and neurobiological mechanisms as well as influences from the larger society. A mounting body of evidence has begun to demonstrate that this process is a dynamic one, involving the creation of a chain of risk with contributions to outcome from three sets of factors—neurobiologically determined and regulated life course processes not specifically related to alcohol; other life course processes, such as disadvantaged socioeconomic status, also not specifically related to alcohol; and factors pertaining to alcohol, such as group norms about use. A series of recent studies shows that measures of behavioral undercontrol in early childhood are predictive of adult alcohol disorder. Although this work is only one part of the complex developmental puzzle of how early risk leads to clinical disorder, it indicates that the process is one involving neurobiological vulnerability, psychosocial factors that support the vulnerability, and a culture that makes alcohol available for use. Solving this developmental puzzle will require multidisciplinary efforts to formulate models of causal processes at different mechanistic levels and at multiple stages in the life course of risk and clinical disorder.

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Alcohol and Violence

Of the 11.1 million victims of violent crime each year, almost one in four, or 2.7 million, report that the offender had been drinking alcohol prior to committing the crime (Greenfeld 1998). Among the attacks that were committed by current or former intimate partners of the victims, two out of three of the offenders had been drinking prior to the attack (Greenfeld 1998). Over the years, consistent findings such as these have stimulated research into factors that might contribute to alcohol-related violence and the question of whether alcohol use is not merely associated with, but perhaps a cause of, violence.

Alcohol-related violence is the result of complex interactions between individual and environmental factors that either promote or inhibit violence. Findings from numerous studies implicate several variables—including personality factors, individual expectancies, situational elements, and sociocultural influences—that may interact with alcohol's pharmacologic effects. What is not clear is whether and under what circumstances these interactions may combine to lead to violent episodes. It is also not known what interventions might prevent or reduce the likelihood of alcohol-related violence.

In recent years, however, using increasingly sophisticated methodology, researchers have made advances in understanding the individual and environmental factors related to alcohol and violence and in addressing the issue of causation. In addition, the field is progressing as a result of new theoretical frameworks that describe the complex interplay between individual and environmental influences and incorporate an "interactional level" that is influenced by each. This section focuses on recent developments in these areas.

Studies at the individual level include investigations of alcohol use by both the offender and the victim. Regarding the offenders, research has long indicated that there is an association between drinking and the perpetration of violent acts (for reviews see Collins 1981, 1989; Lipsey et al. 1997; Pernanen 1976, 1981, 1991; Roizen 1993, 1997). More recent research has extended this finding by examining related items of interest such as variations by the amount of alcohol used, the severity of the ensuing injuries, and the social relationship between the offender and the victim.

Regarding the victims of alcohol-linked violence, studies have investigated risk factors for becoming a victim and have examined whether alcohol consumption by the victims, as well as the offenders, might influence those risks. Although the study of alcohol use by victims is newer and somewhat less developed, it is proceeding along some of the same avenues as research on offenders, such as looking at the relationships between offenders and victims.

This section also reviews studies about environmental factors in the relationship between alcohol and violence. These include studies of individual bars and street locations as well as studies of comparative crime rates across cities and States. A key variable in this research is sometimes alcohol availability rather than alcohol consumption. The expectation is that decreased availability might lead to decreased consumption, which might lead in turn to lower rates of violence. Availability is of interest because it is a potential "policy lever" that could be manipulated if a causal relationship between availability and violence rates were firmly established.

An important goal of this research is to advance beyond simply finding that violence rates increase with increasing alcohol consumption, to move toward scientific results that would strengthen our ability to conclude whether this relationship is causal. Two kinds of environmental or policy-based studies are useful steps in this direction:

those that gather data at set intervals over time, and those that gather data both across time and at different locations.

Researchers pursue across-time studies by collecting data in several waves over time (longitudinal survey studies) or by analyzing regularly collected data series, such as annual homicide rates for cities (time-series studies). These study designs help to establish the temporal relationships between variables, an important step toward demonstrating causality. Even though, for example, variables A and B might be related in the sense that whenever A happens, B also happens, A cannot be said to cause B unless A happens before B. Furthermore, when data are collected regularly over time, studies can reveal such associations as two variables rising and falling in synchrony. Demonstration of this kind of relationship would provide more persuasive evidence of an underlying causality than, for example, the finding of a one-time connection among variables through a cross-sectional study. In either case, however, an apparent relationship between two variables may actually be caused by a third, unknown factor. Thus, studies that attempt to establish causality must not only determine the timing of events, but also identify and measure the effects of any intervening factors that may have affected the outcome.

More effective than the across-time approach alone is one that also gathers data from several different locations (across time and across space, or a "pooled, cross-sectional, time-series analysis"). These designs give researchers a particularly strong basis for attributing causality in the findings. Recent work on environmental contributions to violence has pursued both paths in order to gain deeper insights into the question of causality.

Also included in this section is a review of some recent theoretical developments in the field of alcohol and violence. In addition to advances made through research, the knowledge base in this field can increase through the development of new conceptualizations to explain facts or events. After emerging, these conceptualizations become shared among scientists and eventually are tested in studies. Thus, a look at the developing theories is a preview of the kinds of empirical studies that are likely to be conducted soon.

Finally, a few words on the scope of this review. First, it does not address self-inflicted violence (that is, suicide). Second, it focuses on epidemiologic or population-based studies and thus omits ample research using laboratory animals (for reviews of this literature see Brain et al. 1993; Higley and Linnoila 1997; Miczek et al. 1997; Yudko et al. 1997) and human laboratory experimental studies (for recent meta-analyses of this literature see Bushman 1997; Lipsey et al. 1997). These studies suggest that there is no simple or inevitable relationship between alcohol and aggression. Psychopharmacologic, personality, cognitive, and situational factors all appear to play important roles in influencing whether violence will occur. Nevertheless, experimental findings do suggest that, in laboratory settings, alcohol tends to increase aggressive responses in a way that might be interpreted as relatively strong support for a causal effect of alcohol consumption on violence.

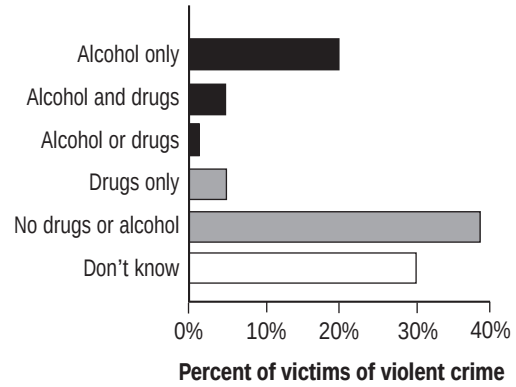
Individual-Level Studies: Drinking by Offenders

The National Crime Victimization Survey (NCVS) has found consistently that alcohol is more likely than other drugs to be involved in substance-related violence. According to data from 1992 through 1995, nearly one-fourth of all victims of violent incidents were reasonably certain that one or more of the offenders had been drinking alcohol before committing the offense (Greenfeld 1998). In 20 percent of all incidents the offender used alcohol only; in 5 percent the offender used both alcohol and other drugs; and in 1 percent the offender was known to be under the influence but it was not known whether the offender was using alcohol or drugs (figure 1). By comparison, in only 5 percent of the incidents was the assailant reported to be under the influence of drugs but not alcohol. Thus, despite the popular conception that violent crime is strongly linked to drug use by offenders, this study indicates that

there is actually a much greater probability that any given violent incident will be related to alcohol use than to use of other drugs by the offender.

Furthermore, the 25-percent estimate of drinking among offenders reported by the NCVS is likely to be an underestimate. This is because homicides, which are omitted from the NCVS data, consistently have a higher proportion of alcohol involvement than do the less serious forms of violence that are included in the NCVS (for reviews see Collins and Messerschmidt 1993; Lipsey et al. 1997; Murdoch et al. 1990; Pernanen 1991; Roizen 1993). For example, in one recent study where 268 homicide offenders were interviewed about their crimes, 32 percent reported being intoxicated at the time of the offense (Spunt et al. 1994, 1995). In a study of 1,768 homicide case records in New York State in 1984 through 1988, more than 47 percent of the homicides involved alcohol use by the offender (Goldstein et al. 1992). In addition, according to the Bureau of Justice Statistics, convicted murderers in State prisons reported that alcohol was a factor in half the murders they had committed, with alcohol involvement higher in murders of intimates (54 percent) than murders of acquaintances (50 percent) or strangers (47 percent) (Green-feld 1998).

Figure 1: Among victims of violent crime, percentage who were certain that the offender had been drinking or using other drugs before committing the crime



Source: Greenfeld 1998.

Not only is the use of alcohol prevalent among offenders, but the amount of alcohol consumed at the time of the offense is likely to be quite high (Greenfeld 1998). In one study, the estimated average blood alcohol concentration (BAC) of offenders who had been drinking was in the range of double or triple the thresholds of impairment most commonly used in State driving while intoxicated (DWI) laws. The study estimated average BAC's of 0.18 percent for probationers, 0.20 percent for local jail inmates, and 0.28 percent for State prisoners at the time of their offense, while blood alcohol limits for DWI are usually either 0.08 or 0.10 percent (Greenfeld 1998).

A broad-based review of the literature on individual-level studies of offenders' drinking and violence—among both adolescents and adults—yielded a somewhat similar picture of the relationship between drinking and violent behavior (Lipsey et al. 1997). This review of 129 studies published between 1950 and 1994 found repeated evidence of an overall relationship between greater alcohol use and criminal and domestic violence, with particularly strong evidence in studies of domestic violence. However, when researchers accounted for a greater number of "control variables" (such as gender, age, social class, criminal status, childhood abuse, and use of other drugs in addition to alcohol), they tended to find that these control variables weakened the strength of the original relationship between violence and alcohol consumption, in some cases to the point of no association. For example, in 6 of the 14 studies of criminal violence that had data on control variables, no statistically significant relationship between alcohol and violence remained after the influence of control variables was removed. In the domestic violence studies, however, while control variables reduced the association, 11 of the 13 studies reported statistically significant levels of association that remained after the analysis controlled for other variables. The researchers concluded that, although research to date shows substantial evidence of an association between alcohol and violence that is consistent with a causal relationship, it will not be possible to state conclusively

that alcohol causes violence until further research using a wider array of control variables is conducted.

Alcohol and the Severity of Violence and Injuries

Studies have generally found that the more serious the crime or injuries, the more likely alcohol was involved. For example, a recent study showed that drinking offenders committed 15 percent of robberies, 26 percent of aggravated and simple assaults, and 37 percent of rapes and sexual assaults (Greenfeld 1998). Moreover, as noted previously, homicides are more likely to involve alcohol than are less serious crimes.

An earlier study on injury severity showed that the use of alcohol by men was associated with more severe violence and a greater severity of injuries among victims who were intimate partners (Stets 1990). More recently, researchers using NCVS data from 1992 and 1993 found a significant association between assailant alcohol use and injury severity for men's assaults on intimate female partners (Martin and Bachman 1997). This link between increased alcohol use and greater injury severity persisted even after the researchers made statistical adjustments for the victim's marital status, victim's age, and place of injury occurrence.

Another recent study also found that alcohol consumption by husbands increased the severity of domestic violence (Leonard and Quigley 1999). In this survey of marital violence among newlyweds, researchers found that physically aggressive episodes were four times as likely as verbally aggressive episodes to involve the husband's drinking. In cases where both physically and verbally aggressive episodes occurred during their first year of marriage, couples reported nearly twice as much overall alcohol involvement in the physically aggressive episodes than in the verbally aggressive episodes.

A study using NCVS data from 1992 through 1994 found that alcohol use by perpetrators did not affect the likelihood that rape would be completed or that medical treatment for the victim would be needed, but did increase the chances that the victim would suffer additional physical injuries beyond the trauma of sexual assault (Martin and Bachman 1998). Thirty-nine percent of the victims who perceived the offender to have been drinking were injured, whereas 25 percent who did not perceive the offender to have been drinking were injured. When the investigators conducted a second analysis that controlled for a range of variables in addition to assailant drinking (such as the victim's race, age, and income as well as presence of a weapon, place of the attack, and physical resistance), the offender's use of alcohol was still positively associated with the likelihood of additional injuries, but was not statistically significant.

Attacks on Intimate Partners Versus Strangers

As mentioned previously, research has also indicated that violence against intimate partners is much more likely to involve alcohol than is violence against strangers. In NCVS data, alcohol was used by 67 percent of persons who victimized an intimate (that is, a current or former spouse, intimate partner, or boyfriend or girlfriend) compared with 38 percent of those who victimized an acquaintance and 31 percent who victimized a stranger (Greenfeld 1998).

In other research, investigators found that half of alcoholic men who were receiving treatment had been violent toward an intimate partner in the year before alcoholism treatment (O'Farrell and Murphy 1995). The same researchers reported that levels of domestic violence significantly decreased after behavioral marital therapy, particularly among alcoholics who did not relapse.

The Role of Personality Factors

Other studies have tried to examine the development of both alcohol use and violent behavior during adolescence and youth. The aim of these studies has been to understand how links form between alcohol use and violence during the period when the personality is developing.

The Rutgers Health and Human Development Project collected three waves of data on New Jersey adolescents (aged 12 through 18) in 1982 through 1984, 1985 through 1987, and 1992 through 1994 (White et al. 1993*a*,*b*; White 1997). The results of this research project indicated that the apparent connection between aggression and alcohol use in adolescents was actually caused by a third factor—a proclivity for exhibiting generalized problem behavior—that caused both heavy drinking and aggression. (In this study, "aggression" was defined to include (1) hurting someone badly, (2) using a weapon in a fight, (3) vandalism, (4) hitting parents, or (5) fighting at school. As most of these items also indicate violence, the conclusions about aggression may be taken to generally apply to violence as well.)

The Buffalo Longitudinal Survey of Young Men was similar in that it focused on younger subjects (aged 16 through 19), used a research design that collected data in waves over time, and examined underlying personality factors at work in the alcohol-violence connection (Zhang et al. 1997). The study contained two analyses: one predicted the probability that a person would commit an assault, and the other predicted how frequently assaults would occur among those who did commit them. In the first analysis, offenders' drinking patterns did not independently contribute to the probability that they would commit an assault, but the patterns did act in concert with such personality factors as deviant attitudes, aggressiveness, and hostility to raise that probability. In the other analysis, involving those who did commit assaults, increased drinking was directly related to greater frequency of assault.

In sum, recent research on the relationship between offenders' drinking and the perpetration of violence has continued to show that offenders' drinking is related to violence, that the amount of alcohol consumed tends to be larger in more serious offenses, and that the connection between drinking and violence is stronger where the relationship between perpetrator and victim is closer. Studies are now trying to explore these issues further, largely through examining the interactions between personality and situational factors and both alcohol use and violence in youth.

Individual-Level Studies: Drinking by Victims

Researchers have also examined the matter of drinking by the victims of violence. While alcohol consumption by a victim does not excuse an offender's actions, drinking may reduce a person's awareness of or ability to respond to threatening situations, place a person in a social situation or environment that is more violence prone, or mark a potential victim as an easy target.

Much of the data on the connection between alcohol and violent injuries has come from studies carried out in hospital emergency rooms. Reviews of these studies have found that persons in emergency rooms with violence-related injuries were two to five times as likely as persons injured from all other causes to have some alcohol in their bloodstream or to be intoxicated (Cherpitel 1994, 1997). In addition, persons consuming larger amounts of alcohol were found to be at greater risk for violence-related injuries than those consuming smaller amounts (Borges et al. 1998).

A substantial amount of the research on victims' drinking has focused on the victims of sexual assaults. Researchers have found positive associations between alcohol use and sexual assault in studies of college students (Abbey et al. 1996, 1998; Muehlenhard and Linton 1987), convicted rapists (Ullman and Knight 1993), and spouses involved in marital rape (Russell 1990). One study of 52 women bar drinkers reported that most of the women (85 percent) had experienced some form of nonsexual physical aggression and one-third (33 percent) had experienced attempted or completed rape associated with drinking in a bar (Parks and Miller 1997). Although the researchers found that the risk of nonsexual victimization was not related to how frequently the women went to bars, they found that the women who went to bars more often had a

greater risk of sexual victimization. Other research shows that increased likelihood of victimization among drinking and intoxicated women may be related to their impaired cognitive and motor functions, which reduces the ability to perceive risk or avoid aggression, and the perpetrators' expectancies of increased sexual availability (Abbey et al. 1996).

Although many studies have found an association between alcohol consumption and domestic violence, both in general population samples (see Kantor and Straus 1987; Leonard and Senchak 1993) and in studies of batterers (see O'Farrell and Murphy 1995), findings regarding alcohol use by victims are mixed. One recent study found that there is little evidence that the wife's drinking is associated with the husband's aggression (Leonard and Quigley 1999). Also, a review of the literature on the "intoxication-victimization" hypothesis, which suggests that women "under the influence" of alcohol or drugs may become targets of male aggression, found mixed evidence supporting an association between women's intoxication and physical assaults by husbands (Kantor and Asdigian 1997). An analysis by the same researchers of data from the 1992 National Alcohol and Family Violence Survey indicated that the wife's alcohol use did not have significant effects on husband-to-wife violence when the husband's drinking, use of drugs, and selected sociodemographic variables were accounted for in the analysis (Kantor and Asdigian 1997). The researchers concluded that there is little evidence that women's drinking provokes or even precedes aggression by husbands. In short, the evidence for a connection between victims' drinking and the experience of violent victimization is not as clear in the case of partner or spouse abuse as it is in sexual assaults by other perpetrators.

Environmental Influences

An alternative to studying the individuals involved in violent events (whether offenders or victims) is to study the places where violence occurs. Several recent studies have taken this approach. In some older research, criminologists studying the geographic distribution of violence had found that alcohol availability was a key factor in identifying where crimes of violence occurred. In an investigation of locations in a large U.S. city to which police were dispatched to handle violent crimes, researchers found that on-site alcohol outlets such as bars and restaurants were among the "hottest" of the "hot spots" for violence (Sherman et al. 1989). In another large U.S. city, researchers found that city blocks with bars had higher rates of assaults, robberies, and rapes than other blocks, even after the analysis accounted for the impact of unemployment and poverty (Roncek and Maier 1991).

A number of studies have analyzed the characteristics of bars that are most strongly associated with violence. The characteristics include the type of drinking establishment, the physical and social environments, the types of patrons, and the role of bar workers. For example, bars with a reputation for violence, skid row bars, and discotheques are more likely than others to experience violent incidents (Homel and Clark 1994). Bars that are unclean, poorly ventilated, and dimly lit, and those patronized primarily by groups of males rather than solo males and couples, are also more likely than others to experience violent incidents (Homel and Clark 1994). The same study found that barroom environments predictive of aggression were those where there was swearing, sexual activity, prostitution, drug use, drug dealing, and an "anything goes" atmosphere. In other research, aggression has also been found to be associated with lack of control by bar workers, low staff-to-patron ratios, crowding, and failure to engage in responsible serving practices (Graham 1985; Homel et al. 1994; Stockwell et al. 1993).

Studies Across Different Locations

Other recent studies have focused on the effects of alcohol outlet density on violence across cities, with mixed findings. A study of 74 cities in Los Angeles County found that rates of assault reported to the police were significantly associated with the density of outlets selling alcohol for consumption either on or off the premises

(Scribner et al. 1995). A 1-percent increase in the density of outlets was associated with a 0.62-percent increase in the rate of violent offenses. However, a study using the same methodology to analyze data from 223 municipalities in New Jersey with populations greater than 10,000 found no significant association between outlet density and violence, after the researchers accounted for variables similar to those used in the Los Angeles study (Gorman et al. 1998).

In interpreting these conflicting findings across sites, researchers have speculated that outlet density may be related to violent assaults "only when certain conditions prevail, for example, when average population size is large, alcohol outlets density crosses a certain threshold, and/or alcohol is sold through certain types of 'easy access' retail outlets such as mini-markets" (Gorman et al. 1998, p. 99). Other researchers have made the similar argument that if alcohol outlets dominate a location, then this feature of the local environment might act to stimulate crime by attracting certain types of activities, such as drug sales, prostitution, and gang activities (Alaniz et al. 1998).

Studies Across Time

In an unusual recent study, a series of local policy changes in Barrow, Alaska, provided the basis for a natural experiment in the form of an across-time study (Chiu et al. 1997). During a 33-month period, referenda passed by the citizens at first imposed, then withdrew, and finally reimposed a total ban on alcohol sales in the Alaskan village. Research findings indicated significant decreases in emergency room visits (including those for assaults) when alcohol was banned, increases to levels of the pre-ban period when the ban was lifted, and significant declines again when the ban was reimposed by Barrow voters. The ability to provide contrasts between periods when the policy was in force and periods when it was suspended makes this an especially persuasive study.

In one recent study that focused solely on homicide, researchers conducted a time-series analysis of annual U.S. homicide rates and annual estimates of U.S. beer, wine, and spirits consumption for the years 1934 through 1994 (Parker and Cartmill 1998). The study found evidence for a link between alcohol consumption and homicide across races, with the effects being stronger for whites than nonwhites. The findings indicated that homicide rates for whites rose with rising consumption of spirits, were unrelated to beer consumption, and rose with falling consumption of wine. The analysis of nonwhite homicide rates contained much less evidence of a link, in that beer was the only beverage for which consumption increased with increasing homicide rates, and this relationship was found in some but not all of the statistical components of the study. Although the researchers reported that declining alcohol consumption is related to the falling rate of homicide in the United States, they noted that "it would be inappropriate to claim that a decline in alcohol consumption is the most important or the only reason why homicide rates are falling" (Parker and Cartmill 1998, p. 1374).

Studies Across Time and Different Locations

Studies with particularly strong research designs are those that take advantage of data collected both over time and across different locations. Among these was a study of alcohol consumption (based on sales data), State-level beer taxes, and rates of homicide, rape, robbery, and assault (from the Federal Bureau of Investigation's [FBI] Uniform Crime Report) (Cook and Moore 1993). This analysis used annual data for each of the contiguous 48 states for the years 1979 through 1988 in a pooled, cross-sectional, time-series analysis. The study found significant relationships between alcohol consumption and crime rates for rape, assault, and robbery, but not for homicide. It also found that variations in the beer tax were associated with changes in alcohol consumption, with consumption being lower when taxes were higher. The researchers controlled for the effects of a number of variables, including poverty and State racial composition.

Another example of an analysis conducted both over time and across different locations involved data collected across 256 large U.S. cities over a

period of 20 years to see how changes in alcohol outlet density were related to changes in the homicide rate (Parker and Rebhun 1995). This study controlled for such theoretically relevant variables as poverty, median family income, family structure, social bonds, racial composition, migration, region, participation by females in the labor force, and population density (Parker and Rebhun 1995). The study analyzed the relationship between alcohol availability (measured by the number of liquor stores per 1,000 population) and homicide rates reported in the FBI's Uniform Crime Report series. Although analyses were conducted for 1960, 1970, and 1980, only in 1970 did the investigators find a significant, direct relationship between alcohol availability and homicide.

Another study by the same investigators took a somewhat different tack by examining the relationship between minimum legal drinking age laws and rates for youth homicides (Parker and Rebhun 1995). Although this approach differs from one focusing on the effects of consumption or alcohol availability, the general intent is similar since the researchers reasoned that restricting alcohol access by raising the minimum drinking age would reduce alcohol consumption and consequently reduce violence. The results did not provide strong confirmation of a link between raising the minimum purchase age and homicide rates. In only one of the six analyses conducted (homicides of victims aged 21 through 24 in which the victim and the assailant knew each other) did the researchers find that raising the minimum age had a significant effect on reducing homicide rates.

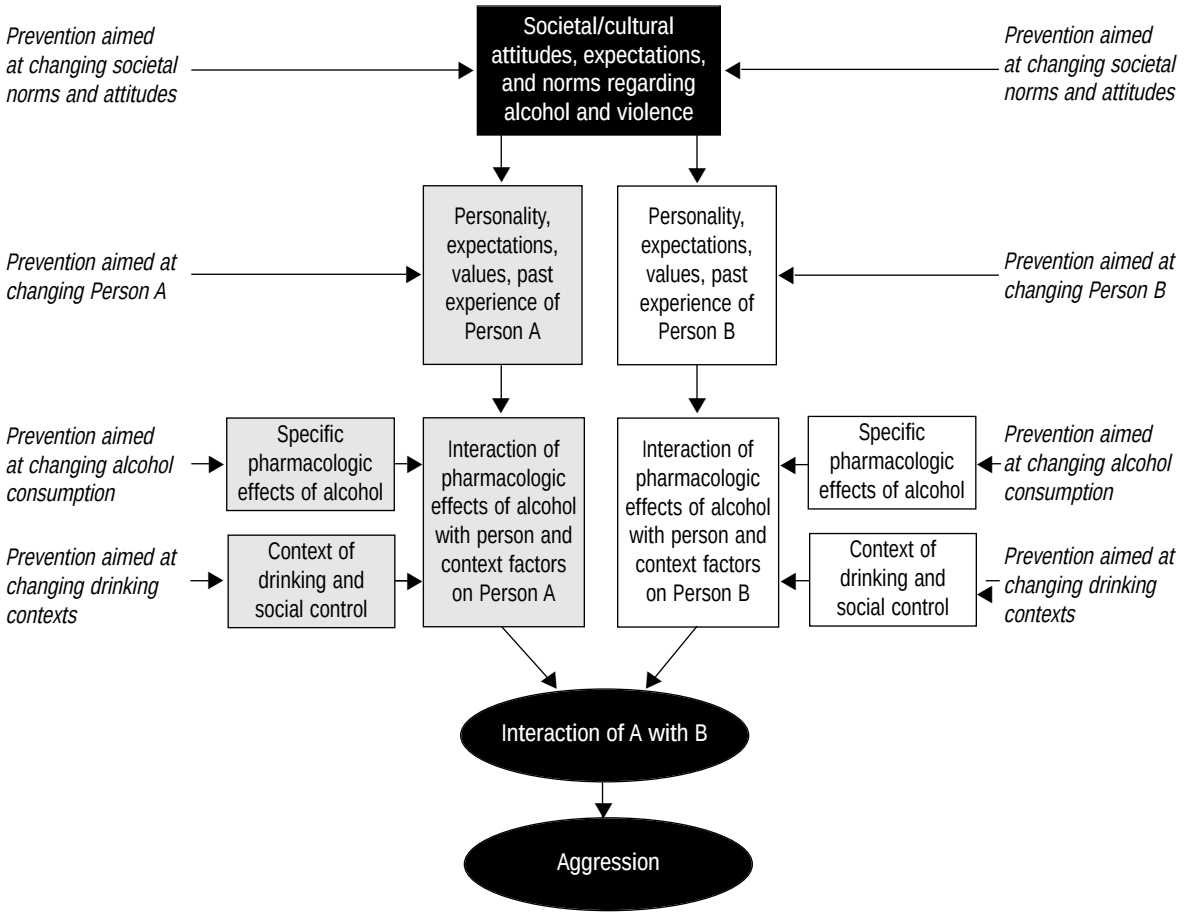
In summary, while environmental studies have suggested the potential for preventing violence through reducing alcohol availability, they are less than conclusive in demonstrating a causal role of alcohol availability in the occurrence of violent events. Not all studies have found a significant relationship between alcohol availability (or alcohol consumption) and rates of violence. It is not clear, for example, why cross-sectional studies (such as the individual-level studies described earlier) consistently show that alcohol is involved in a higher proportion of homicides than less serious crimes, whereas longitudinal studies at the environmental level do not show a consistent connection between homicide and consumption rates. In some cases, studies have not accounted for appropriate variables that can affect a relationship between consumption and violence. In other cases, such as the Barrow, Alaska, study, researchers are uncertain how far the results should be generalized beyond the particular cultural and social setting in which the study was done. Despite these remaining limitations, the convergence of environmental studies on the basic finding that alcohol availability and violence are positively related, taken together with the results of individual-level studies suggesting a relationship between alcohol consumption and violence, has increased the scientific community's confidence that alcohol availability plays a causal role in the generation of violence. However, additional research is needed to determine how alcohol availability interacts with other factors in the causal process leading to violence.

Theoretical Developments

Recent progress has also been made in constructing theoretical models to explain the alcohol-violence link. Two such recent approaches deserve some discussion here, as they can be expected to supply some of the theoretical framework that will guide future research in this area.

The first of these two theories, called the "selective disinhibition theory," proposes that alcohol's effect in a situation with the potential for violence depends on contextual factors specific to the situation, the actors involved and their relationships with one another, and the impact of bystanders (Parker and Rebhun 1995). The theory holds that individuals are constrained from engaging in violence by standards, or norms, they have internalized concerning proper conduct in an interpersonal argument. Individuals may, however, also have alternative norms that support the use of violence in some situations. Particularly in a situation with interpersonal conflict (such as an open display of disrespect) and weak environmental support for norms that forbid

Figure 2: Factors contributing to intoxicated aggression: the example of aggression involving two people (showing opportunities for prevention at different levels)



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violence (such as a bar with an "anything goes" atmosphere), alcohol use may be more likely to relax, or "disinhibit," any antiviolence norms and lead to an escalation into violent behavior. In addition, in situations that require a conscious decision to refrain from violence when it is likely to resolve the situation in one's favor, the use of alcohol may undermine the constraint of active antiviolence norms. Thus, the selective nature of alcohol-related violence can be seen as a product of impaired rationality and the nature of the social situation (Parker and Rebhun 1995). This theory has received support indirectly from analyses of data collected at the Statewide and communitywide levels (Alaniz et al. 1998; Parker 1995; Parker and Rebhun 1995), but it has not been tested directly at the individual or small-group levels.

The other theoretical development is an effort to more fully specify the multiple causes and processes underlying intoxicated aggression. Based on a multidisciplinary perspective, this model shows that societal and cultural factors related to both intoxication and aggression provide the background for alcohol-related violence that emerges from the social interaction of at least two individuals (figure 2). What emerges, however, depends on cultural framing of shared attitudes and expectancies of their society, the characteristics of each individual (including his or her personality, history of violence, and

alcohol-related expectancies), the psychopharmacologic and expectancy effects of alcohol on the brain and related cognitive functions, and the influence of the drinking context (Graham et al. 1998). Each of these factors has been addressed in a wide range of studies but not previously synthesized in a single model.

In Closing

Studies of violent incidents have continued to find that alcohol use often precedes violent events and that the amount of drinking is related to the severity of the subsequent violence. Research has been advancing beyond confirmation of these basic relationships toward an examination of the personality and situational factors that interact with both alcohol use and violence. One area of research is focusing on youthful perpetrators in the hope of offering findings that will be relevant for successful interventions. Research has also focused on alcohol use by the victims of violence. Here, research has concentrated on sexual assaults and domestic abuse. Findings have indicated that the connection between victims' drinking and violent attacks is not as clear in the case of partner or spouse abuse as it is in sexual assaults by other perpetrators. Studies have also focused attention on the environments where violence has occurred. Such analyses continue to find that violence is more prevalent in localities where alcohol is more widely available. However, research has yet to determine how availability interacts with other factors in the causal process leading up to the generation of violence.

To assist in the development of policies and intervention programs to reduce or prevent alcohol-related violence, future investigations will need to focus further on (1) identifying the individual and environmental conditions and situations in which alcohol use may cause violence; (2) determining the interrelationships among these individual and environmental factors that lead to violence with alcohol consumption; (3) elucidating the biological and psychosocial processes through which alcohol consumption may lead to escalating aggression and violence; (4) determining the role of alcohol consumption in specific high-risk environments, such as bars and gangs, and in specific social contexts, such as the family; and (5) improving treatment for individuals who abuse alcohol and have a history of domestic or other violence. Policies and intervention programs based on understandings from such research will need to be implemented and, of equal importance, evaluated rigorously to provide guidance for continuing efforts to reduce or prevent alcohol-related violence.

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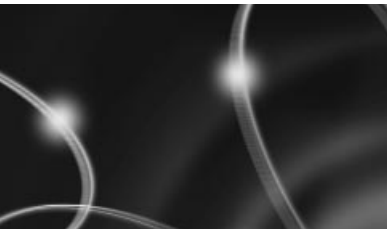
Alcohol and the Brain: Neuroscience and Neurobehavior



Twenty-five years ago, a Report to the U.S. Congress on Alcohol and Health *stated, "No one knows how alcohol intoxicates" (U.S. Department of Health, Education, and Welfare 1974, p. 93). Since then, discoveries in brain science have given alcohol researchers the means to begin to understand the variety of cellular effects of alcohol and how those effects translate into behavior. These fundamental discoveries include an understanding of neurotransmitters, the chemical message carriers in the brain; the cell receptors to which the neurotransmitters dock; and the biochemical message relays that link receptor binding and the metabolism of the cell and, ultimately, brain activity.*

Included in this chapter are highlights of some recent directions in this research, beginning with an overview on the cell-to-cell communication that underlies brain activity and that is disrupted in multiple ways by alcohol. As each section illustrates, the research effort has been aimed at dissecting the effects of alcohol down to the most fundamental level—defining what the precise chemical and molecular steps are by which alcohol slows the transmission of neural messages in the brain and how the brain responds to counter these effects.

As the sections in this chapter illustrate, this approach has led to a remarkably detailed, though still incomplete, picture. Effects on neurotransmitters are described with details that include the flux of charged ions into and out of the cell, the carrier molecules that shuttle neurotransmitters between neurons, the enzymes that enable or disable all this activity, and the genes that may be turned on and off in response to alcohol's presence.

Impressive as these discoveries have been, the challenge remains to reassemble the system and understand how the totality of effects of alcohol works in individuals. The impulse to drink too much cannot be understood in terms of one neurotransmitter any more than it can be attributed to one life event. Research on brain chemicals is one avenue to understanding how alcohol can change brain function and structure and why and how some individuals are from birth more sensitive to these effects than others. As important, this research is

perhaps the only way to identify pharmaceuticals that can interrupt these alcohol-based effects. However, single brain chemicals act in the context of a system that is dauntingly complex. Among the avenues scientists are exploring to address this complexity is the use of animals genetically engineered to have specific changes in neurotransmitters or in the proteins that are involved in mediating neurotransmitter responses. In this way, the effects of biochemical changes can be observed, not only in terms of chains of chemical events, but in terms of the behavior of intact animals. Even so, different neurotransmitters interact with each other; further, the absence of one key neurochemical from birth can have widespread developmental effects, and can be compensated for by other systems in the animal. For this reason, scientists are looking at the possibility of studies in animals in which several such genes are disabled—or in which the genes can be turned on and off in specific tissues or at specific times.

While the disassembling of the alcohol response is already providing clues to how those at risk might be identified and how alcoholism might be treated medically, future research also will require understanding all the component parts as a system that does not preordain behavior, but to some degree, sets the stage.

Reference

U.S. Department of Health, Education, and Welfare, National Institute on Alcohol Abuse and Alcoholism. *Second Special Report to the U.S. Congress on Alcohol and Health.* DHEW Pub. No. HSM-72-9099. Rockville, MD: U.S. Department of Health, Education, and Welfare, National Institute on Alcohol Abuse and Alcoholism, 1974.

Setting the Stage: The Structure and Function of Neurons

The changes in behavior seen soon after consumption of alcohol—the acute effects of alcohol collectively referred to as intoxication—include impaired coordination of movements; errors in judgment about movements, distances, and time; impaired learning and memory; and sedation. Drinking moderate amounts of alcohol can produce a general depressant effect on behavior, whereas intake of large amounts of alcohol can lead to loss of consciousness and even coma or death from respiratory failure. These effects—as well as the euphoria and anxiety reduction seen with alcohol—all result from alcohol's actions on the brain.

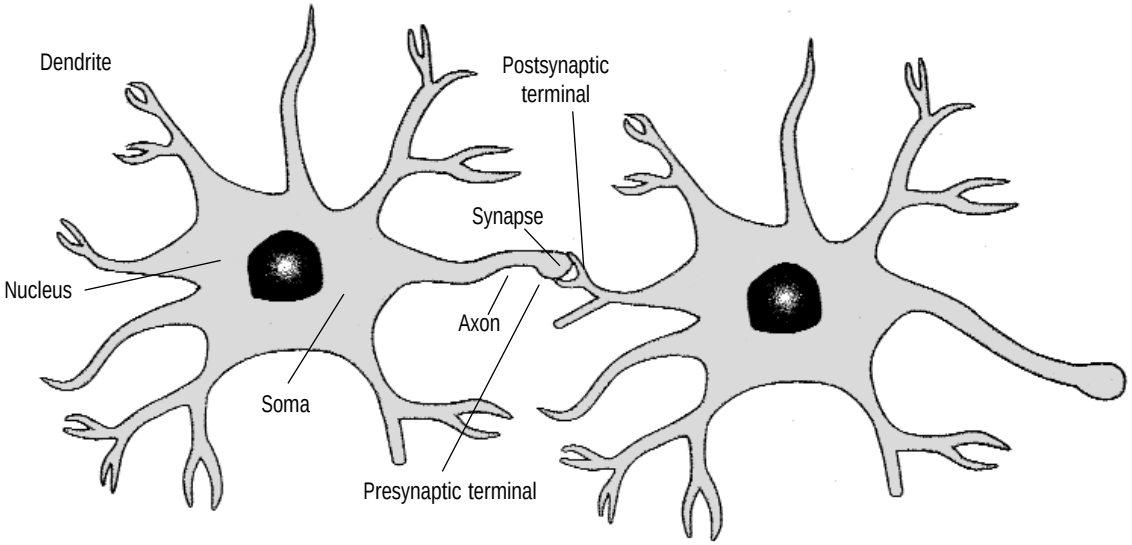
Exposure of the brain to alcohol initiates a process of adaptation that works to counteract the altered brain function resulting from initial exposure to alcohol. This adaptation or change in brain function is responsible for the processes called alcohol tolerance, alcohol dependence, and the alcohol withdrawal syndrome. Tolerance describes the process by which the brain becomes resistant to the effects of alcohol that lead to intoxication. This process results in a decrease in the amount of intoxication with time after alcohol drinking or after repeated alcohol drinking sessions, even when the amount of alcohol in the brain is the same as that which would originally have produced intoxication. For example, a level of brain alcohol that would produce movement problems minutes after beginning drinking will not produce the same severe intoxication hours after drinking was initiated. Further, in an individual who drinks heavily and often, the amount of intoxication produced by a particular level of alcohol in the brain is less than that in an individual who is drinking for the first time. These progressive changes in the behavioral effects of alcohol result when the brain becomes tolerant to its presence.

Prolonged exposure to alcohol can also cause the brain to become dependent on the presence of alcohol. Individuals who have been drinking steadily for long periods of time need to continue drinking to maintain an appropriate level of brain activity. These individuals will often report a strong desire, or craving, for alcohol and will become anxious and restless if deprived of alcohol for any significant period of time. Alcohol-dependent individuals will consume alcohol when given the opportunity, almost without regard to the social or environmental context. Laboratory animals also can exhibit signs of alcohol dependence that are manifest as heavy drinking whenever alcohol is available. Changes in the brain with long-term alcohol exposure appear to be the cause of alcohol dependence.

Cessation of drinking following long-term drinking will result in the development of a withdrawal syndrome. In the case of alcohol, withdrawal symptoms range from agitation and intense anxiety to tremors, full-blown seizures, and delusions. This withdrawal syndrome is another consequence of the adaptive changes the brain undergoes to continue functioning despite the presence of alcohol. As withdrawal progresses, the brain becomes free from the influence of the alcohol and its activity becomes markedly abnormal, with undesirable consequences for the mental, emotional, and behavioral status of the individual undergoing withdrawal.

Prolonged alcohol abuse will also result in the loss of brain nerve cells, or neurons. This effect appears to result from the direct toxic effects of alcohol and its metabolites in combination with the secondary consequences of the poor nutritional status of alcohol abusers and the neuronal damage that occurs during withdrawal (Charness 1993; Tsai et al. 1995). The section "The

Figure 1: Structural features of a presynaptic and postsynaptic neuron



Nerve cells called neurons contain different compartments that have distinct functions. The treelike dendrites receive chemical signals from other neurons and transmit electrical signals called synaptic potentials to the soma. The soma adds up these electrical signals from the dendrites, and if they are sufficiently large, it produces an electrical signal called the action potential that is conducted to the end of the cablelike axon. At the end of the axon is the axon terminal. This small, knob-shaped structure contains the neurotransmitter molecules that are released when the action potential reaches the axon terminal. These molecules act on other cells, and this is the basis for communication within the brain. The soma is also the site of the nucleus, which is responsible for controlling gene expression.

Source: Charness 1990.

Neurotoxicity of Alcohol" later in this chapter discusses neuronal loss and its consequences.

As will become clear in this and the accompanying sections in this chapter, alcohol alters the function of the brain by changing communication within and between neurons, the ultimate result being changes in brain activity and behavior.

Structure and Function of Neurons

Neurons are cells that are specialized to receive and rapidly conduct chemical and electrical signals. They have a distinctive shape with several appendages, or processes, extending from a rounded center (figure 1). Most neurons in the brain and spinal cord contain specific cellular compartments. Dendrites are treelike appendages that spread out in several directions from the rounded center of the cell; they are specialized to receive information from other cells. Chemicals released from other neurons interact with dendrites to initiate electrical impulses that can travel the length of the dendrite to the center of the neuron.

The neuronal center, or soma, contains the nucleus. The nucleus houses the cell's genetic material, deoxyribonucleic acid (DNA), which contains the information needed to synthesize the different proteins that the cell uses to function. Proteins are manufactured within the neuronal soma by a two-stage process (see the box "From DNA to Protein: How Genetic Information Is Realized"). The specific sequence of the nucleotide base molecules in the DNA within the nucleus gives rise to a unique sequence of the nucleotides in the corresponding messenger ribonucleic acid (mRNA). This process of RNA synthesis, called transcription, takes place within the neuronal nucleus. The RNA is then transported outside of the nucleus, to the ribosomes, where the amino acid building-block molecules of proteins are assembled in an order based on the sequence of nucleotide molecules in the RNA. This process is called translation. After the protein is synthesized, it can be moved to the appropriate part of the neuron to perform its given function.

From DNA to Protein: How Genetic Information Is Realized

All the genetic information necessary to create and maintain an organism is encoded in long, threadlike deoxyribonucleic acid (DNA) molecules in the nucleus of each of the organism's cells. But how is this information converted into the proteins that compose a significant portion of the cell's components and drive most chemical reactions in the body? This conversion, called gene expression, is a complex biochemical process that consists of several steps occurring in the cell nucleus and in the cytoplasm. To better understand how gene expression works, it helps to review briefly the chemical structure of DNA. The characteristic design of DNA molecules is the basis for the reactions involved in gene expression.

The building blocks of DNA, the nucleotides, are sugar molecules linked to organic bases. DNA includes four different organic bases: adenine (represented by the letter A), cytosine (C), guanine (G), and thymine (T). The order in which they are arranged specifies which amino acids will be linked to form a protein. Because more than four amino acids exist and are necessary to produce a protein, a triplet of three nucleotides represents (that is, codes for) one specific amino acid in the final protein. For example, the nucleotide triplet ATG codes for the amino acid methionine, and the triplet TGG codes for the amino acid tryptophan. The section of a DNA molecule containing the information needed to make one specific protein is called a gene.

DNA is a double-stranded molecule: two chains of nucleotides face each other and are connected through specific bonds. Because of the nature of these bonds, each nucleotide can bind to only one other particular nucleotide. For example, the nucleotide containing A always pairs with the nucleotide containing T, and the nucleotide containing C always pairs with the nucleotide containing G. The composition of the second strand therefore depends on the composition of the first strand. Accordingly, the strands are called complementary. This also means that if the nucleotide sequence of one strand is known, the sequence of the second strand can automatically be inferred.

Transcription

To convert the information encoded in the DNA of one gene into a protein, the first step is to copy, or transcribe, one of the DNA strands into another nucleic acid molecule called messenger ribonucleic acid (mRNA). This process is performed by specific enzymes in the cell nucleus.

There are different kinds of RNA in the cell that have different functions but the same chemical structure. RNA molecules are similar in their chemical composition to DNA molecules. The main differences are that the sugar component differs between DNA and RNA and that the organic base T present in DNA is replaced by the base uracil (U) in RNA. In addition, RNA molecules are single stranded; unlike DNA, they do not have a complementary strand.

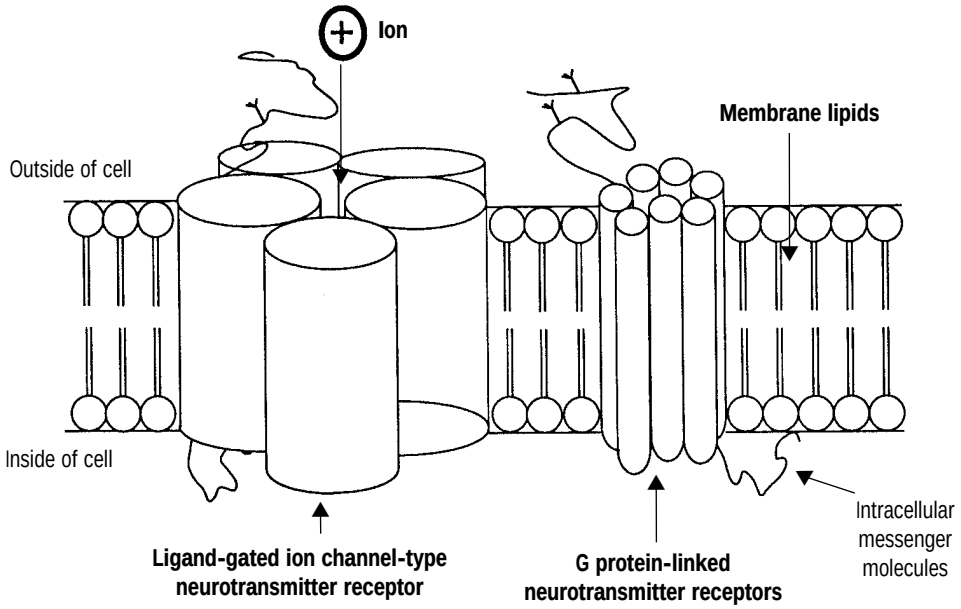
During transcription, the DNA sequence representing one gene is converted into mRNA. Only one strand of the double-stranded DNA molecule, however, serves as a template for mRNA synthesis; RNA nucleotides are guided to the DNA sequence that is being transcribed and temporarily bind to it. Again, only one specific RNA nucleotide can bind to each DNA nucleotide (for example, the RNA nucleotide containing A pairs with the DNA nucleotide containing T, and the RNA nucleotide containing C pairs with the DNA nucleotide containing G). This specificity guarantees that the genetic information contained in the DNA is accurately converted into mRNA. As with the DNA template, the sequence of a triplet of nucleotides in the RNA codes for one amino acid in the final protein.

After all the information for one gene has been copied into an mRNA molecule, the DNA and mRNA molecules separate. The mRNA then undergoes some additional modifications in the cell's nucleus before it is transported to the cytoplasm for the next step, the translation into the protein product.

Translation

In the cell's cytoplasm, macromolecules called ribosomes attach to, and slide along, the mRNA. In this manner, the ribosomes "read" the sequence of the mRNA's nucleotide triplets. According to that sequence, the ribosomes recruit a second kind of RNA, transfer RNA (tRNA), which guide the amino acids needed for protein synthesis to the mRNA-ribosome complex. One end of each tRNA molecule has a region that recognizes one specific nucleotide triplet on the mRNA. Another region of each tRNA molecule is attached to a specific amino acid. Thus, by recruiting tRNA molecules that recognize the nucleotide sequence of the mRNA, the ribosomes also retain the right amino acids in the right order to form the protein encoded by the gene represented in the mRNA. Specific enzymes then connect the amino acids until the complete protein is synthesized. Because each mRNA molecule can be read consecutively by several ribosomes, many protein molecules can be derived from just one mRNA template.

Figure 2: The lipid bilayer, including neurotransmitter receptors



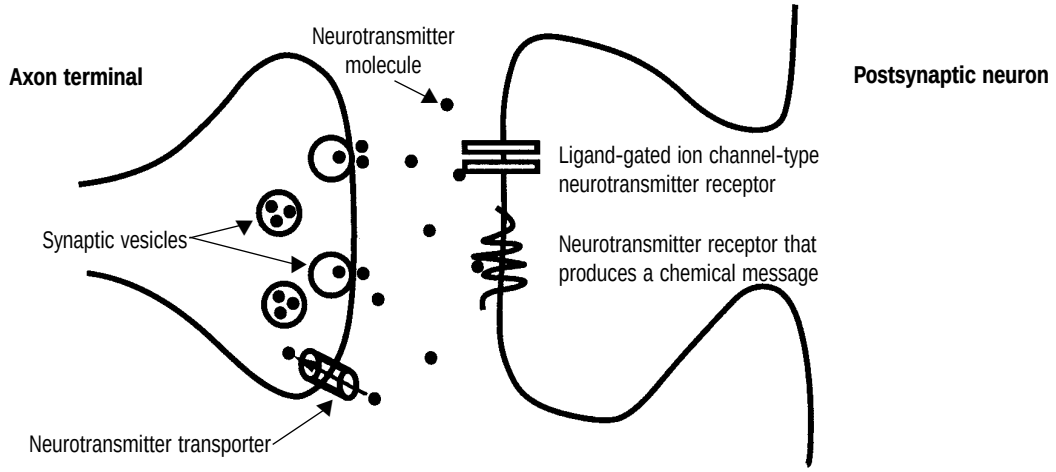
The cell membrane consist of two rows, or a bilayer, of lipid molecules with proteins inserted into the membrane. Two types of proteins that serve as receptors for brain neurotransmitters are depicted. Binding of neurotransmitters to G protein receptors leads to the binding and breakdown of guanosine triphosphate (GTP) and, in some cases, to the production of small-molecular-weight molecules known as second messengers.

In addition to housing the cell's genetic code, the soma is where electrical impulses from different dendrites mix. A single appendage known as the axon extends from the cell body; the end of the axon is called the axon terminal. Axons are specialized for carrying electrical signals arising from the soma. Unlike dendrites, axons and axon terminals are specialized for sending information from one nerve cell to the next. Nerve cells usually have only one axon, in contrast to the multiple dendrites that are found on each neuron.

The boundaries of all animal cells, including neurons, are defined by a membrane, known as the lipid bilayer, that consists of a double layer of fatty lipid molecules (figure 2). The purposes of this bilayer membrane are to separate the inside of the cell (intracellular environment) from the environment outside the cell (extracellular environment) and to separate one cell from another. This bilayer allows each cell to act independently of neighboring cells but still receive chemical and electrical information from other cells and from the extracellular environment.

Embedded within the lipids in the membrane are a variety of specialized proteins, many of which serve to communicate to the cell information coming from the extracellular environment or from other cells. Proteins in one class serve as channels through which ions (electrically charged atoms, in this case) can pass through the membrane from outside the cell to the inside of the neuron. Ion channel proteins are often classified according to how they are opened. Those that open in response to changes in the electrical charge, or potential, of the cell membrane are known as voltage-gated ion channels. Other ion channels bind to specific molecules in the extracellular environment and open the channel; these are ligand-gated ion channels (see figure 2). The movement of ions

Figure 3: Synaptic transmission



Schematic representation of a synapse between two neurons in the brain. The presynaptic axon terminal contains neurotransmitter molecules packaged in synaptic vesicles that are released into the synaptic cleft. The neurotransmitter molecules in the synaptic cleft bind to neurotransmitter receptors that reside in the membrane of the dendrite of a postsynaptic neuron. Removal of a neurotransmitter from the synaptic cleft is performed by neurotransmitter transporters that return the neurotransmitter to the inside of the neuron.

through these channel proteins produces electrical signals in the cell. The normal operation of both voltage-gated and ligand-gated ion channels is critical for maintaining proper neuronal signaling.

Communication Within and Between Neurons

Electrical signals help fulfill the neuron's major role—to communicate information quickly so that the brain can carry out its many functions. Transmission of information by nerve cells is accomplished through the opening of ion channels along the entire length of the neuron. When impulses from different dendrites mix and produce an electrical signal that exceeds a certain voltage threshold, a summed electrical signal originating in the soma is created. The cell fires in response to the summed electrical signal in an all-or-none manner: no new signal is triggered if the threshold is not reached, but if the threshold is reached, the electrical impulse or action potential that is conducted down the axon arrives at the axon terminal essentially unaltered relative to its size at the soma.

At the axon terminal, the action potential initiates a sequence of biochemical events that leads to the release of a neurotransmitter into the synapse, the gap between two neurons positioned close together (figure 3). The neurotransmitter—a chemical messenger of which there are many types in the brain—then acts on the next cell. Through this process, the axon terminal turns the electrical signal in the neuron into a chemical signal that allows for transmission of information in the brain.

The presynaptic side of the synapse, the axon terminal, is specially designed to release neurotransmitters. Neurotransmitters are stored in small membrane-bounded packets, called vesicles, inside the axon terminal. When the action potential reaches the axon terminal, it triggers the combining of the membrane of the vesicle with the membrane of the cell in a process called vesicle fusion. The molecular events linking the action potential to vesicle fusion depend on the presence of calcium ions. The fused vesicle opens and releases its neurotransmitters into the synaptic cleft between the two neurons.

Although several types of neurotransmitters are found throughout the brain and spinal cord, only one or two types of neurotransmitters are released at any given synapse.

After the neurotransmitter is released from its vesicle, it crosses the synaptic cleft. The neurotransmitter then acts on the second, or postsynaptic, neuron. The actions of the neurotransmitter on the postsynaptic neuron begin with the neurotransmitter interacting with, or binding to, specialized proteins called neurotransmitter receptors on the dendrites of the postsynaptic neuron.

Synaptic transmission is tightly controlled by the regulation of the amount of time that the neurotransmitter stays in the synaptic cleft after each instance of transmitter release. Specialized proteins called neurotransmitter transporters regulate neurotransmitter levels in the synaptic cleft. These transporter molecules sit on the membranes of the presynaptic, and sometimes the postsynaptic, neurons facing the synaptic cleft. When neurotransmitter levels in the synaptic cleft are high, the transporter molecules take up the neurotransmitters and return them to the presynaptic terminal, where they are recycled to be used in a new round of synaptic transmission. Changes in the activity of neurotransmitter transporters allow neurotransmitters to remain in the synaptic cleft longer than usual and will thus lengthen the duration of synaptic transmission.

Binding of a particular neurotransmitter molecule released into the synapse by one neuron to its specific receptor on the dendrites of the adjacent neuron produces either an electrical or a chemical signal within the second neuron. The electrical signals are produced by receptors that contain ligand-gated ion channels. Binding of the neurotransmitter ligand to the receptor serves to open the molecular gate of the ligand-gated ion channels.

The types of ions that pass through the membrane's ion protein channels determine the response of the neuron. Neurons become activated when the voltage across their membranes becomes more positive relative to the membrane's voltage at its resting state. At rest, neurons maintain a membrane potential of around –65 millivolts, which means that the interior of the neuron is negatively charged with respect to the fluid surrounding the cell. Entry of positively charged ions, or cations, tends to excite neurons, making them more likely to transmit information from one brain region to the next. Entry of negative ions, or anions, makes the voltage across the cell membrane more negative and discourages the transmission of information from one neuron to the next. Activation of ligand-gated ion channels produces very rapid responses in neurons. The electrical current produced when these receptors are activated occurs within thousandths of a second (milliseconds).

The proteins in the cell membrane that activate production of chemical messages within neurons are another form of neurotransmitter receptor (see figure 2). These receptors do not form ion channels, but instead interact with other proteins inside the cell to stimulate the formation of chemical messengers. Chemical messages within cells generally act more slowly than changes produced when ion channels are activated. Modification of proteins by intracellular messengers occurs over a time course of hundredths of seconds to minutes. Chemical messages to the nucleus can cause alterations in protein expression that can last for hours to days, producing long-lasting changes in the function of individual synapses and cells.

Binding of a neurotransmitter to one of these receptors activates enzymes that stimulate messenger formation in a process known as signal transduction. Through this process, cells receive information about the chemicals outside the cell and respond accordingly. The molecules formed immediately after activation of receptor proteins are called second messengers. (The neurotransmitter is the first messenger.) One of the most common second messengers is cyclic adenosine monophosphate (cAMP).

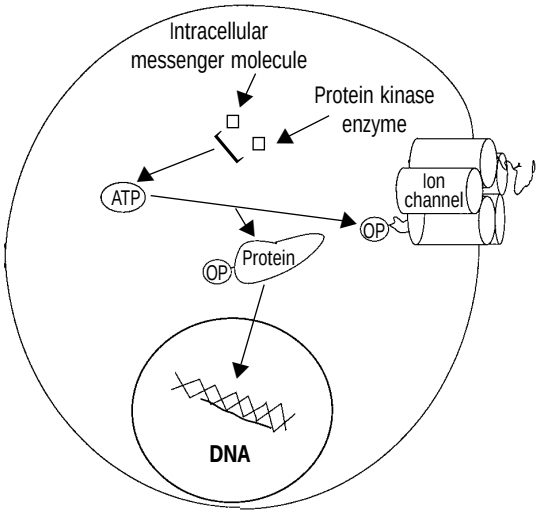
Second messengers can modify proteins by initiating a series of biochemical reactions that lead to the addition or removal of small molecules to or from the protein. This process is called posttranslational modification because it occurs after translation, the last step in the genetically directed synthesis of proteins in the cell. One molecule that is often added to modify proteins is phosphate, which contains phosphorus and oxygen atoms. This process—phosphorylation—is triggered when second messengers activate enzymes known as kinases. Phosphorylation can alter the structure, function, and location of proteins within cells, including ion channel proteins, receptors, and enzymes (figure 4).

Phosphorylation of the proteins that constitute ion channels, receptors, and enzymes is the major control mechanism that neurons use to regulate the activity of these proteins. For example, depending on the type of ion channel, phosphorylation of the channel protein can either shorten or lengthen the time the ion channel is open, thus regulating the flux of ions into the neuron. These changes in ion flux—and the type of ion the affected channels carry—can increase or decrease the excitability of neurons. Because phosphorylation dynamically regulates the activity of neuronal receptors and proteins, neurons also have enzymes (phosphatases) that remove these phosphate groups in order to reverse the effects of phosphorylation. The coordinated activity of both protein kinases and phosphatases ultimately determines the extent of protein phosphorylation of important neuronal proteins. Recent findings suggest that many of the acute and chronic effects of alcohol may be mediated by changes in the level of phosphorylation of key ion channels and receptors.

Second messengers also can trigger biochemical reactions that alter gene expression (the series of steps whereby information contained in DNA leads to the synthesis of proteins). In this case, the intracellular messenger molecule formed inside the cell modifies proteins that can enter the cell nucleus (see figure 4). Once in the nucleus, these specialized proteins interact with DNA and alter how the DNA sequence is "read," or transcribed. For example, a signal to the nucleus might lead to increased production of components of ion channels through the stimulation of the genes that encode for the ion channel protein. Once formed, the protein products encoded by these genes are shipped to different parts of the neuron to perform their functions.

Changes in the amount or structure of proteins normally produced by nerve cells can lead to long-lasting changes in neuronal function. The ability of neurons to respond to extracellular signals through the production of second messengers that can alter DNA expression is key to communication between neurons.

Figure 4: Protein phosphorylation in a cell



The functions of different types of proteins within a cell can be altered by addition of a phosphate molecule (OP) to the protein in a process called protein phosphorylation. Two examples are shown in this illustration. An intracellular messenger molecule interacts with a protein kinase enzyme to stimulate transfer of the phosphate molecule from adenosine triphosphate (ATP) to an ion channel protein residing in the cell membrane. Phosphorylation of this protein could change its function, promote retention of the protein within the membrane, or lead to removal of the protein. Proteins that have the potential to interact with deoxyribonucleic acid (DNA) in the cell nucleus can also be phosphorylated. Phosphorylation of such a protein in the cell cytoplasm, outside of the nucleus, can lead to "translocation" of the protein to the nucleus, where the protein is free to interact with DNA and alter gene expression.

Neurotransmitters

Neurotransmitters clearly shape the stimulation and inhibition of neuronal activity. Many chemicals act as neurotransmitters in the brain. A large number of these neurotransmitters are relatively small molecules, including the amino acids gamma-aminobutyric acid (GABA) and glutamate. Each different neurotransmitter interacts with receptors that are specialized for binding only that neurotransmitter. Thus, a large variety of neurotransmitter receptors exist in the brain. The many possible interactions between the different neurotransmitters and their receptors allow neurons in the brain to generate different responses when their synapses are activated.

GABA

GABA is called an inhibitory neurotransmitter because through interactions with its receptors, GABA affects neurons in a way that reduces their activity. Activating or enhancing the function of GABA receptors usually decreases activity in brain neurons and can decrease activity of the entire brain and body, as occurs in general anesthesia.

GABA influences neuronal activity by binding to and activating several classes of GABA receptors (denoted $GABA_A$, $GABA_B$, and $GABA_C$). The GABA receptor that appears to be most sensitive to alcohol is $GABA_A$. This receptor is a ligand-gated ion channel that is composed of multiple subunits referred to as the alpha (α), beta (β), gamma (γ), delta (δ), epsilon (ε), and rho (ρ) subunits. Each subunit family includes multiple members that differ slightly in their amino acid sequence. Structural analysis of these subunits reveals that each GABA subunit traverses the neuronal membrane four times via transmembrane (TM) domains (designated TMI through TMIV) that are composed of 20 to 25 uncharged or nonpolar amino acids.

$GABA_A$ receptors appear to be assembled into a pentameric (five-unit) structure in which the TMII domains of each subunit face each other to form a pore through which chloride ions flow. The pore is normally closed to prevent flux of chloride ions across the membrane in the absence of a neurotransmitter. Binding of the neurotransmitter GABA to regions of the receptor outside of the cell opens the pore. The subsequent flux of chloride ions (as many as 100 million per second) hyperpolarizes the neuron and makes it much less likely to fire an action potential and, thus, less likely to transmit information from one cell to the next. In this way, GABA is inhibitory.

Glutamate

Glutamate, on the other hand, generally acts as an excitatory neurotransmitter that increases the activity of brain neurons by producing a response that is electrically opposite to that of the inhibitory neurotransmitters. Glutamate binds to specific ligand-gated ion channels and depolarizes the postsynaptic neuronal membrane, making it more likely that the neuron will fire. In this way, these proteins are excitatory; strong activation of glutamate receptors can lead to hyperexcitability of the brain and body—seizures are one manifestation. Within discrete brain regions and in individual neurons, the balance between GABAergic (GABA-activating) and glutaminergic (glutamate-enhancing) synaptic transmission is often the major determinant of the level of activity. By controlling the activity of these excitatory and inhibitory neurons, the brain can rapidly and profoundly alter the excitability of neurons.

In Closing

Alcohol appears to affect the function of several neurotransmitters by altering the communication mechanism between neurons at the point when a neurotransmitter activates its receptor. A large body of evidence suggests that this effect of alcohol on synaptic transmission is the major change in the brain that gives rise to intoxication. The following sections describe in detail some recent findings that are helping scientists understand how alcohol affects brain function.

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From Cell Membrane to Nucleus: The Effects of Alcohol on Brain Neurons

Alcohol alters synaptic transmission; a great deal of research over many years has suggested that this is the major change in the brain that gives rise to intoxication. As described in the first section of this chapter, "Setting the Stage: The Structure and Function of Neurons," a number of neurotransmitters are involved in synaptic communication within the brain. Alcohol affects the functions of several of these neurotransmitters by altering the communication between neurons that occurs when the neurotransmitter activates its receptor.

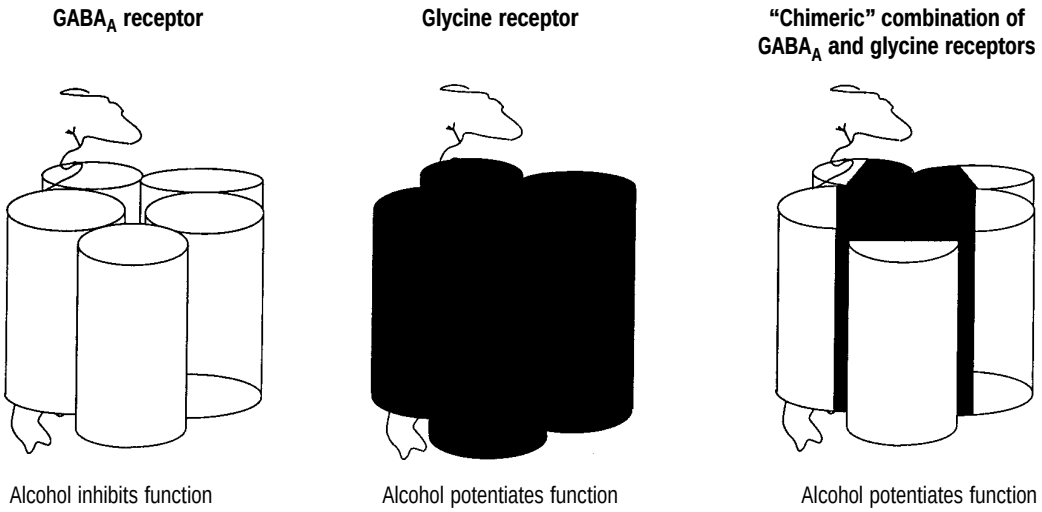
One of the most powerful effects of alcohol is to reduce the pace of brain activity by a combination of effects that reduces the excitatory actions of the neurotransmitter glutamate and enhances the inhibitory actions of the neurotransmitters gamma-aminobutyric acid (GABA) and glycine (Diamond and Gordon 1997; Korpi 1994; Lovinger 1997; Machu 1996; Mascia et al. 1996; Mhatre and Ticku 1993; Mihic et al. 1997; Sanna and Harris 1993). These actions are the main reason that alcohol is often thought of as a depressant.

Alcohol's Effect on Synaptic Transmission During Acute Exposure

The effects of alcohol on excitatory glutaminergic and inhibitory GABAergic and glycinergic synaptic transmission mainly result from alcohol's actions on the ligand-gated ion channels activated by these neurotransmitters. (See the section "Setting the Stage: The Structure and Function of Neurons" earlier in this chapter for background on the processes discussed here.) At synapses that use glutamate, alcohol reduces the activity of the neurotransmitter at ligand-gated ion channel receptors called the *N*-methyl-D-aspartate, or NMDA, class of glutamate receptors (Diamond and Gordon 1997; Lovinger 1996; Tabakoff and Hoffman 1995). Ion flow through the channel that is part of this receptor is reduced. This effect of alcohol may contribute to the memory loss that occurs during acute alcohol exposure, as will be discussed later in this section.

In contrast, alcohol enhances the activity of the inhibitory neurotransmitters GABA and glycine at receptors called $GABA_A$ and glycine ligand-gated ion channels (Aguayo et al. 1996; Celentano et al. 1988; Diamond and Gordon 1997; Korpi 1994; Machu 1996; Mascia et al. 1996; Mhatre and Ticku 1993; Mihic et al. 1997; Sanna and Harris 1993). Exciting new information about the molecular actions of alcohol has come from studies of these receptors. Prior research demonstrated alcohol's opposite actions on two receptors that were similar in molecular structure, the $GABA_A$ receptor (subtype rho [ρ]) and the receptor glycine (subtype α_1) (Mihic and Harris 1996; Mihic et al. 1997). This finding provided an interesting opportunity for investigators to "swap" pieces of the receptors by using genetic recombination techniques (figure 1). By cutting pieces of deoxyribonucleic acid (DNA) that coded for the two different receptors and then ligating, or molecularly stitching them back together, the researchers created DNA coding for chimeric receptors made from combinations of pieces of the receptors with opposite responses to alcohol. This DNA was then introduced into cells that made the corresponding receptor protein, allowing the researchers to examine alcohol's effects on the chimeric receptors. By determining the effects of alcohol on different chimera proteins that contained different combinations of the two receptors, the investigators were able to zero in on which parts of the receptor were important in determining the actions of alcohol. The investigators then compared the amino acid sequence of the receptors in the regions known to confer the differing responses to alcohol. (Proteins are chains whose structure and function are

Figure 1: Defining sites of alcohol action on neurotransmitter receptors



Schematic representations of ligand-gated ion channel type receptors for the neurotransmitters gamma-aminobutyric acid (GABA) and glycine. The function of the $GABA_A$ receptor (rho [ρ] subtype) is inhibited by alcohol, whereas the function of the glycine receptor (alpha [α] subtype) is potentiated by alcohol. Researchers using recombinant deoxyribonucleic acid (DNA) technology created "chimeric" receptors that combined parts of both receptors (Mihic et al. 1997) (white, part derived from $GABA_A$ receptor; black, part derived from glycine receptor). This combination receptor responded to alcohol in a manner that was similar to the response of the glycine receptor; data also suggested that the parts of the receptor that confer alcohol sensitivity appear to reside in part of the receptor within the cell membrane. In addition, the investigators pinpointed specific amino acids within this part of the receptor that played a key role in determining the effect of alcohol. This finding in particular may point toward a specific alcohol interaction site on these receptors.

defined by the sequence of amino acids.) Through these experiments, the investigators were able to pinpoint single-amino acid molecules that conferred a particular response to alcohol within the proteins (Mihic et al. 1997).

Further investigation involved another technique for altering protein structure, site-directed mutagenesis, in which researchers change the DNA coding sequence. This technique is used to make targeted changes in the DNA so that only one amino acid in the protein is altered. The results of these studies indicated that amino acids in the part of the protein that is embedded in the cell membrane are crucial for determining the effect of alcohol on the glycine and $GABA_A$ receptors. This research represents an important step toward identifying the molecular site of action of alcohol at these receptors. Knowing this site of action is expected to be of great help in designing pharmacotherapeutic agents to counteract the effects of alcohol.

Alcohol's Effects on Protein Phosphorylation

In addition to its actions on ligand-gated ion channels, alcohol interacts with other molecules inside neurons. Protein kinases, a class of molecules that have important roles in regulating synaptic transmission and brain function, are enzymes that catalyze the modification of a variety of proteins by promoting the addition of a simple phosphate molecule to specific parts of the proteins (see the section "Setting the Stage: The Structure and Function of Neurons"). This biochemical mechanism, known as protein phosphorylation, is usually activated by intracellular messenger molecules.

Protein phosphorylation can alter the function of a protein by changing the structure of the protein in a subtle way. For example, phosphorylation of some ligand-gated ion channels alters the signaling function of these channels. Thus, it is possible for protein kinase activity to alter

synaptic transmission by altering the function of the receptors involved in transmission. Researchers have long suspected that alcohol exerts some of its effects on brain function by interacting with protein phosphorylation mechanisms.

NMDA-Type Receptors and Fyn Tyrosine Kinase

A recent discovery demonstrates one way in which alcohol's effects on phosphorylation of a ligand-gated ion channel contribute to the intoxicating effects of alcohol and to alcohol tolerance. The NMDA-type glutamate receptor discussed above is altered by phosphorylation of an amino acid known as tyrosine. This alteration takes place through the activity of a protein kinase, known as a protein tyrosine kinase, that is specialized for phosphorylation of the amino acid tyrosine in proteins. The specific kinase involved in the phosphorylation of the NMDA receptors is called Fyn tyrosine kinase.

Mutant mice that lack the gene for Fyn tyrosine kinase (known as Fyn knockout mice) are made using a technique called homologous recombination. This technique involves inserting an altered gene into an embryonic stem cell—a cell that is not differentiated into a specific tissue but has the potential to develop into any type of cell in the organism. The stem cell is then fertilized and implanted into a female mouse to produce embryos. The mice, when mature, have an altered genetic code for the targeted protein. These mice can then breed and establish many generations of animals that have alterations in the expression of a particular protein. The replacement gene in a knockout mouse is nonfunctional; that is, it does not code for an intact, functional protein. Investigators use this experimental approach to examine the roles of many proteins in a variety of cellular and behavioral processes.

Effects of alcohol on Fyn knockout mice have been examined at the level of NMDA receptor molecules, functional synapses, and animal behavior (Miyakawa et al. 1997). Investigators first observed that the Fyn knockout mice were more sensitive to the sedative and movement-incoordinating effects of alcohol than were the matched wild-type control mice (mice without the mutation). In a sleep time test, the animals received an injection of alcohol; the time it took them to get off their backs and stand up was measured. The Fyn knockout mice stayed down longer, indicating that this effect of alcohol lasts longer in the knockout mice than in the control mice.

Because the NMDA receptor has been implicated in the effects of alcohol, the researchers next examined whether alcohol inhibition of synaptic responses mediated by this ligand-gated ion channel was altered in the knockout animals. Interestingly, alcohol inhibited the synaptic response mediated by the NMDA receptor in both wild-type and Fyn knockout mouse synapses. However, the effect in wild-type mice disappeared during the first 20 minutes after alcohol exposure, while the inhibitory effect persisted in the Fyn knockout mice. This loss of alcohol effect within minutes has been called acute tolerance or rapid acute tolerance (Grover et al. 1994; Pearson et al. 1997) and appears to result from molecular changes that counteract the effects of alcohol. Loss of tolerance in the Fyn knockout mice indicates that phosphorylation by Fyn tyrosine kinase is an important step in the loss of alcohol effects on the NMDA receptor.

There are several subtypes of NMDA receptors in the brain. NMDA receptor proteins are complexes composed of a grouping of several individual proteins known as subunits (Anantharam et al. 1992; Ishii et al. 1993; Mishina et al. 1993; Seeburg et al. 1995). The assembly of various receptor subunits confers different functional properties on the receptor. Some evidence indicates that alcohol has more powerful effects on certain NMDA receptor subtypes than on others. For example, alcohol's inhibitory effects on NMDA receptors in neurons appear to be the strongest in receptors that contain a subunit known as NR2B in rats and NRε2 in mice (Fink and Göthert 1996; Lovinger 1995; Yang et al. 1996).

In studies of Fyn knockout mice, treatment with alcohol activates Fyn tyrosine kinase phosphorylation of the NRε2 subunit in wild-type mice; in contrast, phosphorylation of this subunit and the effect of alcohol are absent in the Fyn knockout mice (Miyakawa et al. 1997). Taking together all the findings from the studies of alcohol effects on receptors and the role of Fyn tyrosine kinase, researchers have constructed a scenario in which alcohol produces two important effects on the NMDA receptor. The first effect is inhibition of receptor function, which likely involves an interaction between alcohol and the receptor or an effect of alcohol on the cell membrane at a site very near the receptor. The accumulated evidence for a role of NMDA receptors in acute alcohol intoxication indicates that this inhibitory effect is key in the brain's initial response to alcohol.

The second effect is alcohol activation of Fyn tyrosine kinase, which leads to phosphorylation of the NMDA receptor on the NRε2/2B subunit, counteracting the inhibitory effect of alcohol on the NMDA receptor. The result is a rapid loss of intoxication, even during a single exposure to alcohol. These types of molecular adaptations to alcohol, which lead to behavioral tolerance, appear to alter synaptic communication within the brain. Of note is that Fyn knockout animals have defects in some forms of learning and memory, and they have deficiencies related to long-lasting changes in synaptic transmission that are thought to be involved in learning and memory (Grant et al. 1992). These observations suggest that the NRε2/2B subunit may be involved in the adaptive neuronal processes that store information, including information about alcohol exposure.

How might these molecular effects of alcohol contribute to alcohol abuse and alcoholism? Evidence indicates that sensitivity to alcohol is a predictor of risk for alcoholism. For example, individuals who are able to drink large quantities of alcohol when first exposed to the drug are more likely to keep drinking large quantities and to develop alcohol abuse problems than are persons who can consume only small amounts of alcohol when first drinking.

It is possible that susceptibility to the inhibition of the NMDA receptor by alcohol might differ among individuals, perhaps due to variable expression of NMDA receptor subunits at brain synapses. Individuals with different levels of Fyn tyrosine kinase activity also might differ with respect to the development of rapid tolerance, which could also influence their ability to drink large quantities of alcohol and thus be important in determining susceptibility to alcoholism in different human populations. Although no definitive evidence in humans currently exists to evaluate this hypothesis, the possible role of Fyn tyrosine kinase in determining individual differences in alcohol sensitivity will undoubtedly be explored during the next few years.

Second Messengers and Protein Kinases

Alcohol also may alter the production of intracellular messenger molecules and the distribution of protein kinases in neurons. One way neurotransmitters affect neuronal excitability (other than through receptors that are themselves ion channels) is by acting on receptors that are coupled to intracellular signaling processes. These G protein receptors, so called because they involve the binding and breakdown of guanosine triphosphate (GTP), can influence the activity of the neuron in several ways. For example, neurotransmitter binding to some G protein-coupled receptors leads to the production of small-molecular-weight molecules known as second messengers. One such second-messenger molecule is cyclic adenosine monophosphate (cAMP). The G protein that is activated stimulates an enzyme within cells that leads to rapid production of cAMP, which then interacts with proteins within the cell. The major protein activated by cAMP is known as cAMP-dependent protein kinase. Like the Fyn tyrosine kinase discussed above, this kinase stimulates phosphorylation of proteins within the cell.

The proteins that are phosphorylated upon activation of cAMP-dependent protein kinase include neurotransmitter receptors and neurotransmitter transporters. Phosphorylation of these proteins can lead to changes in protein function, in the distribution of the proteins

within the cell, or both. These changes, in turn, can alter cell function. For example, if either receptor function or the number of receptors at the cell surface changes, the postsynaptic response to a neurotransmitter also changes. If either the actions or the numbers of these neurotransmitter transporters are altered, the duration of neurotransmitter effects within the synapse changes. These types of effects alter communication between neurons and ultimately influence the workings of the entire brain and related animal or human behaviors.

Recent studies indicate that alcohol affects protein kinases in a number of ways. For example, alcohol alters both the amount of protein kinases as well as their intracellular distribution. Protein kinases are found in a number of compartments within cells, but particular kinase molecules are often present within only one part of a cell. This compartmentalization restricts the activity of the kinase so that it can phosphorylate only those proteins in the same part of the cell. This localization, in turn, affects the impact of the kinase on cellular function, because the proteins it phosphorylates have specific functions within that part of the cell. For example, a kinase that is restricted to the nucleus phosphorylates nuclear proteins and most likely affects gene translation. A kinase that is present only in neuronal dendrites may phosphorylate neurotransmitter receptors and alter postsynaptic responses to the neurotransmitter. Thus, the localization of the kinase can determine its impact on the function of an entire neuron.

Scientists recently found that the localization of protein kinases within cells occurs through proteins that attach themselves to the kinases and then anchor the kinases to a particular cellular site (Dell'Aqua and Scott 1997; Mochly-Rosen 1995). Different types of kinases interact with different anchoring proteins. Several different anchoring proteins appear to exist for each kinase, with the various anchoring proteins found in different parts of the cell. Altering the location or number of the anchoring proteins or their ability to interact with the protein kinase appears to change the cellular location of kinases and, hence, the pattern of protein phosphorylation. Such alterations could have important consequences for cellular function.

Long-term exposure to alcohol alters the distribution of cAMP-dependent protein kinase such that a higher concentration of the kinase is found within the cell nucleus during alcohol exposure (Dohrman et al. 1996). Researchers have used a powerful laser confocal microscope to view small parts of neurons and to observe altered distributions of protein kinase. When certain proteins are tagged with fluorescent molecules, they glow when exposed to laser light, making it easy to track these molecules within a cell. Using this technique, researchers have mapped the location of the cAMP-dependent protein kinase within neurons before and after short- and long-term alcohol exposure. The sequestration of the kinase within the cell nucleus following long-term alcohol exposure appears to be the reason for decreased phosphorylation of proteins within the cell cytoplasm and within the membrane enveloping nucleus.

One protein whose function appears to be regulated by cAMP-dependent protein kinase phosphorylation is the transporter for the inhibitory neurotransmitter adenosine. (Neurotransmitter transporters shuttle and help regulate the level of neurotransmitters in the synaptic cleft.) Short-term exposure to alcohol inhibits this transporter molecule in a manner that depends on phosphorylation of the transporter protein or a closely associated protein by the cAMP-dependent protein kinase (Coe et al. 1996). Transporter inhibition increases the extracellular concentration of adenosine because the transporter is no longer able to efficiently remove the neurotransmitter from the synapse. This effect, along with the effects on GABAergic transmission mentioned above, may contribute to the inhibitory effects of alcohol on brain activity.

During chronic alcohol exposure, the sequestering of the kinase in the nucleus leads to reduced transporter phosphorylation, which, in turn, appears to lead to a loss of inhibition of the transporter. Due to this loss, adenosine synapses become more resistant to the effects of alcohol. This resistance translates, over time, to less of an

inhibitory effect with chronic exposure to alcohol. This loss of phosphorylation represents another form of cellular adaptation to alcohol that plays a role in the brain's development of tolerance to and dependence on it.

Long-Term Exposure to Alcohol: Gene Expression, Protein Phosphorylation, and Protein Localization

One way in which alcohol produces a long-lasting change in brain activity is by altering the patterns of expression of proteins that are important for regulating neuronal activity. This regulation often takes place in the nucleus in the form of alterations in gene expression. Messages from the periphery of the cell make their way to the nucleus to interact with DNA and alter gene expression (see the box "From DNA to Protein: How Genetic Information Is Realized" in the previous section).

GABA

Changes in the number or molecular structure of neurotransmitter receptors or other molecules involved in synaptic transmission appear to be involved in the brain's adaptations to the presence of alcohol, which are manifested in tolerance, dependence, and alcohol withdrawal. Two of the neurotransmitter receptors that are sensitive to the acute actions of alcohol are also greatly affected by long-term exposure to alcohol. One of the receptors, $GABA_A$, undergoes structural changes during long-term alcohol exposure. As with the NMDA receptor described above, the $GABA_A$ receptor is a complex of several individual subunit proteins. Different combinations of these subunits can come together to form the receptor channel. One way in which chronic exposure to alcohol affects the $GABA_A$ receptor is to change the expression of different subunit proteins that participate in the formation of the receptor.

The sensitivity of $GABA_A$ receptors to alcohol also appears to be altered as a consequence of long-term exposure to alcohol (Morrow et al. 1988). This loss of alcohol sensitivity may be related to the change in receptor subunit expression (Crews et al. 1996; Mhatre et al. 1993; Morrow 1995). Even when receptor subunit expression is not altered, however, the function of $GABA_A$ receptors is altered by chronic alcohol exposure (Klein et al. 1995). Another mechanism that may contribute to the change in alcohol sensitivity of the $GABA_A$ receptor is a posttranslational modification of the protein—a change that takes place after the last step in gene-directed protein synthesis—such as protein phosphorylation. Research shows that alcohol's effects on the receptor are lost in mice that are genetically engineered to remove the gamma subtype of the phosphorylating enzyme protein kinase C (Harris et al. 1995). Thus, changes in receptor subunit expression and receptor phosphorylation could contribute to alcohol tolerance, because the intoxicating effects of alcohol that involve $GABA_A$ receptors presumably are reduced if these receptors become less sensitive to alcohol.

NMDA

Alterations in the structure or function of NMDA receptor subunit molecules also occur during long-term alcohol exposure. Early reports indicated that the number of NMDA receptors on neurons in brain regions, such as the hippocampus, increased following long-term alcohol exposure (Hoffman 1995). (The hippocampus is a part of the brain thought to play a role in learning and memory as well as in alcohol withdrawal syndrome.) In addition, evidence that NMDA receptor-specific blockers inhibit alcohol withdrawal seizures implicated this receptor in the withdrawal syndrome (Hoffman et al. 1992; Morrisett et al. 1990). Subsequent investigations have provided evidence for increased function of NMDA receptors after chronic alcohol exposure. For example, researchers have examined responses of individual neurons upon exposure to NMDA (a synthetic amino acid that activates the NMDA receptor) by using neurons subjected to long-term alcohol exposure and have compared these responses with those of alcohol-naive neurons. The increases in intracellular calcium produced when the NMDA receptor is activated were enhanced following long-term alcohol exposure (Ahern et al. 1994; Iorio et al. 1992; Smothers et al. 1997).

Alcohol-induced responses of the NMDA receptor appear to be a function of its subunit proteins. The NR1 subunit is present in all receptors and thus seems to be a necessary, or constitutive, element of a functional receptor. The presence or absence of specific NR2 subunits (there are four) is the major factor that underlies variability in the properties of different receptors. Various parts of the brain contain different amounts of each type of NR2 subunit. Certain brain regions contain two of the receptor subtypes and can use either one, or both, as part of the functional NMDA receptor. For example, neurons in the cerebral cortex have receptors that contain both the NR2A and NR2B subunits (Sheng et al. 1994). Changing the amount of either of these subunits changes the functional characteristics of the receptor and alters glutaminergic synaptic transmission within the cerebral cortex.

The increased activity of NMDA receptors after prolonged alcohol exposure most likely arises from increases in the amounts of the particular subunit proteins that contribute to NMDA receptor formation. Brains from animals exposed to alcohol for days to months have been examined to determine whether NMDA receptor subunit expression is altered. Similar experiments have been performed using brain neurons grown in cell culture.

Exposing cultured cerebral cortical neurons to alcohol for a few days increased the amount of ribonucleic acid (RNA) that codes for the NR2B subunit, with little or no change observed in other receptor subunits (Hu et al. 1996). Increased NMDAR2B protein was also observed in these neurons (Follesa and Ticku 1996). This sort of change in the relative amount of each subunit can lead to two consequences with respect to NMDA receptor function. First, the total number of NMDA receptors might increase because a larger amount of subunits is available to construct receptors. This, in turn, could lead to larger synaptic responses at glutaminergic brain synapses. Second, more receptors containing just the NR2B subunit could be expressed, producing a change in the synaptic responses mediated by the receptor. Evidence for increases in relative amounts of receptors containing functional NR2B subunit has been observed following prolonged alcohol exposure (Blevins et al. 1995).

Some research suggests, however, that this long-term, alcohol-induced change in NMDA receptor subunit composition may involve mechanisms other than a simple change in subunit expression (Blevins et al. 1997), as was previously described for the $GABA_A$ receptor (Klein et al. 1995). For example, NMDA receptors containing the NR2B subunit are currently thought to produce longer lasting synaptic responses in the cortex (Carmignoto and Vicini 1992). Responses that last longer will produce a longer lasting excitation of the cell. This extended activity thus may be fundamental to the changes that bring about hyperexcitability of the brain during withdrawal from alcohol.

Alcohol exposure lasting weeks to months leads to increases in the amount of the NR1 and NR2A subunits in several brain regions, including the hippocampus (Snell et al. 1996; Trevisan et al. 1994). The hippocampus plays a key role in learning and memory for certain types of information, and NMDA receptors in this brain region are important to these processes (Kandel et al. 1995). An increase in the amount of the constitutive NR1 subunit of the protein in the hippocampal formation could lead to increased numbers of NMDA receptors in this brain region. Thus, alteration of the number of NMDA receptors is one mechanism that could contribute to the development of memory problems after prolonged alcohol exposure. Increased receptor expression could also contribute to the increased excitability of the brain during withdrawal. Furthermore, excessive activation of NMDA receptors can lead to neuronal injury and death. Thus, increased NMDA receptor expression and function in the hippocampus could contribute to damage in this part of the brain following prolonged alcohol abuse, and this damage could contribute to memory problems. Similar effects are seen in other brain regions, such as the cerebral cortex.

Alcohol Effects on Other Genes

Some genes within neurons appear to be particularly sensitive to alcohol. Several examples of this type of alcohol-sensitive gene have been described in recent studies. For example, neuronal exposure to alcohol leads to increased production of two forms of protein kinase C, an enzyme that mediates protein phosphorylation (Messing et al. 1991). Increased production of these forms results from an increase in the gene-driven production of the RNA that encodes protein kinase C. Thus, researchers suspect that the genes producing these forms of protein kinase C are activated by alcohol. The increased activity of these two forms leads to abnormal growth of neurons (Roivainen et al. 1995). Such improper neuronal growth could contribute to improper brain development as a result of fetal alcohol exposure or improper wiring of neuronal connections, leading to alterations in brain function in adult alcohol abusers. (The chapter on prenatal exposure to alcohol describes in greater detail the impact of alcohol on fetal growth and development.)

In Closing

By altering the function of key proteins—including neurotransmitters and phosphorylating enzymes—within neurons, alcohol can produce changes in synaptic transmission. These rapid changes in the brain result in intoxication. Long-term alcohol exposure produces adaptive changes in the function of these same specialized proteins that lead to alterations in synaptic transmission in a manner that compensates for the lasting presence of alcohol. This adaptation gives rise to tolerance, dependence, and the alcohol withdrawal syndrome. Newly developed techniques for analysis of brain molecules and genetically engineered laboratory animals are allowing researchers to examine the molecular events that are responsible for both the short- and long-term effects of alcohol on the brain. The resulting findings will help scientists understand the effects of alcohol and will also provide the basis for developing pharmaceutical means of diagnosing, treating, and preventing damage from alcohol abuse.

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Acute Actions of Alcohol on the Brain

Unlike many drugs that have a single site of action, alcohol produces a wide spectrum of effects on brain function via interaction with multiple targets. For many years, it was assumed that alcohol's effects on brain function were primarily due to its ability to nonspecifically disrupt or disorder the neuronal membrane. This hypothesis, which originated nearly 100 years ago, has been severely challenged by research carried out over the last 10 years.

A growing body of evidence shows that alcohol exerts significant effects on specific receptor proteins that are embedded in the neuronal plasma membrane. The function of these proteins ultimately underlies all brain function, including thought, speech, vision, and complex behaviors. This view, which is becoming widely accepted, represents a dramatic change in the way we think about alcohol and its effects on brain activity. The factors that precipitated this new way of thinking about alcohol are closely tied to the advances made in the field of molecular neuroscience and to technical advances made in the way that the activity of neurons is studied.

Because of the complexity of the human brain, which is comprised of approximately 1 trillion neurons, scientists have developed techniques to study brain function in simpler systems where there are fewer experimental variables. These techniques include brain cell cultures that permit the behavior of single neurons to be studied, and the use of recombinant or cloned receptors that can be expressed in experimental cells such as frog eggs (*Xenopus* oocytes). Experiments using microdialysis, which allows the fluid that surrounds neurons to be repeatedly sampled, have allowed researchers to examine the effects of alcohol on levels of neurotransmitters in intact animals. Finally, behavioral approaches have allowed scientists to gain important insights into the effects of alcohol on brain function in awake, freely moving animals.

These approaches have resulted in a remarkably detailed understanding of the effects of acute alcohol exposure on many important neuronal proteins that regulate brain activity. By understanding the molecular and cellular sites of action for the acute effects of alcohol, it should be possible to explain how the continued use of alcohol may lead to alcohol dependence or how the abuse of alcohol may result in death or serious brain injury.

The following material is not intended to be an exhaustive literature review. Rather, it is a focused examination of areas that have seen significant progress in the last several years.

Measuring Alcohol's Effects

As with many drugs, alcohol's effects are dose dependent. That is, higher concentrations of alcohol generally produce a larger effect on a particular protein or biological process, or a more marked effect on behavior or function, than lower concentrations do. Because alcohol is administered by drinking and is distributed to the brain by the bloodstream, alcohol concentrations are usually measured in terms of concentration, or percent, in the blood. In most states, for example, individuals with blood alcohol levels (BAL's) or blood alcohol concentrations (BAC's) of 0.1 percent or higher are considered legally intoxicated. (See the box "The ABC's of BAC's" in the chapter on prevention research for additional background.)

Most researchers who conduct alcohol research using in vitro (cellular or test tube) preparations prefer to express concentrations of alcohol as molar concentrations (the amount of alcohol in solution in a given volume of water based on the number of molecules, or moles, of alcohol present). For example, a 0.1-percent BAL is the same as 22.5 millimolar (mM). In these types of experimental research studies, concentrations of

alcohol that are considered relevant with respect to their behavioral effects are generally in the range of 10 to 100 mM. These levels are considered biologically important because it is possible to show significant effects of alcohol on some neuronal proteins, pathways, or systems simply by increasing the alcohol concentration. However, to be considered a relevant target for alcohol's actions, a protein or process should be sensitive to concentrations of alcohol that are associated with changes in human behavior and are easily achieved during alcohol drinking.

Alcohol and Ion Channels

Considerable evidence has accumulated to show that alcohol exerts significant effects on specific receptor proteins that are embedded in the neuronal plasma membrane. Of particular interest are reports that have demonstrated that alcohol alters the function of several important voltage-gated and ligand-gated ion channels. These channels are located predominantly in the synapse, where they mediate and modulate neuronal excitability. Since alcohol's effects are most noticeable at the synapse, these ion channels represent excellent targets for alcohol's anesthetic and intoxicating actions. Recent studies show that alcohol exerts powerful and specific effects on ion channel function and that these effects may be modulated by the subunit makeup and state of phosphorylation of these ion channels (for background on terms used in this discussion see the section "Setting the Stage: The Structure and Function of Neurons" earlier in this chapter).

Inhibitory Ligand-Gated Ion Channels

Research shows that many compounds that produce sedation and anesthesia appear to operate by enhancing the effects of gamma-aminobutyric acid (GABA) on the $GABA_A$ receptor. Among these compounds is the large class of sedative-hypnotic drugs that include benzodiazepines (Valium), barbiturates (pentobarbital), general anesthetics (halothane), and alcohol.

Endogenous (naturally present in an organism) substances also enhance $GABA_A$ receptor function and thus help regulate the activity of the receptor. The cloning of members of the $GABA_A$ family of subunits has revealed that neurons express multiple types of $GABA_A$ receptors that are made up of different subunits, as discussed in the section "From Cell Membrane to Nucleus: The Effects of Alcohol on Brain Neurons" earlier in this chapter. The combination of different receptor subunits yields receptors with different sensitivities to both endogenous compounds such as GABA and exogenous drugs such as alcohol.

GABA Receptors.

Alcohol Potentiation of $GABA_A$ Receptor Function. How alcohol potentiates the effect of GABA on its receptors is not clear. It is likely that the sensitivity of $GABA_A$ receptor to alcohol is complex and subject to multiple levels of regulation. One approach to studying the complexities of the $GABA_A$ receptor subunit composition uses a technique known as recombinant complementary DNA (cDNA) expression systems, in which part of the genetic material (deoxyribonucleic acid, or DNA) from one organism is inserted into the genetic material of a second organism, such as bacteria or *Xenopus* oocytes. Such systems allow investigators to express, or produce, individual or multiple $GABA_A$ receptor subunits in experimental cells that normally do not express these receptors. This technique allows for systematic evaluation of the effects of alcohol on different receptor subunit combinations. This approach has proven valuable in showing that some $GABA_A$ receptor responses in neurons are sensitive to alcohol, whereas others are not. This implies that the subunit makeup of the $GABA_A$ receptor may be an important determinant of sensitivity to alcohol's actions. If true, then differences in the $GABA_A$ receptor subunit composition could underlie the observed differences in alcohol sensitivity between alcoholics and nonalcoholics.

Research using recombinant cDNA expression systems has suggested that the γ_{2L} subunit of the $GABA_A$ receptor is critical to alcohol's potentiating effect (Wafford et al. 1991). Not all such studies have demonstrated a potentiating effect,

however, even in the presence of the γ_{2L} subunit (Sigel et al. 1993). Thus, although this subunit may be necessary for alcohol to have an effect, other factors may be important in determining whether such an effect is observed. These other factors may include phosphorylation (the addition of a phosphate group through enzymes known as protein kinases), which has been shown to influence the regulation of receptor activity; association of the $GABA_A$ subunits with the cellular cytoskeleton (the structural architecture of the cell); and location of the receptor on the cell membrane.

For example, one recent study added to earlier evidence that the phosphorylating enzyme protein kinase C (PKC) is involved in modulating alcohol sensitivity of GABA receptors (Weiner et al. 1997*a*). In this study of brain slices from adult rats, basal (before alcohol treatment) levels of PKC activity correlated with alcohol's potentiation of $GABA_A$ receptor responses. (By varying incubation temperatures of the brain slices, the investigators altered basal PKC activity levels.) Treatment of neurons with drugs that reduced basal PKC activity also reduced the effects of alcohol. Activation of other kinases, such as protein kinase A, also has been shown to enhance the sensitivity of $GABA_A$ receptors to alcohol (Freund and Palmer 1997*a*; Lin et al. 1994). Data from these studies suggest that the state of receptor phosphorylation is important in determining the sensitivity of $GABA_A$ receptors to alcohol. Direct measures of receptor phosphorylation are needed to confirm this suggestion.

Another aspect of ion channel function is emerging from current, ongoing neuroscience research. Recent studies suggest that the neuron is not an unorganized collection of proteins bounded by the lipid membrane, but a highly structured, three-dimensional environment in which the function of a receptor or ion channel is influenced by its location. This spatial organization may be important in clustering together proteins that interact with one another, such as kinases and ion channels like the $GABA_A$ receptor. A recent report illustrated the importance of this clustering to the effects of alcohol (Whatley et al. 1996). In this study, $GABA_A$ receptor subunits were introduced into a cell line that did not normally express these receptors. Alcohol potentiated the GABA responses in these cells; however, agents that affected the cytoskeleton of the cell prevented this potentiation. The disruption of the cytoskeleton may have prevented the $GABA_A$ subunits from being phosphorylated by protein kinases because of a physical separation of the receptor and kinase.

Reinforcing the idea that receptor localization can influence alcohol sensitivity, a study using rat brain slices showed that alcohol potentiated $GABA_A$ receptors located in the synapses on some dendrites of a single neuron but not in others (Weiner et al. 1997*b*). The underlying reason for this striking effect was not elucidated. Nevertheless, taken together, the findings described above suggest that factors other than $GABA_A$ receptor subunit makeup help determine the sensitivity of the brain to alcohol. They also raise the possibility that psychological or pharmacologic interventions that alter neuronal excitability may alter an individual's response to alcohol.

Effects of Alcohol on $GABA_A$ Receptor Knockout Animals. Despite evidence from in vitro studies that $GABA_A$ receptor subunit makeup does not appear to be the sole determinant of alcohol's actions, it is not clear whether this is true in intact animals. One direct approach to testing how specific receptor subunits mediate alcohol's effects is to develop genetically altered animals that are lacking functional specific receptor subunits. These knockout animals have become a valuable tool to examine the involvement of specific receptors in mediating the actions of alcohol on the brain. (Two other sections in this chapter, "From Cell Membrane to Nucleus: The Effects of Alcohol on Brain Neurons" and "Genetic Studies of Alcohol's Actions on the Brain," also discuss knockout animals.)

To date, alcohol sensitivity has been determined in animals lacking the $GABA_A$ receptor subunits

alpha (α), beta (β), and gamma (γ). Studies of mice that lack the α_6 subunit of the $GABA_A$ receptor have shown, for example, that the α_6 subunit does not mediate the sedative-hypnotic actions of alcohol and other depressant agents, as measured by alcohol-induced hypnosis (sleep time) (Homanics et al. 1997). Whether this subunit mediates other actions of alcohol that may occur at nonsedative concentrations remains to be determined.

In another study, scientists compared the anesthetic sensitivity of knockout mice lacking the β_3 subunit of the $GABA_A$ receptor with that of control (or wild-type) mice in which the functional gene is present (Quinlan et al. 1998). Knockout mice showed no significant differences in the sedative effects of alcohol, pentobarbital, or volatile anesthetics (enflurane or halothane) compared with control mice. However, the knockout mice were more resistant to the surgical anesthetic (loss of sensation) effects of the volatile anesthetics. These data indicate that the β_3 subunit does not play a critical role in the sedative effects of alcohol. These findings also suggest the presence of different sites of action for the sedative and anesthetic actions of commonly used surgical anesthetic agents.

Another subunit, the γ_{2L} subunit already mentioned, previously had been shown by some investigators to be important in mediating the potentiating effects of alcohol on $GABA_A$ receptor function (Wafford et al. 1991). (Again, not all such studies have demonstrated a potentiating effect.) If the γ_{2L} subunit is required for this action in intact animals, animals lacking this subunit would be expected to show an altered response to alcohol. Two studies have sought to test this hypothesis by examining the effects of knocking out the gene that codes for the γ_2 subunit of the $GABA_A$ receptor.

A recent study examined the alcohol sensitivity of mice lacking only the γ_{2L} subunit of the $GABA_A$ receptor (Homanics et al. in press). The animals lacking only the γ_{2L} variant of the $GABA_A$ receptor had normal life spans (most mice lacking the entire γ_2 gene die within a few days of birth [Gunther et al. 1995]) and were not significantly different from wild-type mice in their behavioral responses to alcohol, including sleep time, anxiolysis (anxiety reduction), acute functional tolerance, withdrawal hyperexcitability (over-excitability that occurs after exposure to, then removal of, alcohol), and hyperlocomotion (Homanics et al. in press). In addition, in the presence of alcohol, GABA-induced electrical activity in neurons isolated from these knockout mice was stimulated to the same extent as neurons isolated from wild-type mice. Several behavioral effects of alcohol remained unchanged in the knockout mice. These results suggest that the γ_{2L} subunit is not essential for alcohol effects on the $GABA_A$ receptor.

As noted in the section "From Cell Membrane to Nucleus: The Effects of Alcohol on Brain Neurons" earlier in this chapter, scientists have also examined the alcohol sensitivity of mice lacking the γ isoform of the phosphorylating enzyme PKC (PKC-γ). Mutant mice lacking PKC-γ showed a reduced sensitivity to both the sedative and hypothermic effects of alcohol (Harris et al. 1995). In addition, the ability of alcohol to potentiate $GABA_A$ receptor function in brain tissue from these mice was reduced compared with that in control animals. Interestingly, the knockout mice had normal responses to other sedatives such as benzodiazepines and barbiturates that are thought to interact with the $GABA_A$ receptor. Taken with the results of the research described above, these data support the idea that receptor phosphorylation and other posttranslational processes (processes that take place after the last step in gene-directed protein synthesis) may be more important than $GABA_A$ receptor subunit makeup in determining the alcohol sensitivity of these receptors.

Glycine Receptors. Both GABA receptors and glycine receptors—to which the inhibitory neurotransmitter glycine binds—mediate the flux of chloride ions into neurons; this process, in turn, inhibits the cell's ability to fire, or transmit, a nerve impulse. Glycine receptors are found predominantly in the spinal cord, but they also exist in the brains, where they may play a role

in some of the actions of alcohol. As demonstrated using $GABA_A$ receptors, alcohol also potentiates chloride flux—augments the entry of negatively charged chloride ions into the neuron—through recombinant glycine receptors expressed in *Xenopus* oocytes (Mascia et al. 1996). Glycine receptors composed of the α_1 subunit were more sensitive to low concentrations of alcohol than those made from α_2 subunits. This difference was attributed to a change in a single amino acid of the α_2 subunit, suggesting that alcohol may interact with specific amino acids on this ion channel to cause its effects.

This hypothesis is supported further by data suggesting that the potentiation of recombinant glycine and $GABA_A$ receptors by all concentrations of alcohol could be abolished by single-amino acid substitutions in either the GABA transmembrane II (TMII) or TMIII domains of the neuronal cell membrane (Mihic et al. 1997). For example, when the amino acid serine at position 267 in the TMII domain of the glycine α_1 receptor was changed to the amino acid isoleucine, electrical currents generated by this mutant receptor were no longer potentiated by alcohol. Changing the amino acid serine at position 267 to another amino acid, tyrosine, abolished the effects of some but not all anesthetic agents that share some behavioral effects with alcohol. Subsequent work demonstrated that alcohol's effect on recombinant glycine α_1 receptors was inversely correlated with the size of the amino acid at position 267 (Ye et al. 1998). Thus, alcohol potentiated receptor function when small amino acids such as glycine or alanine were substituted at that position. However, substituting large amino acids such as histidine, cysteine, or tyrosine resulted in receptors that were inhibited by alcohol.

These findings provide strong evidence that alcohol interacts with discrete regions of important neuronal proteins to alter their function. Furthermore, alcohol may preferentially partition into pockets defined by specific amino acids in areas of the receptor protein that are important for cell functioning. Alcohol's presence in these pockets may disrupt the normal interactions between various regions of the receptor, leading to altered receptor function. This research also raises the possibility that changes in specific amino acids brought about by either experimental or random changes to an individual's genetic code may lower an individual's sensitivity to the sedative and anesthetic effects of alcohol that appear to be mediated via glycine and $GABA_A$ receptors. Development of experimental animals with glycine receptors possessing specific amino acid substitutions will allow researchers to test these hypotheses.

Excitatory Ligand-Gated Ion Channels

Glutamate Receptors. As the major excitatory amino acid in the brain, glutamate binds to specific ligand-gated ion channels and depolarizes the postsynaptic neuronal membrane, making it more likely that the neuron will "fire." In this way, these proteins serve as excitatory ion channels. Three distinct families of glutamate-activated ion channels are present on the postsynaptic, dendritic membrane of neurons. These receptors are named for compounds that selectively activate one class of receptors but not the others. For example, NMDA receptors are named for the synthetic compound *N*-methyl-D-aspartate (NMDA), whereas AMPA receptors are activated by the synthetic compound alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA). The natural chemical kainate activates a subset of ligand-gated ion channels that are similar in structure to the AMPA family and that are sometimes grouped together in a classification termed AMPA/kainate receptors. Distinct genes for these three classes of glutamate-activated ion channels have now been cloned, allowing researchers to study the effects of alcohol on specific receptor combinations.

NMDA receptors are categorized by constituent subunits: the NR1 subunits and four members of the NR2 family (A, B, C, and D). AMPA/kainate receptors are represented by at least seven subunit types (GluR1 through GluR7) plus two other subunits (KA1 and KA2) that respond selectively to kainate. Slight differences in the amino acid sequence of certain members of each of these families create an additional level of

receptor diversity. For example, there are eight different versions of the NR1 subunit that differ by the absence or presence of three sequences of amino acids.

As a group, the different glutamate receptor subunits are distributed widely throughout the brain, although certain subunits are found in very limited areas. Receptors composed of different subunits show slightly different sensitivities to activation by glutamate; these sensitivities are often manifested in the amount of time that the receptors remain open after being activated. Glutamate receptors also differ in the selectivity of the ions that permeate their pore.

AMPA/kainate receptors are permeable largely to sodium ions and, when activated by glutamate, set off a rapid and large depolarization of the postsynaptic neuron. If enough of these receptors are activated, the cell can fire an action potential, and neuronal signaling proceeds to the next neuron. NMDA receptors allow both sodium and calcium ions to enter the cell. Unlike AMPA/kainate receptors, however, NMDA receptors are blocked by magnesium ions, which are normal constituents of the extracellular fluid that bathes neurons. This block is voltage dependent, meaning that under conditions of relatively low-frequency electrical activity, NMDA receptors are blocked by magnesium ions, allowing few calcium ions to enter the neuron. When more glutamate is released into the synapse, sodium flowing through AMPA/kainate receptors depolarizes the neuron so that the magnesium block of the NMDA receptor is removed, calcium ions can enter the neuron, and the neuron's ability to fire a nerve impulse increases.

Calcium is an important regulator of neuronal function that exerts its effects through its interactions with a wide variety of enzymes and other proteins. For example, substantial evidence suggests that the entrance of calcium ions into the neuron through the NMDA receptor is required for the formation of new memories, such as those that take place during learning. NMDA receptors are also important during the period of development when brain neurons organize themselves into the complex circuits that allow the brain to support people's ability to speak, think, reason, and respond to others. In humans, the period of most intense growth and development of these circuits begins during the last stages of fetal development and accelerates to a peak during the first several years of a person's life. (See the section "Underlying Mechanisms of Alcohol-Induced Damage to the Fetus" in the chapter on prenatal exposure to alcohol for additional information.)

Alcohol Inhibition of NMDA Receptor Function. In contrast to its effects on $GABA_A$ receptors, alcohol has been demonstrated to inhibit NMDA receptors (Fink and Gothert 1990; Lovinger et al. 1989; Popp et al. 1998; Simson et al. 1993; Wong et al. 1997; Woodward and Gonzales 1990). Some areas in the brain contain NMDA receptors that show a reduced sensitivity to the inhibitory effects of alcohol, suggesting that different regions of the brain may use different receptor subunits to assemble mature NMDA receptors. Another possibility is that, as with the $GABA_A$ receptor, intracellular activities such as phosphorylation may render NMDA receptors more or less sensitive to alcohol. Recent research suggests that both of these processes are likely to be involved in mediating alcohol's effects on the brain.

For example, several studies using cloned NMDA receptors expressed in *Xenopus* oocytes indicate that NR1/2A- and NR1/2B-containing NMDA receptors are more sensitive to alcohol than those expressing NR1/2C or NR1/2D subunits (Buller et al. 1995; Chu et al. 1995; Masood et al. 1994; Mirshahi and Woodward 1995). Not all investigators have reported this finding, however, which suggests that other factors may influence the sensitivity of the receptor to alcohol (Kuner et al. 1993). One group found that NR1/2A receptors that were made calcium impermeable by changing a single amino acid in the TMII pore region were less sensitive to alcohol than the wild-type receptor was (Mirshahi and Woodward 1995). Further investigation revealed that NR1/2A receptors were more sensitive to alcohol

when the amount of calcium that entered the oocyte was increased. A small portion of a piece of the NR1 subunit lying inside the cell mediates this calcium-dependent enhancement of the alcohol inhibition (Mirshahi et al. 1998).

Findings from animal studies are consistent with the results obtained using recombinant receptors expressed in a cell line (HEK 293 cells) that NMDA receptors with the NR1/2B combination are more sensitive to inhibition by alcohol than other NMDA receptors are (Blevins et al. 1997; Lovinger 1995; Yang et al. 1996). The magnitude of alcohol's inhibition was sometimes less than that seen when these same receptors were expressed in *Xenopus* oocytes. These results suggest that factors such as phosphorylation or receptor clustering may influence the sensitivity of NMDA receptors to alcohol. Several research groups are actively investigating these factors, which may help explain why NMDA receptors in some brain areas are more sensitive to alcohol than others.

Previous research has shown that the alcohol sensitivity of NMDA receptors in some cerebellar neurons is modulated by PKC (Snell et al. 1994). (The cerebellum is a brain structure primarily involved in balance and motor coordination.) More recent reports suggest that tyrosine kinases (enzymes that phosphorylate the amino acid tyrosine) may also be important in determining the alcohol sensitivity of NMDA receptors. As discussed in a previous section in this chapter ("From Cell Membrane to Nucleus: The Effects of Alcohol on Brain Neurons"), scientists have used a mouse line in which the gene for a specific tyrosine kinase, Fyn tyrosine kinase, was deleted from the mouse's genome (Miyakawa et al. 1997). These mice were more sensitive than normal mice to the sedative actions of alcohol. In addition, NMDA responses in hippocampal slices taken from Fyn tyrosine kinase-deficient mice did not show tolerance to the effects of sustained (15 minutes) alcohol exposure, as those from wild-type mice did. (The hippocampus is a brain structure involved in the consolidation of new memories.) The adaptation of NMDA responses to the inhibitory effects of alcohol (rapid tolerance) observed previously (Grover et al. 1994) may be due to changes in the phosphorylation of neuronal proteins such as NMDA receptors or proteins that interact with the receptor.

Despite these new developments showing that the NMDA receptor's alcohol sensitivity may be modulated by both subunit composition and phosphorylation, it is still not clear how alcohol actually inhibits the receptor. The NMDA receptor has many modulatory sites that control its function, and each one of these is a potential site of action for alcohol. However, to date there is no overwhelming evidence to indicate that alcohol interacts specifically with any of these modulatory sites (Chu et al. 1995; Masood et al. 1994; Mirshahi and Woodward 1995). Analysis of the behavior of single NMDA channels in the presence of alcohol revealed that alcohol did not alter the basic biophysical properties of the channel (channel conductance) or block the open channel (Wright et al. 1996). However, alcohol did reduce the number of times an individual channel would open; exposure to alcohol also decreased the amount of time the channel was open once it was activated. Thus, as with other channel types, these results suggest that alcohol acts at a site or sites on the NMDA receptor that influence the ability of the neurotransmitter to activate or control channel opening. The location of this site has not been identified. The recent findings of a binding site for alcohol on $GABA_A$ and glycine receptor subunits (Mihic et al. 1997) will greatly accelerate the search for a similar site on the NMDA receptor.

Alcohol Inhibition of AMPA/Kainate Receptor Function. Research shows that alcohol also inhibits ion flux through AMPA/kainate receptors. In cultured neurons and preparations of isolated spinal cord, NMDA receptors appear to be more sensitive to alcohol than AMPA/kainate receptors are, while there is less difference in sensitivity in recombinant expression systems than in cultured neurons (Dildy-Mayfield and Harris 1992; Lovinger et al. 1989). Not all neuronal AMPA/kainate receptors display a low alcohol sensitivity, however (Martin et al. 1995). These

findings suggest that factors such as phosphorylation or receptor-receptor communication, which can vary according to the type of experimental preparations used, may influence the alcohol sensitivity of AMPA/kainate receptors in neurons.

Studies by one group showed that the alcohol sensitivity of various GluR AMPA/kainate receptor subunits expressed in *Xenopus* oocytes could be altered by manipulations that increased or decreased intracellular levels of calcium (Dildy-Mayfield and Harris 1995). Alcohol's ability to inhibit the transmission of electrical signals was greatest, for example, in cell preparations containing the highest concentrations of calcium. This potentiation of the alcohol effect was prevented by an inhibitor of PKC, suggesting a role for both calcium and phosphorylation. It is not known whether manipulations that increase calcium would enhance the alcohol sensitivity of AMPA/kainate receptors expressed in neurons. If so, however, these receptors could be inhibited by alcohol during periods of intense neuronal firing when calcium levels inside the neuron are higher.

The results of many studies suggest that alcohol inhibits the two major classes of glutamate-activated ion channels—NMDA and AMPA/kainate—in the brain and spinal cord. Because these channels mediate both rapid and prolonged synaptic signaling, inhibition of these responses may underlie some of the intoxicating and sedative, anesthetic effects of alcohol. Defining the precise structural and physiologic requirements that control the alcohol sensitivity of these important ion channels may lead to the discovery of alcohol-sensitive and alcohol-insensitive forms of these receptors. Unequal distribution of these receptors across brain areas and among individuals could explain the differences in alcohol sensitivity that have been observed in both experimental cell systems and humans.

Nicotinic Receptors. The neurotransmitter acetylcholine activates a multisubunit class of ligand-gated ion channels known as nicotinic receptors. These receptors contribute to neuronal excitability and are closely related to those found in skeletal muscle. The primary function of most nicotinic receptors is to control, or gate, the flux of sodium ions across the neuronal membrane; some members of this family of receptors (the $\alpha 7$ receptors) are also permeable to calcium ions. Previous studies have shown that low concentrations of alcohol (10 micromolar) actually potentiate the effects of acetylcholine on muscle-type nicotinic receptors. As with the $GABA_A$ and glycine receptors, to which the nicotinic receptors are related, these effects are more pronounced at low concentrations of acetylcholine. Such findings suggest that alcohol may affect all three receptor types similarly, perhaps through common sites of action. The physiologic significance of these effects is unknown but warrants further investigation.

Results of recent investigations of the effect of alcohol on nicotinic receptors in cultured cells and on recombinant nicotinic receptors have yielded sometimes conflicting results. Alcohol was found to potentiate or inhibit these ion channels, depending on such factors as the concentration of acetylcholine, the duration of exposure to alcohol, and the concentration of alcohol (Covernton and Connolly 1997; Nagata et al. 1996; Yu et al. 1996).

In a recent study, alcohol reduced the firing of neurons in the cerebellum; this effect was modulated by compounds that acted on nicotinic receptors (Freund and Palmer 1997*b*). These findings suggest that the effects of alcohol on neuronal activity most likely involve multiple subtypes of neurotransmitter receptors, and that the activity of one ion channel can influence the sensitivity of other channels.

Serotonin Receptors. Serotonin (5-HT), an important neurotransmitter in the brain, activates a large family of 5-HT receptors. One member of this family is the $5\text{-}HT_3$ receptor, which is a ligand-gated ion channel that controls the flux of sodium ions into neurons. The $5\text{-}HT_3$ receptor is structurally similar to nicotinic receptors and is sensitive to alcohol. This receptor is expressed in discrete areas of the brain, including the limbic areas of the forebrain (which are involved in the expression of emotional behavior) and hindbrain structures that mediate nausea and vomiting.

These receptors appear to be localized to presynaptic regions of neurons, including axons and axon terminals. This distribution suggests that the 5-HT_3 receptor modulates the regulation of the release of neurotransmitters such as dopamine, acetylcholine, and serotonin. (See the section "Genetic Studies of Alcohol's Actions on the Brain" later in this chapter for further information on 5-HT receptors and alcohol's effect on these receptors.)

As demonstrated with glycine and $GABA_A$ receptors, alcohol potentiates the activity of 5-HT_3 receptors in neurons (Lovinger and White 1991) and in transfected cells (cells in which recombinant genes have been introduced) and *Xenopus* oocytes (Lovinger and Zhou 1994; Machu and Harris 1994). Alcohol appears to affect 5-HT_3 activity through interactions with the 5-HT_3 receptor that result in a more stable, open channel (Zhou and Lovinger 1996). Because of the similarity in amino acid sequence between 5-HT_3 and $GABA_A$ or glycine receptors, researchers have hypothesized that a site of action within the TMII domain of the 5-HT_3 receptor may mediate these effects.

Alcohol's potentiating effects on 5-HT_3 receptor function (discussed in more detail below) may underlie some of the observed increases in dopamine in limbic areas of the forebrain following alcohol consumption or exposure. These increases are thought to be crucial in mediating the rewarding effects of alcohol and many other drugs of abuse.

Voltage-Gated Ion Channels

Unlike ligand-gated ion channels, voltage-gated ion channels are activated when the membrane potential of the neuron is altered. The coordinated activity of voltage-gated sodium and potassium channels underlies the generation and propagation of action potentials along axons. Judging from their structural and genetic similarities, these channels appear to belong to a large family. Voltage-gated calcium channels respond to depolarization of the membrane and allow calcium to enter the neuron. This calcium can trigger the release of neurotransmitter from presynaptic terminals, thereby initiating synaptic signaling. Voltage-gated potassium channels function to repolarize the neuronal membrane after depolarization by gating the flux of positively charged potassium ions out of the neuron. Thus, these voltage-gated channels are crucial for neuronal activity and have been extensively examined for their alcohol sensitivity.

Previous research indicated that voltage-gated sodium channels were particularly insensitive to alcohol at concentrations that are associated with the behavioral effects of alcohol (10 to 100 mM). Voltage-gated calcium channels appeared to be relatively insensitive to the acute actions of alcohol and thus were not thought to be an important target for alcohol sensitivity. However, more recent evidence (discussed below) indicates that some calcium and potassium channels are sensitive to low concentrations of alcohol and thus may contribute to the depressant effects of alcohol on neuronal function.

Calcium Channels. Like other ion channels, voltage-gated calcium channels are subdivided into several classes (T, L, N, P, Q, and others) according to structural and pharmacologic properties. These channels are found on different parts of the neuron, where they provide a pathway for calcium flux during depolarization of the membrane.

Because of the heterogeneous distribution of these channel types on neurons, it has been difficult to accurately assess the effects of alcohol on individual calcium channel subtypes. Scientists use strategies to block or encourage the activity of specific channel subtypes in order to isolate them for observation of alcohol's effects. With use of these manipulations, previous studies using intact neurons showed that alcohol inhibits some calcium channel receptor subtypes. Some subtypes (L and N) were somewhat sensitive to alcohol, whereas others (T and P) appeared to be relatively insensitive to alcohol (Hall et al. 1994; Twombly et al. 1990). More recent studies in a cell line (PC-12) that shares characteristics with neurons also suggest differences in sensitivities of the various subtypes of receptors. In recent

experiments in these cells, incubation with alcohol inhibited the activity of certain channel subtypes (N and P/Q), but only after several minutes (Solem et al. 1997). The effect was not observed in cells treated with an activator of the enzyme protein kinase A or by an inhibitor of a phosphatase (a phosphate-removing enzyme). These results suggest that phosphorylation of a cellular protein may be critical to alcohol's effects on calcium ion channels, although additional research is needed to confirm the extent to which observations in this cell line parallel what occurs in neurons.

Potassium Channels. A wide array of potassium channels have been cloned and grouped into several classes based upon their voltage dependence and sensitivity to intracellular ligands such as calcium and adenosine triphosphate (ATP, a molecule important in the energy metabolism of cells).

Several potassium channels have been found to be relatively insensitive to alcohol concentrations below 100 mM. Scientists have shown that alcohol inhibits one class of these receptors—Shaw2 channels (Covarrubias and Rubin 1993; Covarrubias et al. 1995). Analysis of the inhibitory effect of alcohol on the activity of single channels of this type indicated that alcohol reduced the probability that the channel would enter a long-duration open state. The investigators suggested that the site at which alcohol acted to cause this effect was on a section of the ion channel thought to be involved in controlling the opening or gating of the ion pore of the channels. Results of experiments in which the effects of single-amino acid substitutions at the site were observed suggest that the amino acid sequence—and changes involving more than a single amino acid—played a role in determining alcohol sensitivity. The amino acid sequence may determine the size of a pocket with which alcohol interacts on the channel protein. Results of another study also suggested the existence of a pocket on these channels that mediates alcohol's actions. The cloned channels were studied by expressing them in *Xenopus* oocytes and observing the effects of alcohols with more than eight carbons. The results suggested that the actions of alcohols on these channels were channel specific and therefore due to differences in the amino acid sequence (Chu and Treistman 1997).

Other studies have shown that processes other than the ion channel itself may be the targets for alcohol. Calcium-activated potassium channels are important in regulating neuronal excitability and are activated by increases in intracellular calcium that arise during depolarization of the neuronal membrane. A recent study found that alcohol increases the activity of the BK type of channel in concentrations between 10 and 100 mM (Dopico et al. 1996). This increased activity was manifested by an increase in the probability that the channel would be in an open, conducting state. Although the onset of the alcohol effect was observed as soon as the alcohol was added to the preparation, recovery of the effect upon washout of the alcohol required several minutes, suggesting that processes other than the channel itself may be involved in alcohol's effect. Similar results emerged in another study of alcohol and BK channels; however, the alcohol effect required several seconds to become apparent and its effects reversed after approximately 30 seconds of exposure (Jakab et al. 1997). In addition, the effects of alcohol were blocked by inhibitors of PKC at lower levels of alcohol. Inhibitors of cellular phosphatases enhanced the potentiating effects of alcohol on BK channel activity, suggesting that alcohol-induced phosphorylation of the channel or related proteins underlies this effect.

Alcohol and Neurotransmitter Systems

The research described above clearly shows that alcohol exerts many of its neurobehavioral effects via its direct and indirect modulation of ion channels. Alcohol's opposite effects on excitatory glutaminergic receptors and inhibitory $GABA_A$ and glycine receptors appear to be largely responsible for its intoxicating and sedative effects. However, because alcohol is considered an addictive substance, there is great interest in defining the molecular and cellular sites of action that underlie its addictive potential. A number of studies in this area have focused on the

interaction between alcohol and the neurotransmitters dopamine and 5-HT, both of which have been implicated in the reinforcing properties of alcohol and other drugs of abuse.

Biochemical Studies

A basic hypothesis in the field of addiction biology is that addictive drugs lead to increases in release of the neurotransmitter dopamine, which plays a role in motivation and reinforcement. The increase in dopamine is observed in a specific part of the brain called the nucleus accumbens, which is thought to play a key role in the rewarding or reinforcing effects of alcohol (Imperato and Di Chiara 1986; Wozniak et al. 1991). Several techniques have been developed and used to study the actions of alcohol on dopamine release, including electrophysiology, microdialysis, and in vivo voltammetry.

The basis for these changes in extracellular dopamine is unclear. The changes may result from alcohol's direct effect on the release of dopamine or from alcohol's ability to enhance dopamine release indirectly through effects on other proteins such as ion channels. An example of indirect enhancement is alcohol's potentiation of presynaptic 5-HT_3 receptors, which have been shown to contribute to depolarization-induced neurotransmitter release.

Several studies have examined both direct and indirect effects of alcohol on dopamine release. Research has shown, for example, that a high concentration of alcohol delivered through a microdialysis probe increased dopamine levels in the ventral tegmental area of the brain (Yan et al. 1996). (The ventral tegmental area is an area where dopaminergic fibers originate; these fibers project to forebrain areas thought to be involved in mediating the sensation of reward.) This release of dopamine was not attenuated by the use of a calcium-free solution, indicating that the increase in dopamine levels did *not* result from the presynaptic, calcium-dependent process known as exocytosis, through which neurotransmitters are released. Another study demonstrated that alcohol-induced increases in extracellular levels of dopamine in the striatum, a brain area highly enriched in dopaminergic terminals, occurred only at high concentrations of alcohol (more than 170 mM in the dialysis probe) (Yim et al. 1997). The researchers concluded that when alcohol was given locally through the probe, concentrations of alcohol associated with intoxication had no effect on extracellular levels of dopamine.

These findings have been corroborated by studies using a different technique, in vivo voltammetry, which measures the presence of extracellular dopamine electrochemically. In these studies, alcohol administered locally via microinjection did not alter basal (pretreatment), unstimulated levels of dopamine in the nucleus accumbens (Samson et al. 1997) or the striatum (Lin and Chai 1995; Wang et al. 1997). Despite this lack of response, alcohol did slow the clearance of both endogenous and exogenous dopamine from the extracellular fluid, suggesting that alcohol may affect the dopamine transporter molecule, which functions to clear the synapse of dopamine following release. During periods of neuronal firing and release of dopamine, alcohol thus may directly prolong the actions of dopamine at postsynaptic receptors.

Evidence for a 5-HT_3-mediated mechanism of alcohol's action on dopamine levels has also been described. One study showed that drugs that selectively activate the 5-HT_3 receptor increased extracellular levels of dopamine as measured by in vivo microdialysis (Campbell et al. 1996). Dopamine levels were also enhanced when animals were given alcohol intraperitoneally (into the abdominal cavity); this increase was blocked by a selective antagonist of 5-HT_3. These results suggest that the effects of ingested alcohol on dopamine release may be mediated via enhancement of 5-HT_3 receptors located on dopaminergic nerve terminals.

A series of studies by Brodie and co-workers demonstrated that alcohol increased the firing rate of neurons in the ventral tegmental area and that the effects of alcohol were augmented in the presence of 5-HT and 5-HT agonists (substances

that stimulate the activity of 5-HT) (Brodie et al. 1990, 1995). Whether these results were due to an effect on 5-HT_3 receptors or on another mechanism could not be determined. However, these data are consistent with the idea that alcohol can alter a cell's firing rate and the release of dopamine in an area of the brain associated with reward and reinforcement.

Neurobehavioral Studies

Following the observation that alcohol potentiated 5-HT_3 electrical activity in isolated neurons, a large number of neurobehavioral studies were performed to examine the involvement of this and other 5-HT receptor subtypes in mediating alcohol's actions on the brain. Many of these studies used the technique of drug discrimination to probe the neural sites of action of alcohol. (See the section "Neurobiological and Neurobehavioral Mechanisms of Chronic Alcohol Drinking" later in this chapter and the box "Animal Models for Alcoholism," which detail the different types of tests and animal models used to study the impact of alcohol exposure on behavior.)

Drug discrimination procedures involve training an animal to recognize the effects or rewards of a particular drug, then testing other drugs to determine whether they can substitute for the training drug. The 5-HT_3 antagonists generally block the discriminative stimulus effects—the effects that enable an animal to distinguish alcohol from other substances—of alcohol, although there is considerable variability in this respect among these agents (see review by Grant 1995). The effects of these drugs on alcohol absorption and on other receptor subtypes complicate interpretation of these tests. The development of more selective agents would help to unravel the role of the 5-HT_3 receptor in mediating the neurobehavioral effects of alcohol.

Recent behavioral studies have revealed that some 5-HT receptors that are G protein coupled—linked to intracellular signaling processes—may be involved in mediating alcohol's effects. In one study, agonists with selectivity at 5-HT_{1B} but not 5-HT_{1A} receptors produced effects that were similar to alcohol in drug discrimination tests (Grant et al. 1997). Interestingly, these effects depended on the training dose of alcohol and were most marked at lower alcohol concentrations. These results are consistent with in vitro findings that show differences in the sensitivity of various receptors to alcohol.

The involvement of the 5-HT_{1B} receptor in mediating some of the effects of alcohol has also been suggested by research on a mouse strain that lacks this receptor subtype. These mice had a twofold elevation in their daily alcohol consumption, compared with wild-type mice, in the presence of normal food and water intakes (Crabbe et al. 1996). (A subsequent study did not replicate this result in knockout mice [Crabbe et al. 1999].) The mutant mice were also less sensitive to the motor-incoordinating effects of alcohol and developed tolerance to these effects at a slower rate than wild-type animals did. Subsequent neurobehavioral studies using these knockout mice showed that 5-HT_{1B} knockout animals had a lower sensitivity to the rewarding effects of alcohol but no change in alcohol's aversive effects (Risinger et al. 1996). Taken together, these results suggest that the 5-HT_{1B} receptor is involved in both alcohol intake and reward, perhaps through a common mechanism. Although this underlying neurochemical mechanism has not yet been identified, researchers have hypothesized that this reduced sensitivity to alcohol's rewarding effects in these animals may result in higher levels of alcohol drinking. Whether these differences are related or due to differences in the effects of alcohol on firing rate and extracellular dopamine levels in the mesolimbic areas of the brains of these mice is not known. (See also the discussion of 5-HT_{1B} knockouts in the section "Genetic Studies of Alcohol's Action on the Brain" later in this chapter.)

In Closing

Both ligand-gated and voltage-sensitive ion channels are important targets for alcohol in the brain. The distribution of many of these channels in synapses and the channels' critical involvement in regulating neuronal excitability make their alcohol sensitivity especially important with

respect to alcohol's behavioral effects. Several conclusions can be reached with respect to the findings of the studies of alcohol sensitivity of various neuronal ion channel proteins.

First, clear and consistent evidence demonstrates that alcohol specifically and selectively alters the function of certain ion channels. In the case of the $GABA_A$ and glycine receptors, compelling evidence exists to suggest that alcohol's effects are mediated by interaction with certain amino acids on the receptor. Using this information, researchers should be able to verify the presence of a similar site of action on other related receptors, such as those activated by acetylcholine and 5-HT, which are similar in composition to $GABA_A$ and glycine receptors.

Elucidation of a primary site of action for alcohol on glutamate-activated ion channels and voltage-sensitive potassium channels is expected to be somewhat more difficult. NMDA and non-NMDA channels share a high degree of structural similarity, especially in their pore regions, but are only remotely related to $GABA_A$ and glycine receptors. Thus, it may be difficult to extrapolate findings directly from one major family of ion channels to another. However, as researchers learn more about the determinants of alcohol sensitivity among different channel types, various techniques, such as site-directed mutagenesis, which leads to a mutation in a specific gene or at a specific location along the DNA strand, can be used to identify the locations of alcohol-binding sites on glutamate and other receptors.

Second, the effects of alcohol on ion flux appear to be mediated not by simple blocking of the ion pore but by alterations in channel gating. Most, if not all, studies that have examined the effects of alcohol on the function of single-ion channels have found that alcohol alters the probability that the channel will be open. These findings suggest that the site that mediates alcohol's actions most likely is located close to those areas that control gating of the channel. Such research results and hypotheses place the focus of attention on the transmembrane domains that traverse the membrane and the amino acids that may serve to couple one transmembrane domain to another.

Finally, it is clear that alcohol does not need to act directly on the channel protein to alter its function. The effects of alcohol on voltage-sensitive calcium channels and perhaps BK channels may involve other cellular processes that are activated by alcohol. Once activated, these other processes can then profoundly alter the function of the ion channel via mechanisms such as phosphorylation or direct protein-protein interaction. One of the rapidly developing areas of neuroscience concerns the organization of ion channels in the neuronal membrane. It is clear that ion channels are not distributed randomly in the membrane, but are localized in clusters in association with other signaling and structural proteins. Researchers have described a whole family of receptor clustering proteins that appear to act as scaffolds that allow complementary receptors and cellular signaling proteins (such as kinases and phosphatases) to be located at the same site. Alcohol's effects on individual ion channels may thus be a sum of its direct action on ion channel gating and its influence on the regulation of ion channel activity by these closely associated processes.

Research on the neurotransmitters and receptors involved in the rewarding aspects of alcohol is providing insight into how alcohol influences the function of these systems and how the changes are manifested in the response to alcohol in an intact organism.

As the cellular and molecular processes involved in the interplay between alcohol and neurons are identified and understood, connections between these processes and the neurobehavioral effects of alcohol will be strengthened. Research, in turn, can then increasingly focus on the development of therapeutic agents that interfere with these processes.

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Neurobiological and Neurobehavioral Mechanisms of Chronic Alcohol Drinking

Alcoholism comprises a set of complex behaviors in which an individual becomes increasingly preoccupied with obtaining alcohol. These behaviors ultimately lead to a loss of control over consumption of the drug and to the development of tolerance, dependence, and impaired social and occupational functioning.

Although valuable information regarding tolerance and dependence has been, and continues to be, gathered through human studies, much of the detailed understanding of the impact of exposure to alcohol on behavior and on the biological mechanisms underlying those behaviors has been obtained through the use of animal models for alcoholism and a variety of in vitro, or cellular, systems. Through the use of cellular systems and animal models, researchers can control the genetic background and experimental conditions under which a specific alcohol-related behavior or neurochemical change occurs.

It is difficult, if not impossible, to obtain an animal model that by itself incorporates all of the signs, symptoms, and behaviors associated with alcoholism. However, several animal models of chronic drinking reflecting the different components of alcoholism, including alcohol-seeking behaviors, have been developed. These models, which remain an integral part of the study of alcoholism, include animals that preferentially drink solutions containing alcohol, animals that self-administer alcohol during withdrawal, animals with a history of dependence that self-administer alcohol, and animals that self-administer alcohol after a period of abstinence from the drug. Genetic models for alcoholism also exist and include animals that have been bred selectively for high alcohol consumption. Studies using such models are uncovering the systemic, cellular, and molecular neurobiological mechanisms that appear to contribute to chronic alcohol consumption. The challenge of current and future studies is to understand which specific cellular and subcellular systems undergo molecular changes to influence tolerance and dependence in motivational systems that lead to chronic drinking.

Reinforcement and Reward in Chronic Drinking

Because alcoholism centers on compulsive, often excessive, use of alcohol, the concept of reinforcement or motivation is a crucial part of this syndrome. A reinforcer is defined as any

Tolerance and Dependence

Tolerance is present when, following prolonged exposure to alcohol, the brain becomes less sensitive to the acute actions of alcohol. For example, research shows that larger doses of alcohol are needed to produce an alcohol-specific effect, such as sedation, in animals that have been given alcohol for several days or weeks compared with animals given the drug the first time. Tolerance appears to occur through adaptations at the cellular and subcellular levels as the brain attempts to overcome the acute effects of alcohol intake; with prolonged alcohol abuse, these adaptations often lead to permanent adverse changes in the structure and function of neurons.

Alcohol dependence is defined as the manifestation of either physical withdrawal symptoms, such as tremors and seizures, after abrupt cessation of alcohol intake or psychological symptoms, such as a negative emotional state after intake ends. The physical and psychological symptoms that occur following termination of alcohol intake are collectively referred to as the alcohol withdrawal syndrome. Alcohol's ability to induce pleasurable feelings, reduce tension and anxiety, and ameliorate the symptoms of withdrawal make it a powerful and "attractive" drug.

event that increases the probability of a response. This explanation also can be used to define reward; in fact, "reinforcement" and "reward" frequently are used interchangeably. However, reward often also connotes an additional emotional value, such as pleasure (White and Wolf 1991). Many sources of reinforcement, such as pleasure, mood elevation, and removal of negative emotional states, contribute to compulsive alcohol use during the course of alcoholism.

The primary pharmacologic action of alcohol produces a direct effect through positive or negative reinforcement. Positive reinforcement refers to a pleasurable or otherwise positive event that increases the likelihood that additional alcohol will be sought. Alcohol itself can serve as a powerful positive reinforcing agent through its ability to induce pleasurable or mood-elevating feelings (so-called euphoric or euphorogenic effects). In contrast, negative reinforcement describes an adverse event or situation that also will lead the individual to obtain more alcohol. Examples of negative reinforcement include situations in which an individual or animal self-medicates in an attempt to overcome an existing aversive state (depression or anxiety) or to treat a drug-generated aversive state (alcohol-related withdrawal) (Wikler 1973). Both the positive and negative types of reinforcement encourage alcohol-seeking behavior and appear to contribute to chronic drinking, alcohol dependence, and a return or relapse to drinking among persons recovering from alcoholism.

The secondary pharmacologic effects of alcohol also can have powerful motivating properties. Conditioned reinforcement—when an individual learns to associate the reinforcing effects of alcohol with a previously neutral event or stimulus—results in secondary positive reinforcing effects. In practical terms, a person entering a familiar bar or pub can experience positive feelings similar to those induced by consumption of alcohol. Secondary reinforcing effects can be negative or positive; someone can also learn to associate particular stimuli with unpleasant aspects of abstinence, such as withdrawal symptoms.

However, alcohol may, under certain conditions, serve as a deterrent to the seeking or obtaining of more alcohol. Research shows that alcohol can be aversive at high doses and, in animals, can cause both place avoidance, in which animals avoid an environment where they have previously received alcohol, and taste avoidance, in which animals avoid a taste previously paired with alcohol ingestion (Cunningham et al. 1992). Alcohol-dependent individuals have what is known as elevated aversion thresholds; that is, they can consume higher levels of alcohol than non-dependent individuals before they stop drinking or avoid alcohol. This elevated aversion threshold may contribute to excessive drinking among dependent persons.

By applying these concepts, researchers can explore the neurobiological bases for the acute positive reinforcing effects of alcohol, the negative reinforcing effects imparted by the dependent state, and the conditioned reinforcing effects associated with protracted abstinence and relapse (Koob et al. 1993).

Insights Into Features of Alcoholism From Animal Models

The importance of animal studies lies in their potential for providing insight into alcoholism in humans. Although not all the factors contributing to alcoholism, including the genes responsible for alcohol-related behaviors, have been discovered, animal models of alcoholism are proving to be instrumental in identifying genetic and biological factors that confer predisposition to alcoholism. Such models enable researchers to perform controlled analyses of genetically and environmentally influenced traits and behaviors that resemble certain aspects of human alcoholism, such as alcohol consumption and preference, innate sensitivity or tolerance to alcohol, and metabolic rate of alcohol elimination. Much of the study of genetics and alcohol-related behaviors or traits is conducted through the use of selectively bred animals, such as alcohol-preferring and alcohol-nonpreferring rats and mice. Additional studies use animals that are trained or conditioned to choose alcohol over water or other usually preferable solutions.

Animal Models for Alcoholism

Validated animal models exist for many of the components of alcoholism. Validation of an animal model focuses on three factors: face validity, reliability, and predictive validity (predictability). Face validity is how similar, at least superficially, a behavioral effect in an animal is to that in humans. Face validity is a valuable starting point in alcohol research studies using animal models but is often difficult to truly achieve. Reliability refers to the consistency and stability of the variable of interest in the animal. Predictive validity refers to how closely and accurately the animal's condition mimics or predicts the condition in humans, based on the behavior of the animal model.

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) of the American Psychiatric Association (1994) defines the criteria that provide a framework for studying the neurobiological bases for the excessive consumption associated with chronic alcohol ingestion (Koob et al. 1998). Of seven behavioral features DSM-IV uses in its criteria to define alcoholism, six have at least somewhat analogous counterparts in animal models, that is, face validity. "Tolerance" to the reinforcing effects of alcohol can be inferred from the increased consumption observed in dependent animals; more research in this area is needed, however. "Characteristic withdrawal syndrome" has both face and predictive validity in animal models. "Persistent desire" can be modeled through conditioned positive reinforcement with alcohol, which has been demonstrated in animals. "Substance taken in larger amounts than intended" could be modeled through monitoring alcohol intake during withdrawal and following periods of abstinence (the "alcohol deprivation effect"). Both of these models have some predictive validity. "Important activities reduced" is difficult to model in animals, but advances in behavioral economics, in which the "cost" of alcohol (the amount of work an animal is willing to do to obtain alcohol) is studied, would be applicable here. "A great deal of time spent in activities necessary to obtain the substance" might be modeled by a progressive ratio-type schedule in which the animal must work increasingly hard to obtain alcohol.

Animal Models for Alcohol-Seeking Behaviors

Animal models for the acute positive reinforcing effects of alcohol and for alcohol-seeking behaviors have been well established and validated (Roberts et al. 1996; Samson 1986, 1987). Two predominant approaches to the study of self-administration of alcohol are oral preference and operant behavior models. In the *oral preference model*, animals are given free access to two different solutions, alcohol and a nonalcohol reinforcer, such as a sweetened water solution; preference for alcohol versus the nonalcoholic fluid is then established by determining which solution is consumed more by the animals. Animals normally consume, at most, small amounts of alcohol, unless they have been bred for a specific genetic predisposition for alcohol preference. Thus, the results of alcohol preference tests provide researchers with information regarding an innate preference or aversion to the pharmacologic effects of alcohol or the extent to which an animal's initial aversion to the taste or smell of alcohol may be overcome to the point where the animal seeks out the alcohol solution. However, this type of task involves little work or effort to obtain alcohol.

In contrast, in *operant behavior models* of self-administration, access to alcohol requires a specific learned behavioral response (or series of responses), such as pressing a lever or running a course through a maze. The amount of alcohol consumed is related to the amount of work an animal is willing to perform. Studies that incorporate an operant behavior model not only can measure preference for alcohol, they can also provide insight into an animal's motivation or persistence to obtain alcohol under a given set of conditions.

Another model used to study alcohol-seeking behaviors in animals involves *conditioned preference tasks*. Through these tasks, animals learn to avoid or seek an environment (place preference vs. place avoidance) or a flavor (taste preference vs. taste avoidance) that previously has been paired with alcohol. Thus, using conditioned preference tasks, researchers are able to assess the reward value of alcohol in association with specific environmental cues.

Studying the Anxiolytic Effects of Alcohol

Alcohol's acute stress-reducing and sedative (anxiolytic) effects, working in concert with its mood-elevating effects, are thought to contribute to the rewarding and positive reinforcing effects of the drug. Alcohol's anxiolytic and mood-elevating effects also may contribute to continued alcohol abuse. The anxiety associated with withdrawal from alcohol use and the early phases of abstinence may motivate a person or an animal to continue to seek alcohol in an effort to relieve that stress or anxiety, thus contributing to the negative reinforcing characteristics of alcohol.

Recognizing the importance of these effects in alcohol abuse and relapse, researchers have developed a series of tests to study the anxiolytic-like properties of alcohol. One type of test involves exposing animals to a situation that generates *approach-avoidance behavior*. In such a test, animals trained operantly to respond to a stimulus such as food or alcohol will then occasionally be given an electrical shock when choosing the stimulus; with time, the animal learns to avoid responding to the food or alcohol. This avoidance behavior can be reversed by a class of drugs known as anxiolytics, such as benzodiazepines, which act as sedatives to reduce stress.

(continued on next page)

Alcohol-associated anxiety-like behavior also may be studied using the *elevated plus maze test*, in which animals are given a choice between spending time on the enclosed versus the sideless (open) arms of a plus-shaped apparatus that is raised above the floor. Experiments show that animals treated with alcohol spend more time on the open arms than animals not exposed to alcohol. The response of the alcohol-treated animals is interpreted as a reduction in anxiety-like behavior.

Another behavioral test, the *social interaction test*, takes advantage of the observation that normal social interactions are suppressed when rats are placed in an unfamiliar and brightly lit environment. Under these conditions, anxiolytic drugs cause a marked increase in social activity.

Drug Discrimination Tests

A wide range of drugs can stimulate or inhibit specific neurotransmitters in the brain. *Drug discrimination tests* are used to determine the extent to which drugs known to activate or block specific neurotransmitter receptors in the brain are perceived as being similar to alcohol or are capable of reducing the subjective effects of alcohol, such as euphoria and anxiety. Drug discrimination tests cannot directly demonstrate the reinforcing properties of alcohol. However, they are important in providing information about neurobiological mechanisms that may contribute to the rewarding effects of alcohol.

In these tests, animals are trained to make one response in the presence of alcohol and a different response when they cannot recognize alcohol. Later, when the animal trained to respond to alcohol is given a new drug that has the same subjective effects of alcohol, the animal will respond as it would for alcohol. Conversely, the alcohol cue can be modified by concurrent administration of potential antagonists (compounds that counter the physiologic effects of alcohol). Discrimination tests and procedures have been and continue to be used to identify the neurotransmitters and receptors that modulate many of the effects of alcohol. Researchers anticipate that drug discrimination tests in particular will lead to the development of highly targeted therapies capable of altering or blocking some of the biochemical effects of alcohol and, in turn, related behaviors.

Alcohol as a Reinforcer

In models and tests designed to study *alcohol as a reinforcer*, alcohol is considered a reinforcer when the presentation of alcohol increases the possibility of a response. A specific pharmacologic effect is implied when intake of alcohol results in a measurable, biologically meaningful blood alcohol level (BAL) or blood alcohol concentration (BAC). (See also the box "The ABC's of BAC's" in the chapter on prevention research.) A meaningful BAC is a level known to produce alcohol-specific effects or behaviors, such as sedation. Results of studies in which the relationship between alcohol and dose has been measured and BAL's have been monitored clearly establish models, such as operant self-administration, drinking preference, and place preference, as reliable means of measuring the positive reinforcing effects of alcohol (Hyytia and Koob 1995; Koob et al. 1994*b*; Rassnick et al. 1993; Samson et al. 1993). These models have been a boon to neuropharmacologic analyses of alcohol reinforcement.

Use of Highly Palatable Solutions To Induce Alcohol Self-Administration

Animals normally have an aversion to the taste of alcohol. Thus, scientists studying the effects of alcohol consumption in laboratory animals, especially high levels of alcohol intake, need to overcome the animals' typical aversion to the drug. One method for inducing high intake of alcohol is to combine the alcohol with a highly palatable solution such as sucrose or saccharin. Numerous studies have shown this approach to be successful. For example, using an operant approach combined with the *sucrose fade-out procedure* (when the sugar sucrose is gradually replaced with alcohol in a solution), researchers showed that rats more reliably self-administered large amounts of alcohol when the sucrose was removed (Files et al. 1995; Hodge et al. 1992; Schwarz-Stevens et al. 1992).

Selective Breeding for High Alcohol Intake

Both alcohol-preferring (P) and alcohol-nonpreferring (NP) lines of rats have been selectively bred to drink high and low amounts of a 10-percent solution of alcohol, respectively, when given continuous access to alcohol in addition to free access to water and food (Li et al. 1982; Lumeng et al. 1977). The *selective breeding for alcohol preference* in P rats decreases the animal's initial sensitivity to alcohol and leads to a more rapid development of tolerance than in animals not bred for this preference (Kurtz et al. 1996). Typically, P rats drink as much as 5 grams of alcohol per kilogram of body weight each day (as opposed to less than 2 grams per kilogram in NP rats) (McBride et al. 1989) and can have BAL's as high as 200 milligrams per deciliter (0.2 percent) under conditions of continuous access with intragastric (directly into the stomach) self-administration (Waller et al. 1984). (By comparison, a BAL of 100 milligrams per deciliter (0.1 percent) is the legal limit of intoxication in most states.)

Similar increases in either initial sensitivity or more rapid development of tolerance also have been observed in the alcohol-preferring C57BL mice (Kakihana et al. 1966; Tabakoff and Ritzmann 1979) and the alcohol-preferring Finnish AA rats (Le and Kiianmaa 1988). The neurochemical differences in these alcohol-preferring animals involve neural substrates, or clusters of neurons or neural tissue in the brain, that are similar to those implicated in the neuroadaptive changes associated with chronic alcohol self-administration. These findings suggest that both environmental and genetic factors can converge to drive excessive drinking.

Self-Administration During Withdrawal: Dependence

Dependence is an important factor in the continued use of alcohol by alcoholics. It is characterized by the appearance of a withdrawal syndrome following the cessation of alcohol use. Dependence leads alcoholics to consume alcohol not simply for its mood-elevating effects but also to avoid or reverse the negative symptoms associated with withdrawal (Cappell and Le Blanc 1981; Edwards 1990). Alcohol dependence is studied experimentally by measuring either physical or motivational signs of withdrawal, some of which may reflect the desire or craving for alcohol. Researchers often use evidence of physical symptoms upon termination of alcohol consumption (physical dependence) as an index of dependence in animals. These physical symptoms, known collectively as the alcohol withdrawal syndrome, range in severity from mild tremors to massive convulsions. Similar symptoms, as well as hallucinations, are seen in humans undergoing withdrawal. The development of alcohol-dependent animal models with the goal of understanding how reward mechanisms mediating alcohol intake differ in dependent and nondependent animals is potentially important for understanding alcoholism and dependence. Measures of reward dysfunction in animals during withdrawal include brain stimulation reward thresholds (the level of brain stimulation needed to elicit a response consistent with reward), conditioned aversions, drug discrimination, and response to natural rewards. Developing animal models for the negative reinforcement associated with alcohol dependence has proven difficult, however, especially with rodents.

Attempts to develop reliable and useful models of alcohol consumption in dependent rats have taken into consideration various factors that influence dependence, such as consumption of alcohol to overcome symptoms of withdrawal. In one study, for example, rats were trained to consume 10-percent alcohol prior to continuous exposure to alcohol in a liquid diet or air vapor. During this training phase, alcohol was established as a reinforcer, and potential taste aversions were overcome. The animals were maintained at blood alcohol levels (BAL's, also called blood alcohol concentrations, or BAC's) associated with mild to moderate physical withdrawal symptoms. (See the box "The ABC's of BAC's" in the chapter on prevention research for more information.) Therefore, any withdrawal symptoms that the rats did exhibit would be predictably quite mild and would not be expected to interfere with their ability to self-administer alcohol. Results of this study showed that the dependent rats consumed more alcohol than the nondependent control rats did. Rats with BAL's higher than 100 milligrams per deciliter (0.1 percent) at the time of withdrawal from the liquid diet sustained high levels of alcohol self-administration throughout four withdrawal sessions (Schulteis et al. 1996). Thus, above and beyond the training effects, dependent rats consumed more alcohol than nondependent rats did, even when withdrawal symptoms were mild.

In a subsequent study, rats were trained to lever press for 10-percent alcohol using the saccharin fade-out procedure, in which saccharin in a water solution was gradually replaced with alcohol to increase the amount of alcohol the rats would consume (Roberts et al. 1996). Over the course of five 12-hour periods of withdrawal, the rats were allowed to respond for alcohol and water. Dependent rats, who maintained BAL's above 100 milligrams per deciliter (0.1 percent) during the entire withdrawal period, responded to a greater degree than nondependent controls did. In addition, dependent rats allowed to respond for alcohol avoided the withdrawal symptomatology present in dependent rats not allowed to respond for alcohol during the withdrawal phase. Responses across withdrawal sessions appeared to become more stable, suggesting that the rats learned to respond in a manner that controls their BAL and minimizes or avoids withdrawal.

Alcohol Self-Administration Following Periods of Abstinence in Rats With a History of Limited Access: Craving

A predominant feature of human alcohol abuse and alcoholism is a reported desire or craving to

consume alcohol that is accompanied by frequent bouts of excessive drinking following periods of abstinence. These and other factors, such as the mood-altering and anxiety-reducing effects of alcohol, may be responsible for relapse to excessive alcohol drinking. Studies in rats, mice, and monkeys have shown increases in alcohol consumption following periods of forced abstinence (Kornet et al. 1990, 1991; LeMagen 1960; Salimov and Salimova 1993; Sinclair 1979; Sinclair and Senter 1967, 1968; Spanagel et al. 1996; Wolffgramm and Heyne 1995). Two aspects of drug dependence could contribute to these increases. One reflects the negative reinforcement produced by self-medication of a withdrawal state seen in animals who have prolonged access to alcohol. The other process involves changes in the positive reinforcing properties of alcohol seen in abstinent animals and may reflect changes other than negative reinforcement. Developing a reliable model of excessive drinking has led to reevaluation of the alcohol deprivation effect in animals with limited access to alcohol and would likely be important to understanding changes in the reinforcing effects of alcohol that occur with abstinence.

For example, rats trained to lever press for 10-percent alcohol and water using the saccharin fade-out procedure established stable baseline responding for alcohol. They were then subjected to various alcohol deprivation periods (3, 5, 7, 14, or 28 days) during which no alcohol was available (Heyser et al. 1997). Responding for alcohol increased as a function of the duration of the deprivation period, compared with baseline levels. This increase was temporary and returned to baseline levels within 2 to 3 days. The shortest effective deprivation period (the shortest interval after which consumption increased) was 5 days, and the rats showed no signs of withdrawal. Thus, this transient increase in response for alcohol does not appear to be related to the manifestation of dependence and withdrawal. Rather, this increase may reflect changes in alcohol's positive reinforcement properties. These results may provide a useful tool to elucidate neuropharmacologic mechanisms underlying human alcohol-seeking behavior and relapse.

Alcohol Self-Administration Following Periods of Abstinence in Rats With a Prior History of Dependence: Relapse

Relapse, or the return to alcohol abuse following periods of abstinence, is one of the principal characteristics of dependence on alcohol. Even so, little is understood about the neurobiological factors involved in this phenomenon. Research suggests that the development of dependence plays an important role in the maintenance of compulsive use and relapse following periods of abstinence.

Dependence is, in fact, the basis of the negative reinforcement theory of alcoholism that suggests that alcoholics continue to drink to avoid withdrawal symptoms (Cappell and Le Blanc 1981; Hershon 1977). In more modern conceptualizations, this theory suggests that alcoholics drink to avoid the negative effect (emotional state) associated with withdrawal (Koob and Le Moal 1997). However, because relapse can occur even after withdrawal signs have ceased, the neurochemical changes that occur during the development of dependence may persist after the overt signs of withdrawal are no longer present. Indeed, research using animal models has shown that prior dependence lowers the dependence threshold. In other words, previously dependent animals made dependent again display more severe withdrawal symptoms than do animals receiving alcohol for the first time (Baker and Cannon 1979; Becker and Hale 1993; Becker et al. 1997; Branchey et al. 1971). This finding supports the notion that alcohol experience and, in particular, the development of dependence can lead to relatively permanent alterations in responsiveness to alcohol. Thus, a relapse model would allow research into the long-lasting changes in the alcohol reward system produced by prior dependence.

Future research should include studies in which animals previously made dependent are allowed to consume alcohol. Enhanced responding for alcohol in animals without a history of dependence that are given extended training in operant tasks also warrants further study. The possibility

that the total experience with alcohol is a major predictor of the degree to which alcohol consumption resumes after abstinence is another important question for future investigations.

Alcoholism and the Neural Structures of Reward

Research suggests that the neural substrates—the tissues and neural components changed by exposure to alcohol—and neuropharmacologic mechanisms associated with the motivational effects of alcohol withdrawal may play a role in the negative reinforcement associated with alcohol dependence. Thus, the same neural systems implicated in the positive reinforcing effects of alcohol also appear to be involved in the aversive motivational effects of alcohol withdrawal.

Acute alcohol withdrawal is characterized by symptoms that fall into four main categories: autonomic system hyperactivity, neuronal excitation and seizures, distortions of perception, and motivational effects. Autonomic system hyperactivity includes hypertension (high blood pressure) and increased heart rate. Neuronal excitation includes tremors and seizures. Distortions of perception include hallucinations, delirium, and disturbed sleep. Motivational effects include restlessness, anxiety, dysphoria (a sense of ill-being), and depression-like symptoms. Although animal models exist for many of these symptoms and physical signs have been used to explore the neural basis for alcohol withdrawal (Meert 1994), motivational measures are a more important focus.

Measurement of reward thresholds throughout the course of alcohol withdrawal has shown that these thresholds are increased following chronic administration of alcohol and all other major drugs of abuse, including opiates, psychostimulants, and nicotine. Stated another way, the amount of stimulation required to produce the same reward or effect increases when drug administration is discontinued. This effect, which can last for up to 72 hours depending on the drug and dose administered, may reflect changes in the activity of the same system—the midbrain-forebrain system—implicated in the positive reinforcing effects of alcohol and other drugs (Legault and Wise 1994; Leith and Barrett 1976; Markou and Koob 1991, 1992; Parsons et al. 1995).

Extended Amygdala

Information about the anatomy and function of the brain suggests that the neurological structures associated with the reinforcing actions of alcohol and other drugs may involve a common neural circuitry that forms a separate entity within the basal forebrain, the extended amygdala (Alheid and Heimer 1988). The term extended amygdala refers to a large structure composed of several smaller basal forebrain structures that are similar in cell structure, function, and neural connectivity (Alheid and Heimer 1988). This system has extensive connections to brain regions that play central roles in reinforcement and reward.

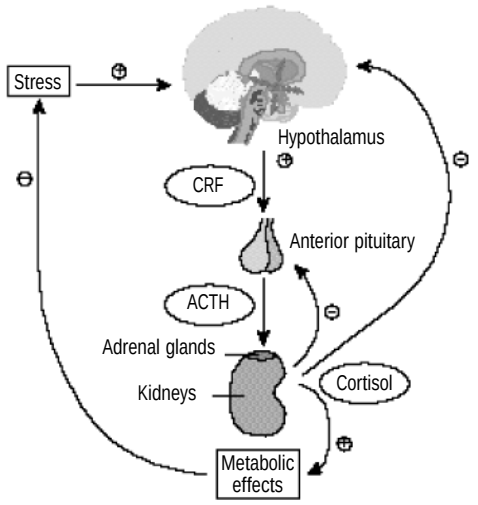
Rats trained to self-administer alcohol during withdrawal show neurochemical and neuropharmacologic changes indicative of alterations in gamma-aminobutyric acid-activating (GABAergic), dopaminergic, and serotonergic function in specific components of the extended amygdala. (Previous sections in this chapter provide background on these neurotransmitters and alcohol's impact on neurotransmitter function.) For example, inhibitory GABAergic mechanisms in the central nucleus of the amygdala have been implicated in the acute reinforcing effects of alcohol (Heyser et al. 1995; Hyytia and Koob 1995). One study showed a reduction in alcohol self-administration in nondependent rats following injections of a highly selective and potent GABA antagonist (an agent that blocks or reverses GABA's usual actions or effects) into the nucleus accumbens and central nucleus of the amygdala, with the most sensitive site being the central nucleus of the amygdala (Hyytia and Koob 1995). (The nucleus accumbens is a brain structure implicated in the reward properties of drugs of abuse—the medial nucleus accumbens is encompassed in the extended amygdala described above.) Other investigations have demonstrated selective activation of dopaminergic transmission in the shell of the nucleus accumbens in response to

acute administration of virtually all major drugs of abuse (Pontieri et al. 1995, 1996; Tanda et al. 1997).

Additional research suggests that the extended amygdala may be involved in the negative reinforcement effects associated with alcohol withdrawal. Rats lever pressing for alcohol during withdrawal showed a return toward baseline levels of dopamine and serotonin in the nucleus accumbens, in contrast with the usual decreases in these neurotransmitters during acute withdrawal (Weiss et al. 1996). A subsequent study revealed that the central nucleus of the amygdala was particularly sensitive to the suppressant effects of GABA agonists on alcohol self-administration by dependent rats (Roberts et al. 1996). (Agonists are agents that mimic the actions or effects of other agents.) Other supporting data include evidence for the activation of corticotropin-releasing factor (CRF) systems in the central nucleus of the amygdala during alcohol withdrawal (Merlo-Pich et al. 1995), and for the blocking of the anxiogenic-like responses associated with alcohol withdrawal following injection of CRF antagonists into the central nucleus. CRF is a neuropeptide that is critical to the body's response to stress.[1] It is secreted in the hypothalamus, the brain stem, and the limbic system, a network of brain structures that together function in the expression of emotional behavior (figure 1).

The research on the extended amygdala may ultimately link recent developments in the neurobiology of drug reward with existing knowledge of the substrates for emotional behavior (Davis 1997), essentially bridging what have been largely independent research pursuits. Perhaps more important, this neuronal circuit is well situated to be modeled to explore the neurobiological mechanisms associated with vulnerability to relapse and with concepts such as craving, both of which may involve secondary conditioned reinforcement.

Figure 1: The hypothalamic-pituitary-adrenal axis



In response to almost any type of stress, either physical or psychological, the hypothalamus secretes corticotropin-releasing factor (CRF), which in turn increases secretion of adrenocortotropic hormone (ACTH) by the anterior pituitary gland. In response, within minutes, the adrenal glands, located atop the two kidneys, increase secretion of cortisol. The released cortisol initiates a series of metabolic effects aimed at alleviating the harmful effects of the stress state and, through direct negative feedback to both the hypothalamus and the anterior pituitary, decreases the concentration of ACTH and cortisol in the blood once the state of stress abates. + = Excites; – = Inhibits.

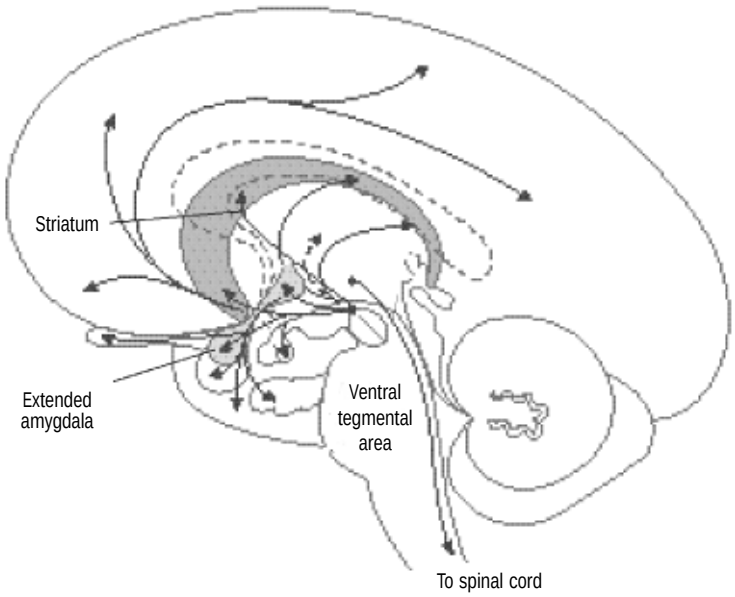
Source: Emanuele and Emanuele 1997.

Hippocampus and Ventral Tegmental Area

Researchers have hypothesized that alcohol's effects on GABAergic neurotransmission involve alteration in the expression of GABA receptor subunits in specific regions of the brain that occur with chronic treatment or alcohol. A recent study suggests that these effects are found not only in the (cerebral) cortex but also in the hippocampus, a brain structure involved in the consolidation of new memories, and the ventral tegmental area (VTA) (Charlton et al. 1997). The VTA is the source of dopamine in the mesolimbic system, a region of the brain involved in the mediation of

[1]Stress-induced physical demands, psychological distress, and adaptive changes initiate a cascade of neural and endocrine (or neuroendocrine) events that lead to the release of glucocorticoid hormones from the adrenal glands. These hormones, in turn, have widespread effects on the body's metabolic and immunologic processes. The activation of this neuroendocrine system involves the hypothalamic-pituitary-adrenal axis, which refers to the brain structures and endocrine glands in the system. (The hypothalamus is a brain structure involved in the maintenance of the internal environment and in mediating hunger, thirst, and emotional drives.) Release of CRF from the hypothalamus activates this stress-response system.

Figure 2: Dopaminergic pathways in the brain



Most dopamine-containing neurons are located within the midbrain, extending to the striatum as well as to various sites in the forebrain. Dopamine modulates such varied functions as emotion, aggression, cognition, the coordination of movement, and aspects of the development of addiction.

Source: Adapted from Heimer 1995.

alcohol reinforcement. The cell bodies of this mesolimbic dopamine system originate in the VTA and send projections to the nucleus accumbens and basal forebrain, transmitting information to the dopamine receptors in these brain areas (figure 2). Exposing laboratory animals to alcohol for 12 consecutive weeks decreased $GABA_A$ α_1 subunit activity in the VTA and hippocampus, suggesting potential changes in brain structures implicated in the rewarding and cognitive effects of alcohol, respectively. Researchers failed to detect a similar change in these regions after only 4 weeks of exposure to alcohol—a clue to the involvement of these areas specifically with chronic alcohol exposure.

Neurochemical and Molecular Adaptations to Alcohol

Research suggests that the brain attempts to overcome the acute effects of alcohol through adaptations at the cellular and subcellular levels. With prolonged alcohol abuse, these adaptations can lead to permanent adverse changes in the structure and function of neurons. Understanding the mechanisms of these adaptations may ultimately lead to therapeutic interventions to prevent the neurological abnormalities associated with protracted alcohol use and abuse.

Tolerance and withdrawal are key to the idea that neuroadaptive processes are initiated to counter the acute effects of alcohol. Historically, most models of alcoholism have emphasized the development of tolerance and withdrawal. In contrast, some more recent discussions have reduced tolerance and withdrawal to optional criteria, while other current conceptual models in animals emphasize selective aspects of tolerance and withdrawal, focusing on motivational measures rather than physical signs (Koob 1992).

Another neuroadaptive process that has been proposed as a key element in the development of

motivational aspects of alcoholism is sensitization, which is the opposite of tolerance. In brief, sensitization is the increased response to alcohol or the effects of alcohol that follows repeated intermittent exposures (Stewart and Badiani 1993). In general, sensitization is more likely to occur with intermittent, repeated exposure to alcohol (or other drugs of abuse); in contrast, tolerance is more likely to occur with continuous exposure. Some authors have suggested that sensitization may play a role in drug dependence by causing a shift toward or a progressive increase in the desire (wanting or craving) of drugs of abuse through repeated exposure to such drugs; these authors used the transition to a pathologically strong wanting or craving to define compulsive use (Robinson and Berridge 1993).

Alcohol-related neuroadaptive processes appear to persist long after the alcohol has cleared from the brain. Such neuroadaptations are under investigation at all levels of alcoholism research, from behavioral to molecular studies (Koob and Bloom 1988). Motivational hypotheses involving both sensitization (Stewart and Badiani 1993) and changes in the central nervous system that counter initial neuroadaptive alterations (Wikler 1973) have been generated; these hypotheses have particular relevance to the phenomena associated with excessive consumption of alcohol (Wikler 1973). Both neuroadaptive models incorporate the concept of change in reward function that accompanies the development of alcohol or drug dependence (sensitization and counteradaptive mechanisms) (Koob 1996).

Reinforcement and Withdrawal

Although the study of the mechanisms for the physical signs of alcohol withdrawal can provide clues to the nature of the neuroadaptive responses that chronic alcohol exposure produces, the emotional or affective aspects of alcohol withdrawal have the most motivational relevance (Koob and Le Moal 1997). The two major categories of responses that reflect motivational measures are anxiogenic-like responses (those that produce anxiety or stress) and changes in reward function. Neural substrates for the physical signs of alcohol withdrawal historically have involved substrates for central nervous system rebound hyperexcitability (the excessive brain activity seen after exposure to, and then removal of, the activity-dampening effects of alcohol); these signs reflect a decrease in function of one of the major inhibitory brain neurotransmitters, GABA, or an increase in function of one of the major excitatory brain neurotransmitters, glutamate (Grant et al. 1990; Hoffman and Tabakoff 1994; Morrisett et al. 1990). Additional research has begun to implicate other neurotransmitter/neuromodulatory systems that could contribute to a hyperexcitable state, including serotonin, dopamine, norepinephrine, adenosine, gangliosides, and neurosteroids (table 1) (Adams et al. 1995; Concas et al. 1994; Crabbe 1992; Finn et al. 1995; Grant et al. 1990; Hoffman and Tabakoff 1994; Kotlinska and Liljequist 1996; Meert 1994; Morrisett et al. 1990; Snell et al. 1996).

Anxiogenic-Like Responses in Alcoholism

Sedative-hypnotic drugs, such as barbiturates, benzodiazepines, and alcohol, all acutely produce a characteristic euphoria, disinhibition, anxiety reduction, sedation, and hypnosis. These drugs exert antianxiety or anxiety-reducing (anxiolytic) effects that reduce aggressive behavior normally exhibited by laboratory animals in conflict situations. This anticonflict effect correlates well with these drugs' ability to act as anxiolytics in humans in a clinic or treatment setting (Sepinwall and Cook 1978) and may be a major component of the reinforcing actions of these drugs.

The sedative and anxiety-reducing effects of sedative-hypnotics are associated with facilitation of the $GABA_A$ receptor (Richards et al. 1991), but the actions of sedative-hypnotics on this receptor are complex. These drugs do not bind directly to the GABA-binding site on the $GABA_A$ receptor; instead, they appear to bind to other sites on the $GABA_A$ receptor complex, through which they facilitate activation of the receptor by GABA. Support for the role of the GABA

Table 1: Agents shown to suppress alcohol withdrawal

Neurotransmitter system	Agent	Dependent measure	Reference
		Physical Signs	
GABAergic	Diazepam	Seizures	Crabbe 1992
	Abecarnil	Seizures	Crabbe 1992
Serotonergic	Buspirone	Tremor	Meert 1994
	Mianserin	Tremor	Meert 1994
	Fluoxetine	Tremor	Meert 1994
Dopaminergic	Haloperidol	Tremor	Meert 1994
Noradrenergic	Propranolol	Tremor	Meert 1994
Glutaminergic	Nitric oxide antagonist	Tremor, rigidity	Adams et al. 1995
	MK 801	Seizures	Grant et al. 1990; Morrisett et al. 1990
	Glycine antagonists	Seizures	Hoffman and Tabakoff 1994
	Polyamine antagonists	Seizures	Kotlinska and Liljequist 1996
Adenosine	A-1 antagonist	Tremors, seizures	Concas et al. 1994
	Gangliosides	Tremors, seizures	Snell et al. 1996
Neurosteroidal	3α-Hydroxy-5α-pregnan-20-one	Seizures	Finn et al. 1995
		Motivational Signs	
GABAergic	Chlordiazepoxide	Open field	Meert 1994
	Flumazenil	Open field	Moy et al. 1997
		Social interaction	File et al. 1989, 1992
		Shuttle box avoidance	Criswell and Breese 1993
	Muscimol	Alcohol self-administration in dependence	Roberts et al. 1996
Serotonergic	Ritanserin	Open field	Meert 1994
	Mianserin	Open field	Lal et al. 1993; Meert 1994
	5-HT_3 antagonists	Plus maze	Costall et al. 1990
	Tianeptine	Social interaction	File et al. 1993
Noradrenergic	Propranolol	Open field	Meert 1994
Neuropeptidergic	Corticotropin-releasing factor antagonist	Plus maze	Baldwin et al. 1991

receptor in association with alcohol's anxiety-reducing effects is found in studies showing that the anxiogenic-like effects of alcohol withdrawal are blocked by administration of GABA agonists (Meert 1994). Numerous other neurotransmitter systems have been implicated in the anxiogenic-like effects of alcohol withdrawal, including serotonergic, noradrenergic, and neuropeptidergic

systems (see table 1) (Baldwin et al. 1991; Costall et al. 1990; Criswell and Breese 1993; File et al. 1989, 1992, 1993; Koob et al. 1994; Lal et al. 1993; Meert 1994; Moy et al. 1997; Rassnick et al. 1993; Sarnyai et al. 1995).

Compromised Reward: Clues From Other Sedative-Hypnotic Drugs

Studies of the neuropharmacologic basis for the anxiolytic properties of sedative-hypnotics provided some of the first clues to the reinforcing properties and abuse potential of these drugs (Koob and Britton 1996). Research demonstrating the ability of GABA antagonists to reverse many of the behavioral effects of alcohol led to the hypothesis that GABA has a role in the intoxicating effects of alcohol (Frye and Breese 1982; Liljequist and Engel 1982). More recent studies have shown a reduction in self-administration of alcohol among rats following microinjection of potent GABA antagonists into the brain, with the most effective area to date being the central nucleus of the amygdala (Hyytia and Koob 1995).

The antagonist actions of alcohol toward the *N*-methyl-D-aspartate (NMDA) receptor (a receptor for the excitatory neurotransmitter glutamate) also appear to contribute to the intoxicating effects of alcohol (Hoffman et al. 1989; Lovinger et al. 1989) and perhaps to the dissociative effects (antisocial and aggressive behaviors, memory and learning deficits) seen in people with high BAL's (Tsai et al. 1995). As with the effect of sedative-hypnotics on the $GABA_A$ receptor, alcohol inhibits the functioning of the NMDA receptor not by blocking the glutamate binding site but via a more complex effect on the receptor unit; this complex interaction decreases the glutamate-induced flux of sodium and calcium through the receptor channel, which, in turn, interferes with neurons' ability to transmit information (Fitzgerald and Nestler 1995). (Other sections in this chapter discuss in detail alcohol's effect on the NMDA receptor.) Whether alcohol's effect on the NMDA receptor also contributes to alcohol's reinforcing effects remains to be established. Alcohol can also exert more general inhibitory effects on voltage-gated ion channels, particularly sodium and calcium channels (Fitzgerald and Nestler 1995). These actions occur only with extremely high BAC's and do not appear to be involved in the reinforcing actions of alcohol, but they may contribute to the severe nervous system depression, even coma, that often accompanies severe intoxication.

Other Neurotransmitters

In addition to its initial effects on the $GABA_A$ and NMDA receptors, alcohol may influence several other neurotransmitter systems in the brain that are believed to be involved in alcohol's reinforcing properties. Neurochemical systems, such as the serotonergic and opioid peptide systems, likely contribute to the mediation of alcohol's reinforcing actions; in fact, researchers have suggested that multiple neurotransmitters combine to orchestrate the reward profile of alcohol (Engel et al. 1992). (Opioid peptides are endogenous compounds, naturally occurring in the body rather than externally supplied, with opiate-like activity.) A large body of evidence also implicates dopamine in the reinforcing actions of low doses of alcohol that do not induce dependence. More specifically, studies show that dopamine receptor antagonists reduce lever pressing for alcohol in nondependent rats (Pfeffer and Samson 1988). In addition, extracellular dopamine levels have been shown to increase in nondependent rats self-administering low doses of alcohol (Weiss et al. 1992).

Further research suggests that modulation of various aspects of serotonergic transmission, including increases in the synaptic availability of serotonin (5-HT), blockade of 5-HT reuptake, and blockade of certain 5-HT receptor subtypes, can decrease alcohol intake (Sellers et al. 1992). $5\text{-}HT_3$ receptor antagonists appear to decrease self-administration of alcohol (Fadda et al. 1991; Hodge et al. 1993), and $5\text{-}HT_2$ receptor antagonists, including some agents with both $5\text{-}HT_2$ receptor antagonist action and $5\text{-}HT_{1A}$ receptor agonist activity, selectively decrease acute alcohol reinforcement (Roberts et al. 1998). Several double-blind, placebo-controlled clinical studies (studies in which neither the investigator

nor the study participant knows which treatment the participant is given) have reported that selective serotonin reuptake inhibitors (SSRI's) produced modest decreases in alcohol consumption in humans (Naranjo et al. 1990). One such inhibitor, fluoxetine (Prozac), has been shown to reduce depressive symptoms and alcohol consumption in depressed alcoholics (Cornelius et al. 1997), but it may be of limited use in preventing relapse in nondepressed alcoholics (Janiri et al. 1996; Kranzler et al. 1995). The findings of clinical trials using SSRI's have been equivocal (Johnson et al 1999).

The opioid receptor antagonists, naloxone and naltrexone, also reduce alcohol self-administration in several animal models, implicating opioid peptide systems in acute alcohol reinforcement (Hubbell et al. 1991). However, some data suggest that antagonists of specific opioid receptor subtypes in certain brain regions might have more selective effects (Hyytia 1993). Of note are double-blind, placebo-controlled clinical trials in which naltrexone significantly reduced alcohol consumption, frequency of relapse, and craving for alcohol in humans (O'Malley et al. 1992; Volpicelli et al. 1992). These data suggest that alcohol's interactions with opioid neurotransmission may contribute to certain aspects of alcohol reinforcement, particularly those important to the motivation associated with relapse.

The same neurotransmitter systems implicated in the acute reinforcing effects of alcohol may be changed by withdrawal from chronic alcohol administration. The changes associated with withdrawal include decreased dopaminergic and serotonergic transmission in the nucleus accumbens (Rossetti et al. 1992; Weiss et al. 1996) and decreased GABAergic and increased NMDA glutaminergic transmission (Fitzgerald and Nestler 1995; Roberts et al. 1996; Weiss et al. 1996).

Stress-Related Systems

As mentioned above, pituitary adrenal function is also activated during dependence and acute withdrawal from alcohol and other drugs of abuse in humans (Guaza and Borrell 1984; Roberts et al. 1992). Several studies indicate that abnormal control (dysregulation) of pituitary adrenal function persists during early abstinence (Costa et al. 1996; Kreek 1987; Kreek et al. 1984; Muller et al. 1989). Both stress and repeated administration of glucocorticoids can augment the behavioral effects of psychostimulants, and some researchers have hypothesized that circulating glucocorticoids can function to maintain a sensitized state (Piazza and Le Moal 1996, 1997).

CRF function outside of the pituitary-adrenal axis (the complement of interactions between the pituitary and adrenal glands) also appears to be activated during acute withdrawal from alcohol and many other major drugs of abuse (cocaine, opiates, cannabinoids) and, thus, may mediate behavioral aspects of stress associated with abstinence (Heinrichs et al. 1995; Koob et al. 1994; Richter and Weiss 1999; Rodriguez de Fonseca et al. 1997). How this activation contributes to the decreased reward associated with acute withdrawal or prolonged abstinence remains to be determined (Koob and Bloom 1988; Koob and Le Moal 1997).

Alcoholism: Lasting Changes in the Brain

Research into the molecular and cellular mechanisms of alcohol dependence has begun to focus on changes in neurochemical systems known to be highly sensitive to the acute effects of alcohol. A large body of evidence has documented that chronic alcohol administration reduces GABAergic neurotransmission.

Prolonged alcoholism also is associated with a decreased ability of alcohol to potentiate GABA-stimulated chlorine flux, which alters GABA's normal inhibitory effects on neuronal activity and transmission of information (Frank et al. 1972; Morrow et al. 1988). However, in the absence of evidence of a decreased number of GABA receptor sites following long-term exposure to alcohol (Karobath et al. 1980), it appears that alcohol may instead alter the composition or function of GABAergic receptors. Subsequent research has demonstrated that chronic alcohol intake can decrease expression of the α_1–α_5 subunits of the GABA complex in the cerebral

cortex (Devaud et al. 1995; Mhatre et al. 1993) as well as other subunits (Devaud et al. 1997; Tabakoff and Hoffman 1996). Interestingly, chronic intermittent exposure to alcohol results in a long-lasting "kindling" effect, in which the symptoms of alcohol withdrawal increase in severity with repeated episodes of intoxication and multiple attempts to stop drinking; this effect is paralleled by an increase in the $GABA_A$ α_4 subunit (Mahmoudi et al. 1997).

Chronic alcohol consumption is also associated with increases in specific subunits (NR1 and NR2A) of NMDA receptors (Trevisan et al. 1994). For example, long-term exposure to alcohol has been shown to upregulate (stimulate) NMDA receptor function in cultures of neurons from the cortex (Hu and Ticku 1995). Another study showed that chronic alcohol treatment increased the number of NR2A and NR2B messenger ribonucleic acid subunits—a signal that the cell is synthesizing the proteins encoded by ribonucleic acid—during withdrawal but not prior to withdrawal (Follesa and Ticku 1995). Consistent with these observations, prolonged alcohol intake enhanced NMDA-stimulated nitric oxide formation without causing an increase in the number of receptors, suggesting the presence of other possible receptor sites for alcohol to enhance NMDA receptor function (Chandler et al. 1997). Research suggests that nitric oxide, a gas with neurotransmitter and neurotoxic actions, is the chemical mediator linking excitatory neurotransmission, a process that leads to significant increases in intracellular calcium, and cell death. Alcohol withdrawal also results in increased extracellular concentrations of glutamate in the striatum, a part of the brain where up-regulation of the NR1 and GluR1 subunits of the glutamate receptor complex has been observed following long-term exposure to alcohol (Rossetti and Carboni 1995).

Such findings link the neuroadaptive changes in the glutamate complex to the motivational systems implicated by pharmacologic and neurochemical studies (Ortiz et al. 1995). Defining the relationship between the molecular changes in alcohol-receptive elements such as the $GABA_A$ subunits and the specific aspects of the motivation for excessive alcohol consumption outlined above provides a challenge for future research.

Other modifications in receptor function following protracted alcohol exposure include changes in calcium ion channels. In animals, calcium ion channel antagonists have been shown to attenuate alcohol withdrawal symptoms, particularly those associated with physical signs and seizures (Colombo et al. 1995; Watson and Little 1997). Histologic (tissue and cell) studies indicate that alcohol withdrawal excitability in the hippocampus involves increased activity of calcium ion channels (Shindou et al. 1994). The ability of chronic alcohol exposure to increase protein kinase C activity could, in turn, regulate calcium ion channels and the expression of genes for these channels (Messing et al. 1990, 1991). Finally, alcohol withdrawal results in decreases in the firing rate and firing pattern of dopaminergic cells in the VTA area of the mesolimbic dopamine system (Diana et al. 1995). Although calcium ion channel antagonists have shown promise in animal studies, additional research is needed to establish the potential of these agents in humans (Johnson et al 1999).

The persistent changes in alcohol reinforcement mechanisms that characterize addiction suggest that the underlying molecular mechanisms are long lasting. Indeed, considerable research is focused on drug-related regulation of gene expression. For example, researchers have hypothesized that two types of transcription factors, CREB and novel Fos-like proteins (termed chronic Fos-related antigens), may be possible mediators of chronic drug action (Hope et al. 1994; Hyman 1996; Widnell et al. 1996). Transcription factors alter the expression of other genes that may contribute to the long-lasting effects of neurotransmitters on alcohol tolerance (Hoffman 1994; Szabo et al. 1996). Alcohol can induce changes in c-*fos* in limbic structures in the brain (Costa et al. 1996; Muller et al. 1989). The challenge for the future will be to relate regulation of a specific transcription factor, such as c-*fos*, to specific features of drug reinforcement in

connection with specific histories of drug administration.

Tolerance

Tolerance to the reinforcing actions of alcohol also may contribute to excessive drinking. As with most studies of withdrawal, until recently, studies of tolerance have focused largely on physical measures, such as loss of the righting reflex and impairment of motor coordination. Evaluation of the neural substrates associated with motivational measures of tolerance suggests that these mechanisms may differ from the neural substrates linked with the physical signs of tolerance.

Researchers have hypothesized that the neural substrates for alcohol tolerance may overlap significantly with those associated with acute withdrawal because tolerance and withdrawal sometimes appear to be components of the same neuroadaptive process. Tolerance also depends on learning processes, as has been well documented in the context of alcohol (Young and Goudie 1995). Molecular mechanisms for tolerance that appear to overlap with those for dependence (Nestler et al. 1993) include increases in intracellular calcium and protein kinase activity that occur in the presence of alcohol and also appear to produce increases in transcription factors, such as c-*fos* and c-*jun*. Acute moderate doses of alcohol also induce the expression of c-*fos* in the extended amygdala, resulting in apparent tolerance with repeated dosing (Ryabinin et al. 1997). Mechanisms for these learning processes may involve several neurotransmitters independent of their role in acute withdrawal, including norepinephrine and 5-HT (Tabakoff and Hoffman 1992), glutamate (Collingridge and Singer 1990; Khanna et al. 1992, 1994), and arginine vasopressin (AVP) (Hoffman 1994). (Of note is that mice with a disrupted subtype of the 5-HT receptor [5-HT_{1B} knockout mice] developed less tolerance than mice with the intact receptor but developed the same level of physical dependence [Crabbe et al. 1996].)

The neurotransmitter AVP is localized in the hypothalamus and basal forebrain; alteration of vasopressin systems influences learning and memory. Administration of a selective AVP antagonist to alcohol-tolerant mice produced an increased rate of loss of tolerance, which is opposite the effect of exogenously (externally) administered AVP (Szabo et al. 1988). One more recent study found that an antagonist to the transcription factor c-*fos* blocked the ability of AVP to maintain alcohol tolerance (Szabo et al. 1996).

Another possible mechanism of tolerance, hypothesized from a cell culture model, involves alcohol-induced changes in the cyclic adenosine monophosphate (cAMP) signaling system, with roles for the enzymes protein kinase A, protein phosphatase, and protein kinase C. (See the sections "Setting the Stage: The Structure and Function of Neurons" and "From Cell Membrane to Nucleus: The Effects of Alcohol on Brain Neurons" earlier in this chapter for additional information about these signaling systems and proteins.) For example, the inhibition of adenosine uptake by certain cell cultures exposed to alcohol (Krauss et al. 1993; Nagy et al. 1990) requires cAMP-dependent protein kinase activity. (Adenosine is a compound with numerous functions, among them that of an inhibitory neurotransmitter.) Inhibition of protein kinase A activity, in turn, mimics alcohol tolerance (in which alcohol no longer inhibits adenosine uptake), which can be prevented by inhibiting protein phosphatase activity (Coe et al. 1996*a*).

In another study, activation of protein kinase C also was shown to produce the characteristics of tolerance in naive cells (cells not previously exposed to alcohol), while inhibition of protein kinase C activity during chronic exposure to alcohol prevented the development of tolerance (Coe et al. 1996*b*). Again, the challenge for future studies will be to identify and understand how these specific cellular systems undergo the changes that are responsible for tolerance to motivational effects of alcohol.

Sensitization

The repeated administration of drugs, including alcohol, can result in an enhancement of their behavioral effects, particularly if the treatment regimen involves intermittent, noncontinuous administration (Phillips et al. 1989). Sensitization has been observed in association with the locomotor stimulant effects of alcohol in mice but not rats; this association is also highly dependent on the strain of mouse being studied, suggesting a strong genetic component to sensitization (Phillips et al. 1997). Studies of the neurochemical substrates for sensitization have focused primarily on increased activity in the mesocorticolimbic dopamine system (Stewart and Badiani 1993; Wise and Leeb 1993). Research suggests a time-dependent chain of neurobiological changes within this system that lead to sensitization (Henry and White 1991; Kalivas and Stewart 1991; White and Wolf 1991), with the likely site of action identified as the dopamine-producing cells in the VTA. One of these studies showed that repeated administration of cocaine produced a decrease in the sensitivity of dopamine D2 autoreceptors (dopamine receptors on a cell that itself releases dopamine); dopaminergic function was enhanced with subsequent injections (White and Wolf 1991). Although the time course of dopaminergic subsensitivity was only 4 to 8 days, behavioral sensitization persisted for weeks. More prolonged effects that last for weeks include changes in the nucleus accumbens, such as supersensitivity of D1 receptors and changes in second-messenger systems (internal cell signaling) (Koob and Nestler 1997), suggesting that the initial events triggered in the VTA are followed by more prolonged neurochemical adaptations. In addition, increased release of dopamine in the nucleus accumbens accompanies the increased behavioral responsivity to psychomotor stimulants such as cocaine or alcohol (Kalivas and Stewart 1991).

Stressors can also cause sensitization to stimulant drugs; research suggests an important role for the hypothalamic-pituitary-adrenal stress axis and the extrahypothalamic CRF system in stress-induced sensitization to psychostimulant drugs (Koob and Cador 1993). In addition, a role for brain glutamate systems in sensitization has been hypothesized from results of studies showing that administration of NMDA receptor antagonists blocks the development of sensitization to psychomotor stimulants (Karler et al. 1989; Wise 1988). The locomotor activation produced by acute doses of alcohol in mice does appear to depend on dopaminergic mechanisms (Koechling et al. 1990). How the neuropharmacologic changes observed with intermittent exposure to stimulants relate to sensitization of the motor-activating effects of alcohol and the potential sensitization to the rewarding effects of alcohol remains a challenge for future studies.

Another form of sensitization that has gained significant clinical interest and that may contribute to excessive drinking and vulnerability to relapse is the enhanced withdrawal responses observed during repeated intoxication and withdrawal, known as a "kindling" effect because of its similarity to the kindling of brain seizures (Ballenger and Post 1978; Becker et al. 1997; Kokka et al. 1993). Mice exposed chronically to alcohol vapors (to produce dependence) and then subjected to repeated withdrawal episodes showed progressive increases in the intensity of withdrawal seizures (Becker and Hale 1993; Becker et al. 1997). Rats subjected to repeated withdrawal from chronic alcohol also showed a kindling effect on seizure activity. This kindling effect subsequently was blocked by administration of diazepam, a drug that enhances GABA activity (Ulrichsen et al. 1995), and has been linked to decreases in $GABA_A$ receptor-mediated inhibition (Kang et al. 1996). The challenge for future research will be to test the hypothesis that these kindling phenomena extend to motivational measures of alcohol-seeking behaviors.

Relapse

The study of neurobiological mechanisms associated with relapse has been limited. Animal models for the study of alcohol relapse are under development (Koob 1995). Neuropharmacologic agents that activate the mesocorticolimbic dopamine system can rapidly reinstate drug self-administration in trained animals, but this activation can be extinguished through intravenous self-administration of alcohol (de Wit

and Stewart 1981; Stewart and de Wit 1987). Chronic alcohol administration with a liquid diet to induce dependence has been shown to produce increases in amphetamine- and cocaine-induced locomotor activity up to 2 months after exposure to alcohol (Manley and Little 1997). These findings suggest that a history of dependence may produce a sensitization of the mesolimbic dopamine system. Consistent with this conclusion is the observation that psychostimulant drugs can potentiate conditioned reinforcing effects produced by alcohol (Slawecki et al. 1998).

Research using other animal models, cell systems, and drugs is limited but shows some promise. Acamprosate, a drug being marketed in Europe to prevent relapse in alcoholics, blocks the increase in drinking observed in nondependent rodents after a forced abstinence (Heyser et al. 1996, 1997; Holter et al. 1997; Spanagel and Zieglgansberger 1997; see also the section "Treatment of Alcohol Dependence With Medications" in the chapter on treatment research). Acamprosate may modulate glutamate activity, possibly by enhancing the effects of glutamate under certain situations (Madamba et al. 1996) and inhibiting glutamate activation in other situations (Spanagel and Zieglgansberger 1997; Zeise et al. 1993).

Similarly, opioid antagonists have been shown to prevent an increase in drinking of alcohol by animals following their exposure to certain stressors (Volpicelli et al. 1986). Subsequent studies demonstrated naltrexone's efficacy in preventing relapse in alcoholics who had undergone detoxification (O'Malley et al. 1992; Volpicelli et al. 1992). Naltrexone may act by modulating some aspect of the mesolimbic dopamine reward circuitry, either presynaptically or postsynaptically (Spanagel and Zieglgansberger 1997). For example, some studies have reported that naloxone administered through a microdialysis probe in the nucleus accumbens inhibits alcohol-induced dopamine release (Benjamin et al. 1993; Widdowson and Holman 1992). Other studies have shown that naloxone blocks the inhibitory effect of endogenous opioids on GABA-releasing neurons in the dopaminergic VTA, resulting ultimately in disinhibition (Spanagel and Zieglgansberger 1997).

Identifying and understanding the neurological substrates and the biochemical and molecular mechanisms underlying relapse following abstinence from alcohol should facilitate the development of treatments and/or therapeutic agents that will reduce or eliminate the likelihood of relapse.

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The Neurotoxicity of Alcohol

The brain is a major target for the actions of alcohol, and heavy alcohol consumption has long been associated with brain damage. Studies clearly indicate that alcohol is neurotoxic, with direct effects on nerve cells. Chronic alcohol abusers are at additional risk for brain injury from related causes, such as poor nutrition, liver disease, and head trauma.

The potential cost to society of alcohol-induced brain damage is enormous. Approximately 14 million Americans—about 7.4 percent of the adult population—meet the diagnostic criteria for alcohol abuse or alcoholism (Grant et al. 1994). On any given day, more than 700,000 people in the United States receive alcoholism treatment in either inpatient or outpatient settings (National Institute on Alcohol Abuse and Alcoholism [NIAAA] 1997). Approximately 9 percent of alcohol-dependent individuals have clinically diagnosable brain disorders (Eckardt and Martin 1986). Indeed, alcoholic dementia is the second-leading cause of adult dementia in the United States, accounting for 10 percent of cases (Eckardt and Martin 1986). It is exceeded only by Alzheimer's disease. Many studies report that 50 to 75 percent of detoxified long-term alcohol-dependent individuals show some degree of cognitive impairment (Eckardt and Martin 1986), suggesting that brain dysfunction may persist even after the individual has stopped drinking.

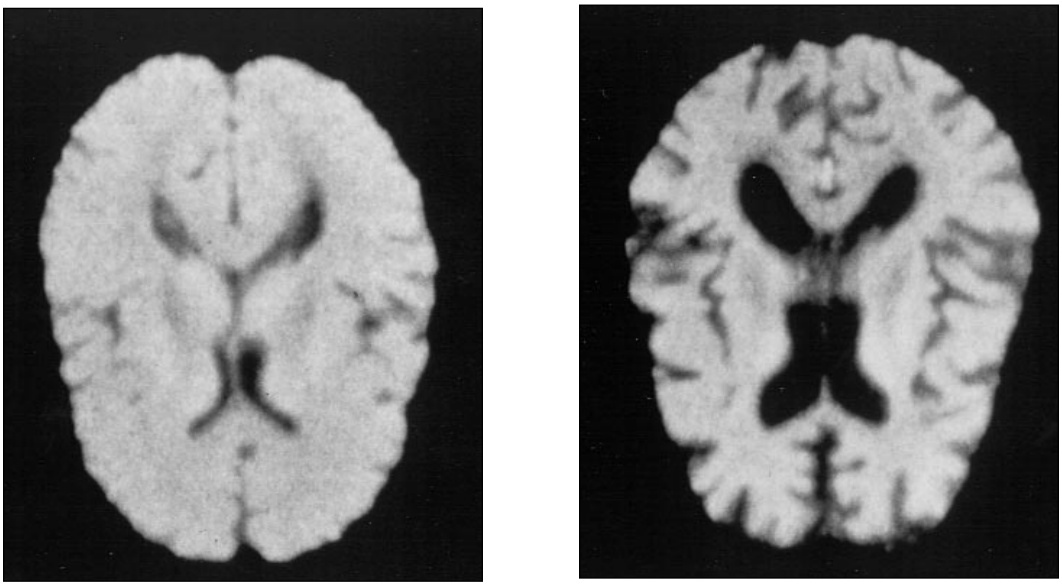
Individual susceptibility to alcohol-induced brain damage is highly variable and is related to many factors, such as gender, genetics, environment, and sociodemographics (Dufour 1993). Susceptibility to alcohol dependence is similarly variable; some people become dependent at much lower levels of consumption than others do. Therefore, it is difficult to specify the levels of alcohol consumption that are likely to lead to alcohol-induced brain damage. There is a serious need for further research in this area.

Neuropathologic Changes

The brain contains as many as 1 trillion nerve cells, or neurons. They come in a variety of shapes and sizes, some looking like old oak trees and others like weather balloons. Many of these cells project into other brain areas where they regulate the activity of those areas, thereby affecting thoughts, consciousness, decisions, mood, and attention. For every nerve cell in the brain that is actively engaged in such things as thoughts, emotions, and movements, there are 10 other cells, called glia, that provide important support to nerve cells. Both of these cell types are damaged by chronic alcohol abuse. Loss of a critical few due to alcohol-induced brain damage may have subtle but important effects on decision-making processes, mood, and behavior.

There appears to be a continuum of brain damage in long-term alcoholics, progressing from moderate deficits in the majority of long-term alcohol abusers to the severe psychosis of Wernicke-Korsakoff syndrome (Butterworth 1995; Pfefferbaum et al. 1996). This syndrome includes Wernicke's encephalopathy and Korsakoff's psychosis, also called Korsakoff's amnestic syndrome. Wernicke's encephalopathy is associated with thiamine deficiency resulting from malnutrition. Prompt treatment with massive doses of thiamine may improve symptoms of this disorder, which include confusion, ataxia (disordered gait), and visual abnormalities. Patients have characteristic brain lesions that may be detected by magnetic resonance imaging (MRI). Korsakoff's psychosis is characterized by anterograde amnesia, where the individual is unable to retain new information (Eckardt et al. 1981). For example, the patient views as total strangers people who were encountered moments before. The memory dysfunction correlates with the presence of lesions in the thalamus, a brain structure involved in the routing of sensory information in the brain

Figure 1: Reduced brain mass in alcoholics



Axial magnetic resonance images from a healthy 57-year-old man (left) and a 57-year-old man with a history of heavy alcohol consumption (right). Images are courtesy of Dr. Adolf Pfefferbaum.

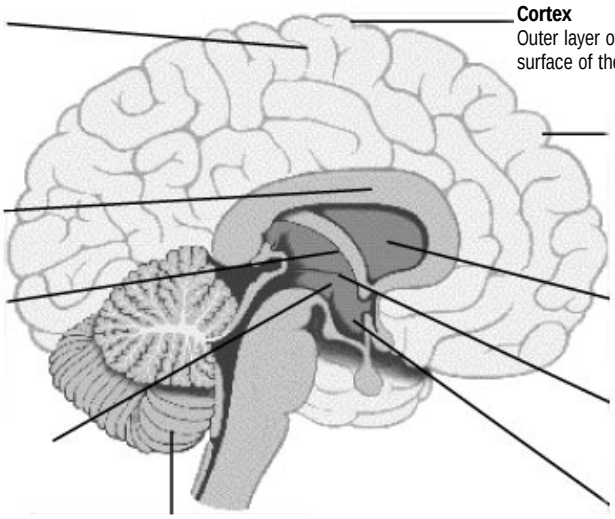
(Victor et al. 1989). Although these two conditions usually occur in sequence, they may exist independently; not all patients with Wernicke's encephalopathy progress to Korsakoff's psychosis, and Korsakoff's psychosis may occur without a preceding episode of Wernicke's encephalopathy.

Extremely heavy alcohol consumption for a prolonged period is generally required to produce the most severe organic brain disease. One study that compared Wernicke-Korsakoff patients with alcoholics who did not have serious neuropsychological deficits found that both age of onset and duration of heavy drinking correlated with the development of Korsakoff's psychosis (Jacobson 1990). Those with Wernicke-Korsakoff syndrome began consuming approximately 12 drinks a day at age 25 and drank at that level for 27 years.

Morphological Changes

Postmortem studies of brain tissue in both humans and animals suggest that chronic heavy alcohol use changes brain structure. These observations are supported by imaging analyses. For example, studies using MRI and computed tomography (CT) show enlargement of the cerebral ventricles (cavities within the brain that are filled with cerebrospinal fluid) and sulci (furrows on the surface of the cerebrum) in most alcoholics. Enlargement of these structures reflects a shrinkage of brain mass (figure 1), consistent with postmortem studies that show reduced brain weight in alcoholics. In severe alcoholics, the reductions in weight of the cerebral hemispheres and the cerebellum (a brain structure predominantly involved in balance and movement; see figure 2) are significant compared with nondrinkers and moderate drinkers (Harper and Kril 1993). The reduced brain mass is probably due to a combination of actual loss of nerve cells and reduction in cell size. With sustained abstinence for 1 to 5 months, the defect begins to disappear. This recovery probably involves increases in neuronal cell size, number and size of the supporting glial cells, and arborization (branching) of nerve endings (Franke et al. 1997). However, neurons that die are lost forever.

Figure 2: Anatomy of the brain



Source: Mattson et al. 1994.

Data from tissue and quantitative morphometry (structural) studies demonstrate selective neuronal loss, reduced arborization, and reduction of synaptic complexity in specific brain regions of alcoholics. The frontal lobes (of the cerebrum)—whose functions encompass the initiation of motor activity and the integration of behavior, intellect, and emotion—appear to be particularly sensitive to alcohol-induced changes (Jernigan et al. 1991). They show the greatest decrease in mass and account for much of the associated ventricular enlargement. Both gray matter, which is composed largely of neurons, and white matter, which is composed of myelinated nerve fibers, appear to be decreased. (The myelin sheath around nerve fibers facilitates the conduction of nerve impulses.) There appears to be a selective loss of white matter, particularly in the frontal lobes, but it is uncertain how the observed cellular lesions relate to this loss. One reason these changes are more evident is the greater proportion of white matter to cortical gray matter in the frontal regions. (Cortical refers to the cerebral cortex, a thin layer of gray matter on the surface of the cerebrum. It is most extensively developed in humans; among its functions, it is the center for intellectual capacity.) Alcoholics with severe brain disorders, such as Wernicke-Korsakoff syndrome, show more significant reduction in white matter and more extensive brain degeneration than do alcoholics with less severe disorders.

Investigators have found a 22-percent reduction in the number of neurons in the superior frontal cortex and motor cortex of alcoholics compared with nonalcoholic controls, but no significant differences in other areas of the cortex (Harper et al. 1987). Recent studies of alcoholics have reported a relationship between temporal lobe shrinkage and a history of alcohol withdrawal seizures, while frontal lobe shrinkage occurs in alcoholics regardless of their seizure history (Sullivan et al. 1996). A decrease in the amount of *N*-acetylaspartate in the frontal lobe, a measure of neuron viability, is another indication of frontal lobe degeneration in alcoholics (Jagannathan et al. 1996). The findings of severe damage to the frontal cortex in alcoholics are consistent with clinical and neuroradiological findings, which

suggest that the frontal lobe may be more susceptible than other cortical regions to alcohol-induced brain damage. The large neurons that are lost in this frontal region (the pyramidal neurons) are also recognized as being more vulnerable in Alzheimer's disease and as part of the normal aging process.

Recent studies have found that in addition to the global shrinkage of brain regions, neurons in certain structures called nuclei are selectively lost with chronic alcohol abuse. Nuclei are clusters of neurons that have broad-ranging functions in brain activity; they are distinguishable by cell type or by clear demarcation from the surrounding tissue. Perhaps the most extensively studied nuclei are the cholinergic nuclei in the basal forebrain. Neurons within these nuclei are involved with the production and release of acetylcholine, a neurotransmitter associated with many important physiologic functions. Both human and animal studies suggest that this region is particularly susceptible to damage in alcoholic subjects. Researchers have reported that Korsakoff's psychosis causes both neuronal loss and shrinkage in this area, with one study reporting a significant loss of neurons (Arendt 1993). Neurons in the cholinergic nuclei are also lost in Alzheimer's disease.

Other brain nuclei that appear to be particularly sensitive are the locus ceruleus and the raphe nuclei. These nuclei are small but important because their neuronal processes project throughout the brain and modulate global aspects of brain activity. For example, lesions in the locus ceruleus, which contains many of the noradrenergic neurons (those that secrete the neurotransmitter norepinephrine) in the brain, may impair attention and information processing and may affect learning and memory. Several studies have reported significant noradrenergic cell loss in the locus ceruleus (Arango et al. 1996; Arendt et al. 1995; Lu et al. 1997), but not all studies have found this loss (Harper and Kril 1993). The median and dorsal raphe nuclei together provide the primary source of serotonergic axons in the cerebral cortex. These neurons secrete serotonin, a neurotransmitter that affects multiple actions in the brain, including the regulation of mood states, thinking patterns, appetite, sleep, and even behavior, such as alcohol drinking. The serotonergic system appears to be disrupted in alcoholics, particularly in severe alcoholics (Baker et al. 1996; Halliday et al. 1995). Recent studies of alcoholics have found a reduction of up to 50 percent in the number of serotonergic neurons from both these raphe nuclei compared with nonalcoholic controls. Further, chemical studies have shown abnormally low levels of serotonergic metabolites in the cerebrospinal fluid of alcoholics with Wernicke-Korsakoff syndrome.

Specific types of brain cells appear to be disrupted. Recent studies have indicated that certain neurons containing the peptide vasopressin may be sensitive to chronic alcohol-induced neurotoxicity in both humans and animals (Harding et al. 1996; Madeira et al. 1997). Vasopressin is a hormone that is involved in the regulation of both physiologic processes and neurobehavioral function. Damage to neurons containing vasopressin and other peptides could disrupt a variety of hormone functions as well as the daily rhythms that are important for healthy living. Further studies are needed to determine whether additional specific cell groups within the brain are particularly susceptible to damage. Neuronal loss in small but functionally significant brain areas could result in global changes in attention, mood, and personality that are difficult to quantify but have a great impact on brain function and overall behavior.

Recent animal studies have found that long-term alcohol intoxication is not necessary for brain damage to occur. As little as a few days of intoxication can lead to neuronal loss in several specific areas of the cerebral cortex (Collins et al. 1996). These findings are consistent with recent studies in human alcoholics that report damage to one of these cortical areas (Ibanez et al. 1995) and significant shrinkage of the hippocampus, an area involved in learning and memory (Harding et al. 1997). Chronic alcohol treatment of animals has shown that hippocampal damage is correlated with deficits in spatial learning and memory (Franke et al. 1997). These studies indicate that

cortical and hippocampal damage can occur in animals with both chronic and short-term alcohol exposure. This suggests that, in humans, relatively short durations of alcohol abuse are likely to cause some form of damage.

Exciting new studies have begun to address the effects of gender on alcohol-induced brain damage. Interestingly, alcoholic women appear to have an increased sensitivity for brain damage compared with alcoholic men (Hommer et al. 1996). This difference appears to be true for liver and heart damage as well. Although more men than women are diagnosed as alcoholic, the number of alcoholic women is increasing. Therefore, the increased susceptibility of women to alcoholic brain damage is an area that needs further investigation.

Functional Changes

Chronic alcohol abuse clearly leads to changes in brain function, with the degree of dysfunction dependent upon the duration and amount of alcohol consumed. Many brain functions related to the frontal cortex appear to be affected. Prefrontal (the most anterior part of the cortex) damage typically is associated with changes in personality and cognitive abnormalities. Although these types of changes in brain function are more difficult to assess than physical changes, they are consistent with the morphological changes found in the frontal cortex of alcoholics.

Both clinical and experimental studies support a role for frontal cortical involvement in neuropsychological deficits in alcoholics, particularly those with Korsakoff's psychosis (Oscar-Berman and Hutner 1993). These deficits include dysfunction in emotional control, problem-solving ability, and attention. Electrophysiologic studies using electroencephalograms and event-related potentials have suggested that alcoholics have difficulty differentiating relevant and irrelevant, easy and difficult, and familiar and unfamiliar stimuli (Porjesz and Begleiter 1993). These deficits appear to be consistent for alcoholics and may be related to frontal cortical function.

Alcoholics who do not suffer from Wernicke-Korsakoff syndrome still show greater loss of neuropsychological performance than peer nonalcoholics do on tests of learning, memory, abstracting, problem solving, visuospatial and perceptual motor functioning, and information processing (Parsons 1993). Alcoholics are less accurate and take considerably longer to complete tasks. Many of the deficits appear to recover to age-appropriate levels of performance after 4 to 5 years of abstinence (Parsons 1993). However, even though global cerebral atrophy may return to near normal levels with extended abstinence, not all cognitive functions return. Some abstinent alcoholics appear to have permanent cognitive impairments, particularly in memory and visual-spatial-motor skills (Di Sclafani et al. 1995). Other studies support a loss of logical memory and paired-association learning tasks in alcoholics that may be long lasting (Eckardt et al. 1996).

Recent studies have emphasized the role of the prefrontal cortex in executive cognitive function (ECF) (Hoaken et al. 1998). This is the ability to use higher mental processes such as attention, planning, organization, sequencing, abstract reasoning, and the use of external and internal feedback to adaptively shape future behavior (Foster et al. 1994). ECF processes are dysfunctional in alcoholics and in persons with other diseases showing prefrontal damage (Boller et al. 1995). Changes in ECF and prefrontal cortical characteristics are associated with decreased regulation of human social behavior, including disinhibition syndrome, which is characterized by impulsivity, socially inappropriate behavior, and aggression (Giancola and Zeichner 1995*a*). Disruption of ECF has also been implicated in the underlying aggression associated with substance abuse (Giancola and Zeichner 1995*b*).

Mechanisms of Action

Researchers have only recently begun to elucidate the mechanisms involved in the neurotoxic effects of alcohol on the brain. As research techniques have become more sophisticated and data from experimental and clinical studies have accumulated, however, investigators have had a more

substantial basis for speculation as to the nature of these mechanisms.

NMDA Receptor Supersensitivity

One promising avenue of research involves the interaction between glutamate, an amino acid that is the major excitatory neurotransmitter in the brain, and a specific glutamate receptor, the *N*-methyl-D-aspartate (NMDA) receptor. Glutamate and the NMDA receptors are extensively discussed in other sections of this chapter. The NMDA receptor is inhibited by alcohol at a greater level of sensitivity than is any other known glutamate receptor. The acute alcohol-induced inhibition leads to adaptive changes in the NMDA receptor that make it supersensitive to glutamate during chronic alcohol exposure.

Excessive stimulation of NMDA receptors by glutamate can kill neurons, and chronic alcohol exposure increases sensitivity of neurons to NMDA-stimulated killing (Chandler et al. 1993*a*; Crews and Chandler 1993; Iorio et al. 1993). Excitotoxicity is a term applied to the direct lethal damage to neurons in extreme cases of excessive glutamate receptor activity, usually accompanied by an excessive accumulation of intracellular calcium ions. This neurotoxic property of the receptors appears to play a key role in neurodegenerative diseases in general, as well as in stroke, brain trauma, and other types of brain damage (Crews et al. 1996). The extreme neurodegeneration associated with Wernicke's encephalopathy also appears to involve increases in glutamate-NMDA excitotoxicity. Several studies using cultured neuronal cells have indicated that a few days of chronic alcohol treatment lead to supersensitive NMDA receptor-stimulated calcium flux (an increase in the intracellular concentration of calcium ions) (Ahern et al. 1994; Iorio et al. 1992), as well as NMDA receptor-stimulated excitotoxicity (Chandler et al. 1993*b*; Crews and Chandler 1993; Crews et al. 1993; Iorio et al. 1993) and NMDA receptor-stimulated nitric oxide formation (Chandler et al. 1997). All of these reactions lead to severe neuronal damage.

The administration of an antagonist to NMDA receptors, such as MK-801 (dizocilpine), eliminates both alcohol tolerance (Khanna et al. 1992; Szabo et al. 1994) and withdrawal seizures (Grant et al. 1990), as well as blocks NMDA-stimulated neuronal death (Chandler et al. 1993*a*). In animal studies using thiamine-deficient rats as a model for Wernicke's encephalopathy, extracellular concentrations of glutamate in the brain increased several fold during seizures (Langlais and Zhang 1993). Administration of the NMDA receptor antagonist MK-801 reduced the neurobiological symptoms and the severity of neural lesioning in these animals (Langlais and Mair 1990). These studies and others provide evidence that NMDA receptor supersensitivity may contribute to alcohol tolerance, dependence, and neurotoxicity and to the hyperexcitability and seizures associated with alcohol withdrawal. However, further research is needed in this area.

Hyperexcitability of the central nervous system is a key component of alcohol withdrawal. A supersensitive glutamate-NMDA response appears to be involved, although a reduction in gamma-aminobutyric acid-mediated inhibition also may contribute to this hyperexcitability (Crews et al. 1996). (Gamma-aminobutyric acid is a neurotransmitter that inhibits the activity of nerve cells.) One of the earliest findings suggesting glutamate involvement was the increased binding of radioactively labeled glutamate ([^{3}H]glutamate) in the hippocampus of alcoholics (Michaelis et al. 1990). Although it is not clear which subtype of glutamate receptor is involved, this finding is consistent with increased glutamate receptor density and sensitivity.

The mechanisms of NMDA receptor supersensitivity are not fully understood, but it is clear that chronic alcohol administration can induce this supersensitivity. This supersensitivity could occur through a number of mechanisms, including an increase in the density of NMDA receptors, changes in the NMDA receptor subunit composition, or chemical changes in the NMDA receptor that could change its sensitivity. Some, but not all, studies have found increases in NMDA receptor density. These results, although

inconclusive, suggest that this may be one of the mechanisms underlying chronic alcohol-induced NMDA receptor supersensitivity (Chandler et al. 1997; Crews et al. 1996; Rudolph et al. 1997).

A second mechanism for inducing NMDA receptor supersensitivity could involve changes in the subunit composition of the receptor. The NMDA receptor is thought to be made up of five subunits, and changes in the type of subunit could change NMDA receptor supersensitivity. Studies have reported that the number of subunits expressed during chronic alcohol exposure is altered (Follesa and Ticku 1995, 1996).

Other studies, however, found alcohol-induced NMDA receptor supersensitivity without subunit changes (Chandler et al. 1997), suggesting that other mechanisms, such as phosphorylation, might be involved. This is a chemical reaction that is involved in regulation of receptor activity. Enzymes that phosphorylate (add phosphate to) amino acid residues within the NMDA receptor, including tyrosine kinases such as Fyn tyrosine kinase, may affect NMDA receptor sensitivity during alcohol treatment (Miyakawa et al. 1997). These mechanisms could occur as a continuum, with phosphorylation causing initial supersensitivity, and more prolonged and excessive alcohol consumption causing additional supersensitivity through changes in subunits and slight increases in NMDA receptor density. Because of the consistent finding that NMDA supersensitivity during chronic alcohol treatment leads to increased NMDA receptor-stimulated neuronal excitotoxicity, all of these mechanisms are being further investigated.

Oxidative Stress

Another possible mechanism for alcohol-induced brain damage involves oxidative stress of neurons. As a by-product of alcohol metabolism, free radicals may be formed. These are highly reactive molecular fragments that are capable of inflicting serious damage on cells if they are not quickly neutralized. Normally, free radicals are rapidly inactivated by antioxidants, which are protective molecules that inhibit oxidation. However, if these defenses are impaired, or if there is an overproduction of free radicals, the result is oxidative stress. This imbalance between increased production of free radicals and decreased availability of antioxidants can result in cell death. Free radicals also may attack lipids in cell membranes, causing lipid peroxidation. This is a reaction between oxygen radicals and components of the cell membrane that results in membrane injury and eventual cell death.

Studies examining the effects of both acute and chronic alcohol administration on cellular oxidation in the rat brain have focused primarily on alcohol's effects on the activity of antioxidants, such as alpha-tocopherol, ascorbate, glutathione, catalase, and superoxide dismutase (Ledig et al. 1981; Montoliu et al. 1994; Nordmann 1987; Rouach et al. 1987), or on potential sources of oxidative radicals. One of these sources is nitric oxide, which has been implicated in neuronal toxicity resulting from the formation of highly oxidative metabolites (Crews and Chandler 1993). Another source of oxidative radicals is cytochrome P450 2E1, an enzyme that metabolizes alcohol and is a potent generator of these radicals (Montoliu et al. 1994, 1995). Increases in cytochrome P450 2E1 and other oxidases induced in rats by chronic alcohol administration have been related to increased lipid peroxidation and the formation of reactive oxygen radicals in the brain (Montoliu et al. 1994). However, levels of antioxidant enzymes, such as catalase and superoxide dismutase, appear to increase as a compensatory mechanism (Montoliu et al. 1994).

The brain is particularly susceptible to lipid peroxidation because it consumes a large amount of oxygen and is rich in polyunsaturated fatty acids, which are particularly prone to injury from oxygen radicals. Experiments with cells of rat brains have shown that a single dose of alcohol results in both increases in lipid hydroperoxide levels and decreases in glutathione levels (Nordmann et al. 1990, 1992; Uysal et al. 1986, 1989). It is not clear whether or how this increased oxidation is associated with increased brain damage. Most studies have focused on whole-brain homogenates, rather than on cells of specific brain regions. However, a recent study of

alcohol-induced depression of glutathione and glutamine synthetase levels, two indices of increased oxidative radical formation, used cells from specific brain regions. Researchers found changes only in cells from the striatum (a center involved in the programming of movement), but not in cells from the cerebral cortex or cerebellum (structures involved in balance and motor coordination) (Bondy and Guo 1995).

Oxidative stress has been implicated in the effects of aging and in a variety of neurodegenerative disorders, such as Alzheimer's disease, Parkinsonism, and stroke. Much more research on alcohol-induced neurodegeneration is needed to provide a more complete understanding of how oxidation damages neurons and how other brain cells respond to increased oxidative stress. Alcohol-induced neurodegeneration may be related to an induction of oxidative enzymes; alcohol research provides an opportunity to clearly address this aspect of neurodegeneration, which could impact a broad range of diseases.

Growth Factors

Growth factors are specific protein elements of the brain that stimulate growth and extensions of neurons and that are essential to neurons for their survival and maintenance of normal function. Growth factors also are known to increase the activity of neuronal antioxidant and excitotoxic protective mechanisms. The growth factors include, among others, nerve growth factor (NGF), brain-derived neurotrophic factor (bDNF), neurotrophin 3 (NT-3), and basic fibroblast growth factor (bFGF).

Researchers have found that alcohol alters brain levels of growth factors in rats (Arendt et al. 1995; Baek et al. 1996; MacLennan et al. 1995; Nakano et al. 1996). Recent studies have found that chronic alcohol administration reduces the level of bDNF but does not change the levels of NGF, NT-3, or bFGF (Baek et al. 1996; MacLennan et al. 1995). Receptors for the growth factors remain intact after chronic alcohol abuse (Arendt et al. 1995; MacLennan et al. 1995). This finding presents the promising possibility that growth factors may be used to treat alcohol-induced brain damage as well as other neurodegenerative conditions. Studies of the actions of growth factors and of their role in alcohol-induced brain damage represent an exciting new area of discovery that could provide new approaches to treatment of neurodegeneration.

In Closing

Alcoholism is a progressive disease that starts with experimentation and progresses to addiction, usually over the course of several years. Addiction involves the loss of control over the ability to abstain from the drug and an excessive preoccupation with obtaining and using the drug. Discoveries continue to unravel structure-function aspects of the brain and suggest that some of the behavioral problems of alcoholism may be related to alcohol-induced damage to specific brain areas. While earlier studies focused on alcohol-induced changes in cognition, more recent studies are focusing on the frontal cortex, which is particularly sensitive to alcohol-induced damage, and on the role of this brain region in behavior. Experimental subjects with poor prefrontal functioning appear unable to inhibit impulsive behavior (Lau and Pihl 1996), particularly violence (Lau et al. 1995). Results of neuroimaging studies also indicate that reduction of metabolic functions in the frontal lobes is associated with violence (Raine et al. 1994).

Taken together, these studies suggest that some of the greatest sociopathic problems of alcoholism, such as violence and loss of control over the drug, may be directly related to the neurotoxic effects of alcohol on prefrontal cortical function. This is a particularly exciting hypothesis, because it suggests that it may be possible to detect individuals at risk for addiction through studies of their brain function and to determine whether recovery of normal function is associated with the ability to sustain abstinence. Identification of these individuals would allow focused efforts at prevention and education, with the aim of preventing addiction and its accompanying sociopathic behaviors.

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Genetic Studies of Alcohol's Actions on the Brain

Evidence from twin, family, and adoption studies has firmly established that genetic factors play a major role in the development of alcohol abuse and alcoholism. It is clear that individuals inherit specific genes that increase or decrease their risk for alcoholism, but the identity and location of those genes remain elusive (National Institute on Alcohol Abuse and Alcoholism 1995).

Researchers involved in the Human Genome Project, a massive effort to map the entire human genome, have developed technologies enabling scientists to identify specific chromosomal regions that are likely to contain genes affecting sensitivity to alcohol (Carr et al. 1998; Crabbe et al. 1994). Research focused on these regions, called quantitative trait loci (QTL), is also discussed elsewhere in the section "Animal Genetic Studies on Alcoholism" in the chapter on genetic and psychosocial influences.

Once the QTL for a trait has been provisionally established, it is possible to search the genome or the location of candidate genes of known function that are likely to influence the alcohol-related trait in question. With use of recently developed molecular biological techniques, several of these candidate genes are currently under investigation. Some of these were nominated by mapping studies (the serotonin 1B gene); others were investigated because historical data implicated them in the alcohol-related response of interest (the gene encoding the γ_{2L} subunit of the subtype A gamma-aminobutyric acid [$GABA_A$] receptor). In one case, both pharmacologic data and mapping data converged to implicate a particular gene, that encoding the α_6 subunit of the $GABA_A$ receptor. This report describes the development of animal models for these genetic investigations, reviews recent research on several candidate genes for alcohol-related traits, and describes studies using immediate early genes (IEG's), a class of genes that can be used to identify which brain structures are first activated by a particular stimulus, including the administration of alcohol.

Development of Animal Models

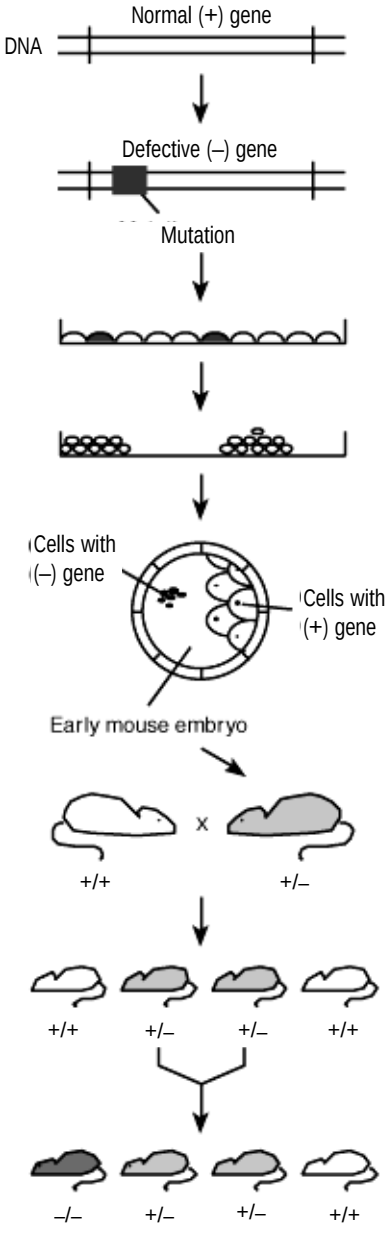
Because the genetic makeup of humans and rodents is similar and their biochemical processes are virtually the same, results of genetic studies with rodents may generally be extrapolated to humans. Investigators have produced many paired strains of rats and mice that are selectively bred to express specific responses to alcohol, such as those that prefer or do not prefer alcohol and those that differ in their susceptibility to alcohol-induced incoordination or loss of righting reflex. (The development of recombinant inbred strains is discussed in the chapter in this report on the etiology of alcoholism.) Recently developed genetic engineering techniques have made it possible to inactivate (knock out) specific genes or to create transgenic mice by inserting foreign genes into the genome. This approach permits investigators to observe whether and how an animal's response to alcohol is altered depending on whether or not the gene is present. Most of the studies described here use strains of knockout or transgenic mice.

Knockout Mice

A powerful approach to analyzing the role of a specific gene in alcohol-related disorders is to inactivate that gene and study the impact of the inactivation on later development and behavior. Through inbreeding and selection, a knockout strain of animals can be produced in which that gene is nonfunctional in every individual animal.

Because two copies of each gene are inherited, one from each parent, it is necessary to inactivate both copies of a given gene. The process of creating a knockout strain requires multiple steps (figure 1) (Homanics and Hiller-Sturmhöfel 1997). Researchers first isolate gene X and transfer it into a short piece of deoxyribonucleic acid (DNA) that is used as a vector. They inactivate the gene, usually by inserting a marker gene that disrupts gene X and also confers a resistance to certain antibiotics. Then they

Figure 1: General procedure for generating knockout mice



Normal (+) gene is isolated.

A mutation to create a defective (–) gene is introduced.

The (–) gene is introduced into embryonal stem (ES) cells in tissue culture; not all all ES cells will incorporate the (–) gene into their DNA.

Cells are grown in a medium that allows only cells with the (–) gene to multiply.

Cells with the (–) gene are injected into mouse embryos.

Embryos develop into chimeric mice expressing the (–) gene in some cells and the (+) gene in other cells; one of the chimeric mice is mated with a normal mouse.

Mouse pups (F_1 animals) carrying a (+) and a (–) gene copy are identified and mated with each other.

The offspring (F_2 animals) are analyzed; about 25 percent will have inherited the (–) gene from both parents and will completely lack the (+) gene.

Source: Homanics and Hiller-Sturmhöfel 1997.

transfer the vector with the defective gene into embryonic stem cells. These are undifferentiated early-stage embryo cells that can eventually develop into every type of cell in the organism. In some stem cells, the defective gene changes places with its normal counterpart in a process called homologous recombination. The altered stem cells are grown in a medium containing antibiotic, in which only the cells that have successfully incorporated the defective gene can survive. These surviving stem cells are then injected into mouse embryos at an early stage of development, and the embryos are implanted into surrogate mothers. Some of the resulting pups are chimeras; some of their cells contain the mutated gene X, while other cells, derived from the embryo's normal stem cells, contain the normal gene X. It is possible, through easily

identifiable phenotypic characteristics of the parents, such as coat color, to ascertain which pups are the chimeras. Although chimeras do not contain the mutated gene in all of their cells, researchers are able to identify those that carry the altered gene in their reproductive cells by mating the chimeras with normal mice and determining which of their offspring carry the mutated gene. Further inbreeding and selection eventually produce a strain of mice that carry the mutated gene in every cell. These are the knockout mice. In experimental work with knockouts, the normal, or wild-type, mice from which they were derived are used as controls. The two strains differ only in the presence or absence of the knockout gene and are otherwise much like identical twins.

Transgenic Mice

In transgenic mice, a foreign gene is permanently integrated into the animal's DNA. Investigators insert the foreign gene into a vector and then inject the vector into a newly fertilized mouse egg. The fertilized egg contains two pronuclei, one from each parent, and the vector is injected into the larger male pronucleus. The pronuclei fuse to form a single nucleus, carrying chromosomes from both parents, and the fertilized egg then develops into an embryo. In a small percentage of embryos, the foreign gene integrates into one of the embryo's chromosomes. The researchers then implant the embryos into surrogate mothers, identify the pups that are positive for the foreign gene, and mate them with normal mice. As with knockouts, these are mice from the same strain and are identical to the transgenic mice except for the altered gene. Subsequent inbreeding and selection eventually produce a strain of mice that contain the foreign gene in all of its cells.

Investigation of Candidate Genes

As more candidate genes are identified, researchers have begun to use knockout or transgenic strains of mice to determine how these genes affect the development of alcohol-related disorders. This report describes current research using knockout or transgenic technology on five candidate genes for alcohol-related traits.

Serotonin Receptor Genes

Studies of alcohol consumption in animals have implicated the neurotransmitter serotonin (5-HT) (LeMarquand et al. 1994*b*). (See the first section of this chapter, "Setting the Stage: The Structure and Function of Neurons and the Brain," for background on neurotransmitters and cell signaling processes discussed here.) Experiments with rats and mice have suggested that neuronal systems using 5-HT may modulate the degree of development of sensitivity and/or tolerance to alcohol-induced ataxia (physical incoordination) and hypothermia (reduced body temperature) (Lê et al. 1980). Clinical studies have reported lowered brain 5-HT activity in a subgroup of aggressive alcoholics (LeMarquand et al. 1994*a*).

There are more than 15 receptors for 5-HT, and experiments so far have been unable to specify which subtype or subtypes of 5-HT receptors mediate the effects of alcohol. One type of receptor, 5-HT_{1B} in rodents, or 5-HT_{1D} in humans, appears to be particularly interesting. In rodents, receptors generally are presynaptic auto- and heteroreceptors. This means that when a nerve terminal containing these receptors is stimulated to release its own neurotransmitter, 5-HT_{1B} autoreceptors inhibit further release of 5-HT from the terminal; in the case of terminals that release other neurotransmitters, such as gamma-aminobutyric acid (GABA) or dopamine-5-HT heteroreceptors prevent further release of these neurotransmitters. In this way, these receptors reestablish brain homeostasis. Interference with 5-HT_{1B} receptor levels might thus exert a cascade of influences on multiple brain systems through the effects on a number of neurotransmitters. Further, it is also potentially important that 5-HT_{1B} heteroreceptors are located on nerve terminals containing the inhibitory neurotransmitter GABA. These terminals project from the nucleus accumbens to the ventral tegmental area, two brain structures which, with their connecting pathways, are thought to be important in drug reward (Koob 1992).

Researchers have developed a strain of knockout mice lacking the 5-HT_{1B} receptor gene. These mice are highly aggressive; the investigators suggest that 5-HT_{1B} receptors play a role in aggressive behavior (Ramboz et al. 1996; Saudou et al. 1994). Brain slice preparations from some brain areas show changes in 5-HT release, suggesting that serotonergic function may be altered and that other 5-HT receptors besides the 5-HT_{1B} may help regulate 5-HT release (Piñeyro et al. 1995).

QTL mapping studies suggested the presence of a gene influencing alcohol consumption in the midportion of mouse chromosome 9 (Crabbe et al. 1994; Phillips et al. 1994; Rodriguez et al. 1995). Because this chromosome region contains the 5-HT_{1B} receptor gene, researchers characterized 5-HT_{1B} knockout mice and their wild-type controls for several alcohol-related traits. For example, alcohol preference drinking is frequently taken as an index of alcohol's reinforcing, or rewarding, properties. When given a choice between solutions of alcohol or tap water, the knockout animals voluntarily drank twice as much alcohol as the wild-type controls, at concentrations of up to 20 percent (Crabbe et al. 1996). After many days of drinking, the knockouts with the strongest preference for alcohol drank between 16 and 28 grams of alcohol per kilogram of body weight during the last 24 hours of the experiment, a very high level of intake, even though water was freely available. (It should be noted that a subsequent study did not replicate this result in knockouts [Crabbe 1999].)

Two other behavioral assays of reinforcement depend upon mice learning to associate a behavioral response with the presence of alcohol as a stimulus. The 5-HT_{1B} knockout mice were tested for conditioned place preference, an experimental design that pairs one environment with alcohol injections, and another environment with saline injections (Risinger et al. 1996). When these animals were subsequently given a choice between the alcohol- and the saline-paired environments, the knockout mice showed no preference for the alcohol-paired environment while the wild-type controls showed the expected alcohol-conditioned place preference. This finding suggests that the knockouts were less sensitive to the reinforcing effects of alcohol in this test.

A conditioned taste aversion test paired daily drinking of a novel-flavored solution with a subsequent alcohol injection, and the animals gradually developed an aversion for the novel solution. (Although drugs like alcohol have rewarding properties that underlie the behavior of animals in conditioned place preference tests, they also can elicit aversion, as observed in this experiment. The level of sensitivity to both the rewarding and aversive effects of alcohol is thought to be involved in the development of dependence.) However, in this test of alcohol's aversive effects, 5-HT_{1B} knockouts and wild-types were equally sensitive, and both developed a dose-dependent aversion (Risinger et al. 1996).

Results of these experiments highlight the need to cautiously interpret the results of studies with genetically altered animals using behavioral assays. Another study comparing 5-HT_{1B} knockout and wild-type mice used a grid test designed to measure alcohol-induced ataxia. In this test, investigators place mice on a wire mesh floor after an injection of alcohol. Intoxicated mice occasionally slip through the grid floor and a foot makes contact with a metal plate. The 5-HT_{1B} knockout mice were half as sensitive as wild-types to the intoxicating effects of alcohol, and they developed tolerance to a lesser extent after repeated testing (Crabbe et al. 1996). However, in consideration of the variations in response to the reinforcement tests, it would be premature to assume that this apparent behavioral insensitivity of knockouts can be extrapolated to all measures of intoxication, even to other tests designed to measure ataxia.

Additional tests with 5-HT_{1B} knockout mice showed that these mice were more sensitive than wild-types to the locomotor stimulant effects of alcohol (Risinger et al. 1996). Tests measuring the severity of acute and chronic withdrawal showed that the knockouts did not differ significantly from wild-types in locomotion,

indicating that they had acquired the same level of physical dependence (Crabbe et al. 1996).

The studies described above illustrate the wide-ranging effects of manipulating a single gene. The results tend to confirm the role of 5-HT in several different responses to alcohol that are important in alcoholism research. These studies suggest new avenues for future research. For example, the entire course of development of these mice occurred after deletion of the 5-HT_{1B} gene, and the brain must have struggled in unknown ways to compensate for the deletion. The compensations are largely successful, as the knockout mice appear normal, generally behave within normal limits, grow at a normal rate, and breed fairly successfully. Future research should aim at identifying the nature of these compensations, as well as determining the nature of the relationship between the genetic deficit and the proclivity for drinking alcohol.

There is currently a high interest in investigating serotonergic systems because recent studies suggest that a class of drugs known as selective serotonin reuptake inhibitors (SSRI's) may be effective in treating alcoholism (Pettinati 1996). The prototypic SSRI is fluoxetine (Prozac). These drugs act to increase binding of 5-HT by prolonging its availability at the site of its receptors after its release from nerve cells.

GABA Receptor Genes

GABA is the principal inhibitory neurotransmitter in the brain. The GABA receptor, which is embedded in the neuronal cell membrane, is composed of a tightly linked set of five protein subunits arranged to form a channel which, when the receptor is activated, opens to allow the passage of chloride ions into the cell. The influx of negatively charged ions decreases the excitability of the cell. The GABA receptor subtype that appears to be the most sensitive to alcohol is $GABA_A$. Many of alcohol's acute and chronic effects appear to involve its actions on $GABA_A$ receptors (Buck 1996; NIAAA 1997).

The effects of alcohol on $GABA_A$ receptors involve the action of other proteins, such as protein kinase C (PKC). This is an enzyme that phosphorylates (adds phosphate groups to) other proteins, thereby altering their function. Phosphorylation by PKC appears to enhance the sensitivity of the $GABA_A$ receptors to alcohol. The gamma subtype of PKC (PKC-γ) has been implicated in alcohol's effect on GABAergic neurons and on subsequent behavior (Harris et al. 1995). To study this relationship further, researchers created a strain of knockout mice lacking the gene coding for PKC-γ. The knockouts were less sensitive than wild-type controls to alcohol-induced hypothermia and to alcohol-induced loss of righting reflex, both measures of alcohol's sedative effects. However, the knockouts and wild-types were equally sensitive to two other sedative drugs that affect the $GABA_A$ receptor (Harris et al. 1995). These findings suggest that PKC-γ may play an important role in mediating the effects of alcohol on the $GABA_A$ receptor, but that other sedatives appear to affect the receptor through a different mechanism.

There is some evidence that one of the subunits of the $GABA_A$ receptor, α_6, may mediate some of the behavioral effects of alcohol. One QTL mapping study sought to identify chromosomal stretches associated with severity of withdrawal symptoms, that is, regions that were inherited with high frequency along with a tendency toward severe withdrawal symptoms. The investigators found such an association (or linkage) on mouse chromosome 11, near genes coding the α_1, α_6, and γ_2 subunits of $GABA_A$ receptors (Buck et al. 1997). However, this is a large chromosomal region containing other genes, so any conclusions regarding the actions of the α_6 subunit gene would be premature. Researchers developed a strain of mice lacking the α_6 subunit and compared these animals with wild-type controls on several measures of behavioral sensitivity to alcohol, pentobarbital, and general anesthetics (Homanics et al. 1997). They found no significant difference between the two strains,

demonstrating that the α_6 subunit is not a requirement for sensitivity to alcohol's sedative-hypnotic effects. However, as with the 5-HT studies discussed above, interpretation of studies with knockout mice must consider the fact that the genes were absent during neurodevelopment, so functional adaptations in the GABA or other neural systems could have compensated for the knockout. (It should also be noted that in a recent study mice in which the α_1 subunit gene was point mutated, no change was observed in alcohol's potentiating effects [Rudolph et al. 1999].)

Dopamine Receptor Genes

Dopamine, another neurotransmitter, has an important role in locomotor response to rewarding drugs (Koob 1992). There are five known dopamine receptors. Researchers have developed a knockout strain of mice lacking one of them, the D4 receptor, and have tested the response of these mice to a number of psychoactive drugs (Rubenstein et al. 1997). The knockout mice are hypersensitive to the acute locomotor stimulant effects of alcohol, cocaine, and methamphetamine. These animals also had enhanced dopamine function in the dorsal striatum, a brain area associated with locomotion. The authors suggest that this receptor modulates drug-stimulated locomotor behaviors.

There are genetic differences in human D4 receptor types, and certain alleles (alternate forms of a gene) may be associated with risk for alcoholism (Geijer et al. 1997; George et al. 1993; Muramatsu et al. 1996) and risk-taking behavior (Benjamin et al. 1996; Ebstein et al. 1996). The human studies are still controversial, and the association with both alcoholism and novelty seeking has been questioned (Malhotra et al. 1996). Further research with D4 knockout mice may prove important in understanding risk for alcoholism and some of the personality factors that are often associated with alcoholism.

Insulin-Like Growth Factor Genes

Insulin-like growth factor I (IGF-I) plays a critical role during development in the proliferation and differentiation of new cells, including brain cells. Using transgenic technology, researchers recently have developed strains of mice characterized by overexpression of IGF-I or its binding protein, IGF-binding protein 1 (one of several such proteins that bind and modulate the action of IGF-1) (Pucilowski et al. 1996). In tests of alcohol-induced loss of righting reflex, IGF-I transgenics were less sensitive than their wild-type controls, and IGF-binding protein 1 transgenics were more sensitive than their controls. There were no significant differences among the strains in sensitivity to alcohol-induced hypothermia or in alcohol-induced ataxia assessed by performance on a rotating drum. After repeated alcohol administration for 8 days, the control animals developed tolerance to both alcohol-induced hypothermia and loss of righting reflex. The IGF-I transgenic mice did not develop tolerance to either effect, but the IGF-binding protein 1 transgenics developed greater tolerance to both effects than did the controls.

Because IGF-I plays a role in the homeostatic regulation of calcium ions in brain tissue, these investigators have speculated that calcium may play a role in the behavioral differences observed in these experiments. Therefore, specific studies of calcium function in these transgenic strains are needed.

Fyn Tyrosine Kinase Genes

Glutamate is the brain's major excitatory neurotransmitter. Alcohol can inhibit this excitatory action by acting on the glutamate receptors. The *N*-methyl-D-aspartate (NMDA) glutamate receptor, an ion channel receptor, is particularly sensitive to alcohol's effects. Fyn tyrosine kinase is a protein kinase that phosphorylates the NMDA receptors, thereby affecting their function. Researchers have developed knockout mice lacking the *fyn* gene to study the effects of Fyn tyrosine kinase on sensitivity to alcohol (Miyakawa et al. 1996, 1997). This work is discussed in detail in the section "From Cell Membrane to Nucleus: The Effects of Alcohol on Brain Neurons" earlier in this chapter.

Knockout mice offer researchers the opportunity to observe the influence of single genes on aspects of alcohol sensitivity that play a role in the incentives that lead people to drink, in the development of dependence, and in the physiologic effects of alcohol, such as withdrawal. Among the avenues that investigators are pursuing that will further enhance the insights possible from this work are the development of multigene knockouts that will allow observation of the mutual influence of multiple genes, creation of knockouts in which the gene deletion is restricted to a certain tissue region, and development of methods to introduce genes that could compensate for the function lost with a knockout gene.

Immediate Early Genes

Gene Expression

Recent research is increasingly making use of knowledge of gene expression to identify the areas of the brain that are acted upon by alcohol (see the box "From DNA to Protein: How Genetic Information Is Realized" in the first section of this chapter for background on gene expression). These techniques depend on an understanding of the steps of gene expression, the first of which is transcription. This is the process of transferring genetic information within the cell from DNA to ribonucleic acid (RNA), specifically messenger RNA (mRNA). Within the cell nucleus, the genetic code is copied, or transcribed, from one strand of DNA to a complementary strand of mRNA. The mRNA then moves from the nucleus into the cytoplasm, where it first binds to structures called ribosomes and then directs the synthesis of a particular protein in a process called translation. The amino acid sequence that has been encoded in the mRNA determines the structural and functional characteristics of the protein. Gene transcription is regulated by transcription factors, proteins that bind to specific regulatory regions within genes and that control the rate at which DNA is copied into mRNA. Promoter sites are regions of the DNA strand where transcription of a particular gene is initiated.

Alcohol consumption results in the nearly immediate response of neurons in certain critical brain areas. As a consequence of this initial response, many brain processes "downstream" are likely to be affected. IEG's are genes that can be used to identify which brain areas are the first to be affected by a given stimulus, such as alcohol. One such gene, c-*fos*, codes for a component of a transcriptional regulatory complex, activator protein 1 (AP-1). AP-1 binds to promoter sites and thus regulates many other genes. In experimental animals, the expression of c-*fos* is increased by many second messengers, such as PKC, in response to a wide variety of stimuli, such as handling or exposure to novel situations. Because c-*fos* induction is both rapid and transient, it can be used as an indicator of which brain regions are most immediately affected by alcohol.

IEG's and Mapping of Brain Regions

Early studies on IEG expression established that acute and chronic alcohol administration could exert effects on IEG expression that were specific to certain brain regions (Davidson et al. 1996). A recent review concludes that areas of the hippocampus, a brain center involved in the consolidation of new memories, are preferentially sensitive to alcohol (Ryabinin 1998). Some studies support the suggestion that alcohol also preferentially affects some behavioral responses, such as certain forms of learning, that are believed to be mediated by the hippocampus.

Reviews of early research (Crabbe 1997; Ryabinin 1998) point out a major difficulty in interpreting IEG expression data. Because so many behavioral endpoints can themselves induce IEG expression, studies must be designed with rigorous behavioral controls. In one study using extremely rigorous control procedures, researchers compared the effects on 38 specific brain areas of two doses of alcohol given acutely or chronically (Ryabinin et al. 1997). Acute alcohol administration induced IEG expression in most brain areas, a pattern of results resembling those from an earlier study (Chang et al. 1995). However, the research group that performed the 1997 study had previously reported a different result following

administration of a slightly higher dose of alcohol when fewer habituation sessions were used (Ryabinin et al. 1995). Other investigators had earlier reported that a single alcohol injection induced c-*fos* expression in the periventricular nucleus of the hypothalamus, but decreased expression of c-*jun*, another IEG, both there and in the hippocampus (Zoeller and Fletcher 1994). The variation in results following relatively small changes in procedures suggests that results cannot necessarily be extrapolated to other situations.

An interesting finding of the 1997 study (Ryabinin et al. 1997) was that acute alcohol administration blocked the novelty-induced increase in Fos protein levels in several hippocampal subregions, while repeated alcohol injections lost their effectiveness. The alcohol response also seemed to be enhanced in some brain areas with chronic administration. This progressive increase, or sensitization, of alcohol's effects on IEG expression resembles the "kindling" of withdrawal responses, in which successive detoxification episodes lead to progressively more severe symptoms. Some researchers have suggested that withdrawal kindling may be a basis for some of the pathologic effects of long-term alcohol abuse on the brain. If proven to be true, this finding would suggest that aggressive treatment of any and all withdrawal episodes in human alcoholics might be beneficial (Becker 1996).

One IEG study used fear conditioning by exposing rats to a novel environment, then subjecting some of these rats to a foot shock paired with the sound of a tone (Melia et al. 1996). After 48 hours, the rats were returned to the novel environment. Reexposure to the environment alone, or to the environment plus the shock-tone pairing, induced c-*fos* expression in both the cortex and the hippocampus. Administration of alcohol before each exposure eliminated the c-*fos* response to novelty and fear conditioning in the hippocampus and attenuated it in the cortex. Other experimenters have also reported that fear-conditioned stimuli induce c-*fos* in both these brain structures, as well as in nearly all of 58 other brain structures studied (Beck and Fibiger 1995).

Investigators have used c-*fos* expression mapping to compare the responses of rodent genotypes known to differ in alcohol sensitivity. One study used two commonly studied inbred mouse strains for their differential behavioral sensitivity to alcohol. The objective of this study was to elucidate differences in areas of the brain that might underlie these differences in sensitivity. The two strains were DBA/2J mice, which are extremely sensitive to alcohol-induced locomotor stimulation, and C57BL/6J mice, which are nonresponsive to this stimulation (Hitzemann and Hitzemann 1997). Several low-to-moderate doses of alcohol increased Fos-like immunoreactivity (an immune-based measure of the presence a protein) in selected limbic areas of the brain in both strains, but the central amygdala in particular was much more responsive at all doses in the DBA/2J strain. There were generally no strain differences in the basal ganglia. The limbic areas are associated with emotion and behavior, while the basal ganglia are associated with motor coordination.

Another IEG study used paired strains of rats genetically selected for alcohol preference or avoidance. Using alcohol-preferring (P) and nonpreferring (NP) rats and Finnish paired strains of alcohol-preferring (AA) and alcohol-avoiding (ANA) rats, investigators studied responses in different areas of the brain to two doses of alcohol compared with saline, using c-*fos* expression as a marker of neuronal activity (Thiele et al. 1997). Several brain areas responded with increases in Fos-like immunoreactivity, and increases in some brain areas were dose dependent. The principal difference characterizing the P and AA rats (vs. NP and ANA rats) was a greatly attenuated response to the high alcohol dose (3 grams per kilogram of body weight) in the locus ceruleus, suggesting that this brain region may play a role in mediating the differences in alcohol preference in these paired strains.

The use of IEG expression to map brain areas for response to alcohol is clearly a growing field of interest, even though these studies of IEG are technically demanding and immediate interpretation may be difficult. Recent experimental results using this approach suggest that alcohol

does indeed preferentially affect specific brain areas, and this hypothesis can now be tested in a variety of ways that will further our understanding of the genetic bases for individual differences in susceptibility to the development of alcoholism.

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Genetic and Psychosocial Influences

Alcohol is available to any adult—and illegally to many minors—in the United States. While a sizeable minority of the population abuses alcohol, most persons abstain or drink safely. In families in which there is abusive drinking, children have an increased risk of abusing alcohol themselves, but most do not develop problems. Understanding why alcohol leads to trouble for many, but not most, people exposed to it is the goal of research on the etiology, or cause, of alcohol abuse and alcoholism.

It is already clear that some vulnerability to developing alcohol-related problems is conveyed genetically, and the idea that inheritance can take many forms has emerged from animal research. Studies in mice have demonstrated that various individual genes or groups of genes can shape very distinct responses to alcohol: for example, a preference for alcohol over water, sensitivity to its intoxicating effects, and the tendency to develop tolerance to it. By identifying the proteins these genes encode and the mechanisms by which the genes influence an animal's biochemical response to alcohol, scientists can gain insight into the features of human alcoholism and provide a basis for developing pharmaceuticals that short-circuit these genetically defined processes.

On a broader scale, one of the goals of research on genetics in humans is to determine to what extent individual differences in alcohol-related behavior are due to genetic versus environmental influence. A recent study in twins found that as much as two-thirds of the variability in drinking behavior in one population could be attributed to genetic factors in both men and women. Other twin studies are investigating the relative magnitude of various influences—genes, parental drinking, and peer influence—on alcohol consumption in youth. Identifying the genes that convey risk of alcoholism is a second major goal of genetic research; scans of the human genome reveal evidence of genes influencing alcoholism in certain chromosomal regions, including one stretch that has plausible candidate genes already known to be located there.

Understanding how inborn vulnerability plays out in the temperament and behavior of an individual in the milieu of parents, peers, and culture is the goal of psychosocial research on the cause of alcoholism. The traits and family characteristics found in children at risk because of a family history of alcoholism also predict risk in children of nonalcoholic parents. If alcoholism represents the end result of a sequence to which many factors contributed—inborn temperament and physiologic response to alcohol, effectiveness of parental nurturing, peer environment, and culture—then the hope is that by understanding the contributors and how they interact, it also will be possible to intervene before vulnerability becomes a destructive illness.

Animal Genetic Studies on Alcoholism

Vulnerability to alcohol dependence and abuse is partly determined by genes. Numerous studies of twins and their families and of different racial/ethnic groups have confirmed this link (Ferguson and Goldberg 1997), but much work remains to be done to identify these genes and understand their role in alcohol abuse and dependence.

Some diseases, such as cystic fibrosis and Huntington's disease, are the result of a change in a single gene. No single gene is responsible for alcohol abuse and dependence, however. Many genes that play roles in a variety of normal human behaviors and sensory perception are involved. Research has not yet pinpointed specific genes that "predispose" a person to alcohol abuse or dependence. Once researchers know the genes and the proteins these genes encode, they will have potent targets for the exploration of the biochemical processes that underlie the response to alcohol.

Identifying all the genes involved is a project of enormous magnitude and difficulty, because of the size of the human genome and the complexity of the behaviors involved in abusive drinking and dependence. The human genome (the sum total of genes carried by each person) consists of approximately 100,000 genes located on 23 pairs of chromosomes. Each gene produces a different protein, and each protein has a specific role in chemical processes in the body that shape how people look, think, feel, and behave. The Human Genome Project (HGP) (supported in the United States by the National Institutes of Health and the U.S. Department of Energy) has been an important impetus to the search for genes related to alcohol behavior. HGP researchers are working toward the goal of identifying every gene and the protein it encodes and mapping each gene to a precise location (locus) on one of the chromosomes. This research is providing the tools with which scientists can investigate the genetic underpinnings of a range of human disorders and conditions, including alcohol abuse and dependence. For example, accurate locations have been determined for thousands of the 80,000 to 100,000 genes in both the human and mouse genomes. As gene mapping progresses, investigators use the knowledge about the locations of these "marker" genes to localize other genes in relation to them. All genetic mapping using rodents, for example, relies heavily on research that has identified genetic markers spanning the entire genome of the mouse and rat (Bihoreau et al. 1997; Dietrich et al. 1994).

Quantitative Trait Loci

If alcohol preference were a single-gene trait, the identity of the gene would conceivably be known by now. Researchers would have discovered that alcohol-dependent mice consistently share a limited (though large) number of marker genes. Because the genetic maps of the mouse and rat are densely covered with known markers, it would then be a relatively simple experimental problem to systematically narrow the search to a single chromosomal region. At that point, the region would be small enough that all the genes in this region could be individually examined for alterations that cause different strains of mice or rats to have differences in alcohol preference.

However, vulnerability to alcohol dependence in humans and alcohol preference in animals (along with many other behavioral responses to alcohol) are complex behaviors that are determined by multiple genes. Such traits are known as multigenic or quantitative traits. Rather than being simply present or absent, such traits are expressed along a spectrum from high to low. Moreover, many genes play a role in contributing to such traits. A technique developed in recent years for conducting the search for genes influencing such traits is called quantitative trait locus (QTL) mapping (Lander and Botstein 1989; Tanksley 1993).

QTL mapping analysis provides a means of locating and measuring the effects of a single QTL on a trait, or phenotype. The markers allow identification of probable locations of genes that influence alcohol-related behaviors. These locations can then be verified using other tests, and specific genes can be sought there (Grisel and Crabbe 1995).

Mapping of a gene—assigning it a position relative to existing markers on a chromosome—is based on the concept of linkage: genes that are close together on the chromosome are more likely to be inherited together than are two genes farther apart. Linkage reflects the fact that when the deoxyribonucleic acid (DNA) strands that constitute paternal and maternal chromosomes recombine after fertilization, a piece of DNA on one chromosome is exchanged for its counterpart on the paired chromosome. The result is a chromosome that contains some maternal genes and some paternal genes. The greater the distance between two genes on the chromosome, the less likely that both genes are from one parent. (Genes that are located on different chromosomes are inherited independently of each other.)

It is important to note that genetic effects related to alcohol that have been shown in animal studies, while certainly detectable and significant, are nonetheless relatively small in magnitude. The variation in an alcohol-related behavior or trait that can be accounted for by the underlying gene or genes (heritability) is almost always less than 40 percent. Thus, even in studies with animal models, in which the environment can be rigidly controlled, a large part of the variation in the behavior is apparently not controlled by genes. Genetic differences between human individuals are so extensive that the genes involved in alcoholism may vary from individual to individual. These factors emphasize the need to view alcohol abuse and dependence as both biologically and environmentally determined.

Creating Rodent Models

Animal genetics researchers use a variety of approaches to selectively breed mice and rats that display alcohol-related traits or behaviors (phenotypes) similar to those of humans. Examples of these phenotypes are alcohol preference, sensitivity to alcohol's hypnotic (sleep-inducing) effects, hypothermia (lowered body temperature) after alcohol ingestion, and behavioral activation (mice that become highly active after drinking are believed to model alcohol's euphoric effects) (Crabbe 1989; Crabbe et al. 1994*a*,*b*). Finding specific genes associated with drinking in animals should provide clues to the genetic underpinnings of alcohol's reinforcing properties, a key to its addictive potential, and insight into individual differences in sensitivity to alcohol's effects. It is known from studies in humans that abnormally low sensitivity to alcohol's effects predicts greater risk for alcoholism later in life (Schuckit 1994).

Because humans and rodents share most of their genes and because these genes produce proteins involved in identical physical processes in both species, the results of animal genetic studies can provide insights into human genetics. Studies of animal genetics are useful because of fundamental limitations in human genetic studies. Researchers cannot manipulate the genomes of human subjects by breeding them in a laboratory or causing mutations in or otherwise manipulating their genes. Neither can they control all the variables in a person's environment. The genetic blueprint of each human subject—except for those of identical twins—is unique, as are each person's background and experiences.

In contrast, laboratory researchers can control the mating of mice and rats over many generations and thereby produce strains of animals in which individuals in each strain are genetically identical. Furthermore, researchers can control the environments of the animals: what they eat, their lifetime access to alcohol, the amount of light they receive, the number of other animals they interact with. Because of the high degree of the animals' genetic similarity and the extent of environmental control, researchers can attribute the differences in an alcohol-related behavior between two genetically dissimilar animal strains to differences in their genetic makeup.

Many researchers use mice from recombinant-inbred (RI) strains, especially mice from the BXD series, which contains 25 different strains. The series was created by crossing two "parental" mouse strains (C57BL/6J and DBA/2J) that are genetically distinct and differ from each other phenotypically in many ways, including many traits related to alcohol action. Next the researchers "inbred" many different pairs of offspring (brother-sister mating), which resulted in different strains of mice. Each mouse within a strain is genetically identical to every other mouse in that strain, but between any two of these strains only 50 percent of their genes are shared—the same amount that human siblings share. Thus, the different alcohol-related traits observed in the parents were "sorted" into individual animals and then "fixed" genetically.

Much of the research described below has narrowed the search for genes responsible for observed phenotypic differences in rodents to possible regions on the chromosomes. Only a few studies have used techniques that allow researchers to say with a high degree of certainty that these regions are the actual sites of the genes and not "red herrings" created by imperfections in their mapping methods. In still fewer studies have researchers concluded that they are very likely at the site of the gene. The researchers in these studies worked largely with BXD mice and with other inbred mice known as LS x SS (LS, or "long-sleep," crossed with SS, or "short-sleep") strains. (LS mice are much more sensitive to the sedative effect of alcohol than SS mice are.) In some cases, RI mice from different strains differ in their preferences for alcohol. When offered two bottles of water, one bottle with plain water and one with alcohol mixed with water, a mouse from one RI strain will display preference for the alcohol-water mix, while a mouse from another RI strain will strongly avoid it, and a mouse from yet another strain will have an intermediate preference. The task for researchers then becomes to look for differences in the genetic makeup of these RI strains that might account for some of the differences in their alcohol preferences.

Some researchers work with types of mice other than RI mice. As will be explained below, doing so allows them be more certain about the locations of the alcohol-related genes they map, but at a much greater investment of effort. One type of mice they use is F_2 mice, which is the "grandchild" of a cross between two parents whose offspring are then crossed (sibling mating). The F_2 share only 50 percent of their genes with each other or with either parent. Like the RI mice, individual F_2 mice vary along the spectrum of alcohol seeking or avoidance, for example. However, each F_2 mouse has its own individual genetic profile. Researchers who work with mice other than those from RI strains have the extra task of genotyping each mouse. That is, they must sample the DNA of each mouse to generate a genetic profile.

Quantitative Trait Loci Mapping

Statistical Methods

Statistical methods play a large role in QTL mapping. They are used to measure the degree of association between a marker and the phenotype to determine the magnitude of the effect (effect size) of the QTL on the phenotype and to assess the statistical significance of the observed association between the marker(s) and the QTL (that is, to estimate the probability that the association is real and has not occurred by chance). If the QTL is close to the marker and has a large effect, then detection and mapping can be performed easily and accurately using simple methods such as regression analysis (McClearn et al. 1991). If the QTL is not close to the marker gene, the simplest statistical tests will result in a lower effect size being attributed to the QTL. A variety of methods exists for assessing the statistical significance of the observed associations. A more complex and statistically optimal method than regression analysis is "interval mapping" (Haley and Knott 1992; Lander and Botstein 1989; Markel et al. 1996). Interval mapping uses two adjacent markers, rather than a single one. The two markers block out an interval on the chromosome, and interval mapping estimates the most

probable location of the QTL in the interval between markers. More recently, still more sophisticated methods have been developed, which result in more accurate QTL mapping (Jansen and Stam 1994; Zeng 1994).

A major concern in QTL mapping is that in any given attempt to assign a QTL to a location on the chromosome, researchers use many independent statistical tests because, as noted above, they are assessing so many individual associations and effects. Under these conditions, statistical principles require researchers to make appropriate corrections to their results to avoid mistaking a random association between a chromosomal region and a trait for a biologically real one. That is, each independent test has a margin of error, and when many tests are conducted, the cumulative effect of the errors must be accounted for (Lander and Kruglyak 1995; Lander and Schork 1994). Such corrections affect the significance of results—that is, they reduce the level of certainty about whether a QTL is really located at the point on the chromosome indicated by the experiment (Belknap 1992, 1998; Belknap et al. 1996; Lander and Kruglyak 1995; Lander and Schork 1994; Neumann 1992).

Recent Studies of Alcohol-Related QTL's

Since the publication of the *Ninth Report to the U.S. Congress on Alcohol and Health* (National Institute on Alcohol Abuse and Alcoholism 1997), researchers have used the techniques described in the previous sections to identify provisional QTL's for genes involved in a number of alcohol-related phenotypes exhibited by mice. Alcohol preference is a phenotype of particular interest—it is thought to reflect the rewarding properties that are closely related to alcohol's addictive potential. Several studies have mapped provisional QTL's for alcohol preference in RI mice. In one series of experiments, mice were given a simple two-bottle choice of drinking water (one with alcohol and one without) (Rodriguez et al. 1995). Another study used a more sophisticated two-bottle-choice method, varying the amount of alcohol and adding saccharin to the water and to the alcohol-water mix (Phillips et al. 1994). Another way to measure alcohol preference is to train mice to expect to receive a shot of alcohol when they go to a certain location in their cage and to observe whether they seek out that location when placed in the cage (conditioned place preference) (Cunningham 1995).

QTL mapping in rodents uses all of the techniques described above: (1) rodents that differ in genes involved in alcohol-related traits and behaviors are crossed (either RI mice or other types), (2) a number of individual mice are tested for the extent to which they display the phenotype, (3) the pattern of genetic markers in each of these mice is determined, (4) statistical tests are conducted to determine whether any of the variation in the phenotype is significantly associated with any marker, and (5) further statistical tests are performed to determine the extent to which the marker affects the expression, or predicts the variation, of the quantitative trait.

Several studies in RI mice have mapped provisional QTL's for sensitivity to alcohol's effects. Mice that become highly active after ingesting alcohol are thought to model alcohol's euphoric effects, and investigators have examined behavioral activation with low doses of alcohol in a one-time (acute) administration and repeated administration (Phillips et al. 1995, 1996). Another indicator of sensitivity to alcohol is loss of righting reflex, a measure of how long it takes for a mouse to right itself after being placed on its back (Markel et al. 1996; Rodriguez et al. 1995). Other research has looked at rapid development of tolerance to alcohol's effects (Gallaher et al. 1996).

The studies in RI mice show that genes have a significant effect on alcohol-related traits and behaviors. Although many of these provisional QTL's will be subsequently confirmed by more refined studies, an unknown number—probably more than half—will likely be found on further examination to be false positives. Researchers are concerned about a second problem with use of the RI strains in gene mapping—that of false negatives, or missing QTL's that are really there. For these reasons, several researchers have

emphasized that subsequent confirmation of provisional QTL's is a statistical necessity (Gora-Maslak et al. 1991; Johnson et al. 1992). Investigators now combine RI mapping and other approaches to provide the necessary confirmation (Belknap et al. 1997; Bennett et al. 1997; Buck et al. 1997; Dudek and Tritto 1995).

However, few studies using the newer methods have been undertaken, largely because they are labor-intensive. These studies are not conducted with RI mice, because of the low statistical power inherent in their use. The studies rely instead on the analysis of various kinds of offspring from matings between inbred parental strains. These offspring (typically, the F_2 generation) vary extensively from one another, both in their alcohol-related behaviors and in their genetic patterns. Any two mice in such an experiment are as related to each other as two human siblings—in other words, they share 50 percent of their genes on average. Use of such mice involves phenotyping and genotyping each individual mouse. Because some experiments have used more than 1,000 mice (Markel and Corley 1994; Markel et al. 1997), performing the necessary assessment of the individual mice for about 100 marker genes throughout their genomes involves 100,000 individual assays. These procedures are time-consuming and costly. It has been estimated that verification of a QTL using this approach represents 2 to 5 person-years of work, depending on the method, the extent of automation, and other factors. The benefit is that the statistical tests used to detect associations between marker genes and phenotypes and to examine the effect size of the QTL on the phenotype produce results that are considerably more reliable because of the extensive variation in the sample examined (in effect, a sample of 1,000 or more versus a sample of 25 using the BXD RI mice).

One study screened the entire genome for major QTL's that might be involved in alcohol preference, and two were identified (Melo et al. 1996). The two QTL's are gender specific, with *Alcp1* being specific to males and *Alcp2* being specific to females. An important series of studies focused on sensitivity to alcohol's sedative-hypnotic effects as measured by loss of righting reflex (Markel and Corley 1994; Markel et al. 1996, 1997). It is important to note that of 12 provisional QTL's previously found in LS x SS RI mice, only 2 or 3 (*Lore1* and *Lore2* and possibly *Lore5*) were confirmed to be real. However, two of the five major QTL's were detected, which suggests that use of RI's may be a more powerful method for mapping QTL's than pure statistical methods suggest (also see Belknap et al. 1997). Three QTL's for withdrawal have also recently been confirmed (Buck et al. 1997).

Shared Gene Actions

In other QTL mapping applications, investigators are interested in whether two distinct phenomena, such as sensitivity to alcohol's effects and alcohol tolerance, result from the same underlying suite of genes rather than entirely separate QTL's. Because of the large number of diverse alcohol-related behaviors currently being investigated, finding whether some gene actions are shared is an important area for further work.

One study concluded that sensitivity and tolerance are not mediated by common genetic factors (Phillips et al. 1996). In contrast, other researchers have presented evidence suggesting commonality in function between genes for sedative-hypnotic sensitivity to alcohol and genes that specify the distribution and levels of a chemical in the brain, neurotensin, that plays a role in addiction (Erwin et al. 1997). Another study evaluated the relationship between sensitivity and tolerance by using three traits: (1) alcohol-induced hypothermia (lowering of body temperature after alcohol ingestion), (2) ataxia (incoordination) as reflected in the animals' ability to remain balanced on a revolving rod (rotarod), and (3) ataxia as indicated by their ability to negotiate a grid on the floor of their cage without stepping through its holes (Crabbe et al. 1996*b*). These investigators were surprised to learn that most measures were not correlated, which indicated that the traits had different genetic determinants. In general, there appear to be many more cases of different genes determining different measures of alcohol action, with relatively little commonality.

Identification of Genes Underlying a QTL

No one has identified the individual gene responsible for differential alcohol sensitivity in rodent models. A number of candidate genes have been proposed (for example, *Htr1b* [Crabbe et al. 1996*b*]) in alcohol action (Crabbe et al. 1996*a*), but whether any candidate is actually the gene underlying the QTL remains to be demonstrated. It seems almost certain that within the next several years the genes underlying several QTL's for diverse alcohol-related phenotypes will be identified. A variety of tools for fine-scale genetic mapping are now available (see review by Darvasi 1998), and these are already being applied to alcohol-related behaviors in an effort to narrow the region of interest.

Investigating Gene Function

QTL analysis provides a means of locating and measuring the effects of a single QTL on a trait, or phenotype (Grisel and Crabbe 1995). Another goal of genetic research on alcohol is to determine the biochemical mechanisms that underlie the actions of specific genes involved and how genetic variations manifest themselves in the behavior of a living organism. The section "Genetic Studies of Alcohol's Actions on the Brain" in the previous chapter discusses research approaches using genetic engineering techniques in animals.

Studies in Invertebrates

Studies of invertebrate species have shown clearly that alterations in single genes can lead to differential alcohol sensitivity. Both *Drosophila melanogaster* (fruit fly) and *Caenorhabditis elegans* (a nematode, a kind of worm) offer considerable promise for identifying individual genes that are involved in alcohol-related behaviors and traits (reviewed in Diamond and Gordon 1997). A number of mutations that alter sensitivity to anesthesia have been shown to affect alcohol sensitivity in the nematode (Morgan and Sedensky 1995). In a recent study, researchers reported that they had discovered a strain of fruit fly that they labeled "cheap date," because, like some humans, these fruit flies were affected by much lower doses of alcohol than others (Moore et al. 1998). To conduct the study, the researchers created thousands of fruit flies in which genes were randomly "knocked out," or disabled, so that the genetically altered strains were unable to produce proteins encoded by the disabled genes. The fruit flies were put inside a large glass column, and alcohol vapor was pumped in to see which ones were more sensitive to its effects. Fruit flies like to stay near the top of the column, which has mesh landings at different levels. As they became inebriated, the fruit flies in the study fell from landing to landing, most reaching the bottom in 20 minutes. Individuals from the "cheap date" strain, which tumbled to the bottom in 15 minutes, were found to be defective in a gene that is known as "amnesiac," so called because fruit flies without this gene have been shown in other studies to have very poor memories. The amnesiac gene stimulates production of a chemical messenger called cyclic adenosine monophosphate (cAMP), which is involved in many key processes in both fruit flies and humans, including memory and responses to some hormones. The study showed that fruit flies with low levels of cAMP are more sensitive to alcohol (Moore et al. 1998). The results suggest that individual differences in the production of cAMP in certain brain cells may contribute to alcohol sensitivity in humans. Results like these provide valuable knowledge to other researchers looking for ways to prevent and treat alcoholism.

In Closing

The ultimate use of QTL studies is the identification of the genes underlying the QTL's. The cloning of these genes would allow a rapid exploration of the biochemical underpinnings of alcohol action and would link behavioral change to underlying genetic predisposition and biochemical action. Although human alcoholism is likely to result from genetic variations different than those found in rodents, the genes identified in mice are almost certain to have human homologues that are also involved in alcohol action and that may predispose to human alcoholism. Such genes and the proteins they encode are potent targets for intervention, both diagnostic and pharmacologic. It seems certain

that these results will be exploited dramatically in the next century to provide a variety of "designer drugs," perhaps targeted to individual problems associated with particular forms of alcohol abuse. Genetic diagnosis in humans could also be used to suggest particular forms of behavioral intervention well before the manifestation of any alcoholic behavior.

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Recent Progress in the Genetics of Alcoholism

At the time of publication of the *Ninth Special Report to the U.S. Congress on Alcohol and Health* (National Institute on Alcohol Abuse and Alcoholism 1997), twin, family, and adoption studies had very firmly established major roles for both genetics and environment in the etiology of alcoholism in men. Although the earlier studies had failed to detect a genetic component of alcoholism in women, the newest studies at that time were beginning to suggest that alcoholism is as strongly genetically influenced in women as it is in men. Since alcoholism does not follow the simple rules of Mendelian inheritance in multigenerational pedigrees, it was clear that alcoholism is a genetically complex disorder, influenced by multiple genes (their precise number unknown) that interact in an unknown fashion with each other and with similarly unknown environmental factors to produce the disease. It also seemed highly likely that alcoholism is genetically heterogeneous, meaning that individuals in different families develop alcoholism under the influence of different predisposing genes. Some twin studies had also begun to suggest a partially shared genetic influence on both alcohol and tobacco use.

Just two of the genes influencing predisposition to alcoholism were known. A defective allele (variant) of the gene *ALDH2*, common in Asian populations, had long been known to substantially (although not completely) protect carriers from developing alcoholism by making them uncomfortable or ill after drinking alcohol. The *ALDH2* gene encodes aldehyde dehydrogenase, one of the two key liver enzymes involved in the metabolism of alcohol to its final end product, acetate. The illness resulting from the defective allele tended to prevent carriers from drinking enough alcohol to become addicted to it. Newer studies were beginning to suggest that alleles of *ADH2* and *ADH3*, genes encoding two forms of liver alcohol dehydrogenase (the enzyme that carries out the first step in alcohol metabolism in the liver), also protected carriers from developing alcoholism, albeit to a lesser extent than did the defective allele of *ALDH2*. The protective alleles of *ADH2* and *ADH3*, also common in Asian populations, encode forms of alcohol dehydrogenase that metabolize alcohol to acetaldehyde more rapidly than other forms of these enzymes do. This rapid metabolism leads to a greater buildup of this toxic product in the bloodstream after consumption of alcohol, thereby producing feelings of discomfort and illness and tending to discourage carriers of these alleles from consuming large amounts of alcohol.

Finally, there was a large controversy about the role in the etiology of alcoholism of a particular allele of *DRD2*, a gene encoding a particular form of brain receptor for dopamine. Dopamine is a neurotransmitter that plays a central role in brain pathways and that mediates the rewarding properties of alcohol and other drugs of abuse. While a large number of papers had concluded that this allele was associated with alcoholism, an even larger number of papers had reached the contrary conclusion. Questions were raised about the methodological validity of a number of the studies and their corresponding findings, the reasons for the inconsistent findings, and—even when the validity of some of the findings was assumed—their precise biological significance.

Findings from Twin/Family Studies

The classic twin study design compares the resemblances for a trait of interest between monozygotic (MZ, identical) twins and dizygotic (DZ, fraternal) twins, in order to determine the extent of genetic influence, or heritability, of the trait. Heritability can be calculated because MZ twins are genetically identical, whereas DZ twins share only half their genes. The method relies on the "equal-environment assumption," that is, that the similarity between the environments of both individuals in a pair of MZ twins is the same as the similarity between the environments of members of pairs of DZ twins. While earlier

twin studies have been severely criticized for not testing this assumption sufficiently, researchers have taken care more recently to collect data on the twins' environments, thereby allowing correction of results for any deviation from this assumption. While twin studies do not identify specific genes influencing a trait, they do provide important information on the trait's genetic architecture (more general properties of its inheritance pattern, such as whether genes act independently of one another, or in concert, to influence a trait), which aspects of the trait are most heritable, whether the same genes are influencing the trait in both genders, and whether multiple traits share any common genetic influences. When data on twins are augmented by data on their family members, the study is termed a twin/family study and can provide more precise information about whether parents transmit a behavioral trait to their offspring genetically or via some aspect of the familial environment (cultural transmission). When detailed data about the environment are collected, twin and twin/family studies can provide information about how environmental factors interact with genetic predisposition to produce a disease.

While earlier twin studies have firmly established substantial heritability of alcoholism in men (on the order of 50 percent), they have generally failed to detect heritability in women. This failure may be due, in part, to the lower rate of alcoholism among women than men, thereby necessitating larger sample sizes to achieve statistically significant results. Since the first studies to report a substantial heritability of alcoholism in women (Kendler et al. 1992), others have reported analysis of a sample of volunteer adult Australian twins consisting of 1,328 MZ pairs and 1,357 DZ pairs (distributed among all possible combinations of genders) (Heath et al. 1997). Of these subjects, about 25 percent of the men and about 6 percent of the women met DSM-IIIR criteria for alcohol dependence. (DSM-IIIR refers to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised,* a standard classification system for mental disorders [American Psychiatric Association 1987].) Analysis of the concordances for alcoholism among the various classes of twins suggested that about two-thirds of the risk of becoming alcoholic was genetically mediated in both men and women, with the remainder of the risk determined by environmental factors not shared by the two members of a given twin pair. The data provided no evidence for a difference in the degree of heritability in men and women, nor any evidence for genetic factors operating in one gender but not the other. This last conclusion was particularly aided by analyses of data from opposite-sex twin pairs, a type of analysis not previously reported. Using the same subject sample, these researchers have more recently demonstrated that childhood conduct disorder is significantly associated with risk for adult alcohol dependence in both men and women, with genetic factors accounting for most of the association in both genders (Slutske et al. 1998). These findings further emphasize the similarities in factors leading to alcoholism in men and women and suggest either that there are common genetic risk factors for conduct disorder and alcoholism in both genders, or that conduct disorder is itself a genetic risk factor for alcoholism. Since the subject sample for these studies came from the general population and because most of the alcoholics contained therein were relatively mildly affected, it is possible that the conclusions of these studies might not apply to very severely affected alcoholics, such as those identified from treatment centers.

Since individuals who eventually become alcoholic typically begin experimenting with alcohol use during adolescence and then proceed through stages of increasingly heavy use until they become addicted, investigators have long been interested in factors influencing initiation of alcohol use during adolescence. The notion that adolescents learn to use alcohol by modeling the alcohol use of their parents is an old one. Investigators tested this notion in a sample of 1,396 Dutch families, each consisting of a pair of adolescent twins and their parents (Koopmans and Boomsma 1996). The twins' alcohol use resembled that of their parents to some extent. For 17-year-olds, this resemblance could best be explained by genetic similarity of children to their parents, rather than

by children modeling their parents' drinking behavior. For 15- to 16-year-olds, while the resemblance of the children's drinking to that of their parents was explained principally by some aspect of the familial environment, the parents' drinking behavior itself accounted for, at best, only a small part of this resemblance. It appears from this study that children's drinking behavior is influenced primarily by genetic factors and by environmental factors other than their parents' alcohol use. This conclusion is consistent with findings from previous studies demonstrating strong peer influences on adolescent alcohol use.

Many, but not all, alcoholics suffer from medical complications of alcoholism, such as liver cirrhosis, pancreatitis, cardiomyopathy, or psychosis due to brain damage. The inconsistency with which medical complications occur in alcoholism has led to the plausible hypothesis that susceptibility to these complications is influenced by genetic factors independent of those influencing susceptibility to alcoholism itself. Researchers tested this hypothesis using 5,933 male MZ twin pairs and 7,554 male DZ twin pairs from the U.S. World War II Era Veteran Twin Registry (Reed et al. 1996). From this sample, 1,239 subjects had a diagnosis of alcoholism according to ICD-9 criteria (one of the two major classification systems used in *International Classification of Disease, Ninth Revision*, to diagnose mental disorders, including alcoholism [World Health Organization 1977]), 392 subjects had liver cirrhosis, and 242 subjects had alcoholic psychosis. Of the alcoholic subjects, 818 had neither cirrhosis nor psychosis, and 421 had either or both of these complications. From the MZ and DZ concordance rates for the three diseases, the investigators calculated heritabilities of 0.59 for alcoholism (in general agreement with results of other studies), 0.47 for liver cirrhosis, and 0.61 for alcoholic psychosis. For each trait, the remainder of the variance in susceptibility was due to environmental factors not shared by members of a twin pair. Using an analytic method that allowed for simultaneous analysis of all three diseases, the investigators calculated that 85 percent of the overall genetic risk was shared for alcoholism, cirrhosis, and psychosis. The small amount of genetic risk not accounted for by these shared factors was due to separate genetic factors for cirrhosis and psychosis, respectively. Although the role of these disorder-specific genetic factors was small, it was significant; removing these factors from the mathematical model resulted in a significantly worse fit to the data. The conclusion about the largely shared genetic susceptibility to all three diseases differs from that of an earlier analysis of part of these data (Hrubec and Omenn 1981), largely as a result of the more sophisticated analytic methods employed.

Why is so much of the genetic part of the risk for cirrhosis and alcoholic psychosis due to factors influencing the risk for alcoholism itself? Overall genetic risk for cirrhosis or psychosis refers to those genetic factors influencing the transformation of a normal (nonalcoholic) person into an alcoholic with cirrhosis or psychosis, respectively. The physiologic pathways leading to these medical complications pass obligatorily through alcohol addiction itself, presumably because such addiction is a precondition for the sustained high levels of consumption necessary to bring about the medical complications. There are multiple pathways leading to alcoholism, each with multiple steps. It seems likely that human populations contain a large amount of variation in the genes influencing many of these steps, leading collectively to a large genetic risk. If the physiologic pathways leading to cirrhosis and psychosis, *given that an individual is already consuming large amounts of alcohol*, are relatively simple with relatively few steps, then there will be relatively few opportunities for genetic variation to influence those steps. Alternatively, regardless of the number of steps in this part of the pathway, human populations might contain relatively little variation in the genes influencing these steps. Either of these situations would result in cirrhosis-specific and psychosis-specific genetic factors accounting for only a small part of the overall genetic risk for these complications.

While many observers have noted that alcoholics smoke very heavily, the reasons for this dual substance use have been poorly understood. Recent twin studies are shedding considerable light on the reasons for this phenomenon. In

one such study, researchers analyzed tobacco and alcohol use versus nonuse in a sample of 2,612 adolescent and young adult Dutch twin pairs (Koopmans et al. 1997). At all ages tested (12 through 25 years), regular alcohol use was highly correlated with regular tobacco use. For 12- to 16-year-olds, shared environmental factors were the principal influence on both alcohol and tobacco use. The same environmental factors (peer pressure very likely prominent among them) influenced both smoking and drinking. For 17- to 25-year-old men, both alcohol and tobacco use were highly genetically determined, with shared environmental influences playing a significant but lesser role. For 17- to 25-year-old women, alcohol use was highly genetically determined, and tobacco use was influenced by both genetic and shared environmental factors. The same genetic factors influenced both alcohol and tobacco use, both in young adult men and women. These findings suggest that while initial exposure to alcohol and nicotine is environmentally influenced, persistence in using these substances is under strong shared genetic influence.

Other investigators analyzed alcohol and tobacco use in 173 adult male MZ twin pairs and 183 adult male DZ twin pairs from the U.S. World War II Era Veteran Twin Registry (Swan et al. 1996). In this sample, both alcohol and tobacco consumption were approximately equally influenced by genetic and shared environmental factors. Correlations between alcohol and tobacco use were largely explained by a common genetic factor influencing use of both substances. There were also specific genetic factors influencing the use of either substance individually. Environmental factors influencing alcohol use were apparently different from those influencing tobacco use. These observations applied to the average range of alcohol and tobacco use, not heavy use. The same investigators analyzed heavy alcohol use (more than 67 drinks per month) and heavy tobacco use (more than 30 cigarettes per day) in a sample of 749 MZ twin pairs and 1,267 DZ twin pairs from the same registry (Swan et al. 1997). The threshold for heavy substance use was set at the top 20 percent of the range of quantity consumed, excluding nonusers from the distribution. This study demonstrated a common genetic influence on both heavy alcohol use and heavy tobacco use as well as genetic influences specific to the heavy use of each substance individually.

The physiologic mechanism of the shared genetic influence on alcohol and tobacco consumption is currently a matter of speculation, as illustrated by the following two hypotheses: Individuals with high reactivity to stress may use both substances for stress relief. Alternatively, use of either substance may induce physiologic tolerance to the other, leading to a need to consume greater amounts of the latter substance in order to experience a subjective effect. Independent twin studies have identified a shared genetic influence between alcoholism and depression (Kendler et al. 1993*a*), as well as between smoking and depression (Kendler et al. 1993*b*). The shared genetic influence on smoking and drinking could thus be related to their respective connections to depression. One study analyzed the relationship between tobacco use and perceived intoxication after consumption of a controlled dose of alcohol in a small sample of Australian twins (194 pairs) (Madden et al. 1997). This exploratory study suggested a complex genetic relationship in women between use of and responses to alcohol and tobacco. There appear to be at least two independent genetic factors involved, one influencing both alcohol and tobacco use, and another influencing smoking and feelings of intoxication after alcohol use but not alcohol use itself. The investigators found that subjects who smoked felt less intoxicated than those who did not. Further laboratory studies are needed to elucidate the biochemical and pharmacologic basis of this finding. The negative genetic correlation between smoking and sensitivity to alcohol, combined with Schuckit's observations that reduced sensitivity to alcohol predicts greater risk of alcoholism (Schuckit 1998), suggests that smoking may increase risk of alcoholism by reducing smokers' sensitivity to alcohol. The results of twin studies on smoking and drinking thus suggest that efforts toward prevention and treatment of alcohol abuse may benefit from inclusion of efforts to abate tobacco use.

Employing a novel conceptualization of "alcoholism treatment seeking" as a trait with both environmental and genetic influences, investigators examined the relationship between alcoholism and propensity to seek treatment for this disorder (True et al. 1996). In a sample of 1,864 MZ pairs and 1,492 DZ pairs of male, primarily Caucasian twins from the U.S. Vietnam Era Twin Registry (composed of pairs of twins who had served in the U.S. armed services between 1965 and 1975), about one-third of the subjects met DSM-IIIR criteria for alcohol dependence. Consistent with other twin studies, genetic influences accounted for 55 percent of the variance in alcoholism risk, with unshared environment accounting for the remainder of the variance. Tendency to seek treatment for alcoholism was highly familial. A mathematical model in which genetic and shared environmental factors each explained almost half the variance in treatment seeking fit the data well. Under this model, the factors influencing treatment seeking were independent of the factors influencing alcoholism itself. While it is not surprising that shared environment influences treatment seeking (through such factors as educational and socioeconomic level), the finding of a genetic influence on the tendency to seek treatment is novel. Perhaps this effect is mediated by known genetic influences on personality.

Findings From Genetic Linkage Studies

Identifying genes influencing predisposition to alcoholism is of critical importance for improving prevention and treatment of alcoholism for two principal reasons. First, it will permit identification of the proteins the genes encode and elucidation of the physiologic pathways in which these proteins function. Every step of every such pathway represents a potential target for prevention or intervention, for example, by design of an appropriately targeted drug. Second, knowledge of the genes influencing predisposition to alcoholism will permit better design of studies to elucidate environmental influences on alcoholism by permitting control of variation at the relevant genes in the subject sample, thereby reducing confusion about whether observed differences between experimental and control subjects are due to environmental or genetic influences.

While twin/family studies (such as those described above) can provide information about the genetic architecture of alcoholism and the relationship between genetic influences on alcoholism and other traits, they do not permit the identification of the specific genes influencing predisposition to alcoholism. Current efforts to identify such genes rely on genetic linkage and association studies. Such studies have received enormous impetus in recent years from the mapping of large numbers of human genetic markers (Broman et al. 1998)—recognizable sites along chromosomal deoxyribonucleic acid (DNA) that act as signposts for researchers—and genes (Schuler et al. 1996) under the Human Genome Project, which is supported by the National Institutes of Health and the U.S. Department of Energy, and from the development of more sophisticated statistical methods for analyzing gene mapping data (Lander and Schork 1994).

Genetic linkage studies can be designed in either of two principal ways. In the first design, investigators track the inheritance of the disease, along with that of genetic markers spanning the entire genome, through multigenerational families affected by the disease. Various complex statistical analyses permit the determination of which markers are cotransmitted with the disease. In the second design, investigators measure the degree of sharing of different marker alleles by members of pairs of siblings (or other relatives) affected by the disease. On average, simply by chance, siblings are expected to share half of the alleles of most of their genes. However, two siblings affected by the same disease will show more frequent sharing of alleles of markers close to genes affecting predisposition to, or progress of, the disease. Under either design, markers shown to be genetically linked to a disease—that is, inherited with the disease more frequently than would be expected by chance—define a chromosomal region(s) likely to contain a gene(s) influencing the disease. The advantage of this approach to gene discovery is that a sufficiently

comprehensive marker map, such as that now being assembled by the Human Genome Project, permits an unbiased search of the entire genome without requiring any prior physiologic hypothesis about which genes might influence the disease. Linkage studies work best for finding genes when the disease under study is influenced by a relatively small number of genes, each exerting a relatively large effect (Broman et al. 1998; Risch and Merikangas 1996).

The results of the first two systematic searches of the entire human genome (termed "genome scans") for genes influencing predisposition to alcoholism have recently been published. The first study, by the Collaborative Study on Genetics of Alcoholism (COGA), a National Institute on Alcohol Abuse and Alcoholism (NIAAA)-supported consortium of investigators at six centers across the United States, reported results from a primarily Caucasian-American sample of 987 individuals from 105 families (Reich et al. 1998). In order to reduce errors in classification of subjects as alcoholic or non-alcoholic, the study defined alcohol-dependent individuals as those meeting two independent criteria for alcoholism: the DSM-IIIR criteria for alcohol dependence, and the Feighner criteria at the definite level (Feighner et al. 1972). This study found suggestive evidence for genes influencing susceptibility to alcoholism on chromosomes 1 and 7 as well as weaker evidence for a gene on chromosome 2. It also reported modest evidence for a gene reducing the risk for alcoholism on chromosome 4. An independent genome scan, based on 152 subjects from a Southwestern American Indian tribe, has been reported by investigators in NIAAA's own research laboratories (Long et al. 1998). With use of the DSM-IIIR definition of alcohol dependence, this study reported suggestive evidence for a gene influencing susceptibility to alcoholism on chromosome 11 as well as suggestive evidence for a protective gene on chromosome 4 in approximately the same region implicated by the COGA study.

Rather than identifying specific genes, these studies have implicated certain chromosomal regions as containing genes influencing susceptibility to alcoholism. Each implicated region contains hundreds of genes, and determination of precisely which genes located therein influence alcoholism will require higher resolution mapping studies in the future. It is not surprising that the two studies implicated different chromosomal regions because (1) American Indians and Caucasian-Americans (of European descent) have different genetic histories and therefore contain different genetic variation, and (2) the physiologic mechanisms leading to alcoholism in American Indians may be different from those in Caucasians. In view of these differences between the two subject populations, it is of interest that both studies found some evidence for a protective gene in the same region of chromosome 4. Plausible candidates for this gene in this region are *ADH2* and *ADH3*, which encode alcohol dehydrogenases and for which some alleles have been shown to reduce susceptibility to alcoholism in Asian populations (Whitfield 1997), and *GABARB1*, which encodes a subunit of a receptor for the major brain inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The function of this receptor is stimulated by alcohol, possibly accounting for alcohol's sedating and motor-discoordinating effects (Suzdak et al. 1986). Long-term consumption of alcohol alters the brain distribution and function of this receptor, possibly playing a role in the development of alcohol dependence (Mitsuyama et al. 1998). Further studies will be required to determine whether any of these candidates is actually the gene inferred by both linkage studies to be responsible for protection from alcohol dependence.

The investigators responsible for both linkage studies have deliberately described their findings as suggestive rather than definitive. They exercise such caution because the observed sibling allele-sharing patterns (from which they have inferred the locations of the genes) deviate significantly from randomness but not so much so that one can be absolutely certain that the inferred genes are real. Certainty about the locations of the genes will require replication of the results of these studies in independent subject samples.

Such studies are now under way. While these first two genome scans have not definitively identified genes influencing predisposition to alcoholism, they nonetheless represent a major step toward that goal. In the intermediate term, further progress will depend on the development of more sophisticated statistical methods that are capable of simultaneously analyzing data not only on alcoholism itself but also on a number of psychological and physiologic traits, such as temperament, sensitivity to alcohol, and various kinds of brain waves that may represent additional dimensions of the disease. These additional dimensions may ultimately constitute essential elements of biologically valid definitions of alcoholism, which will be a natural prerequisite for gene identification. Help in initial localization of disease genes will also come from new statistical methods for analyzing the effects of multiple genes simultaneously rather than one at a time, as most current methods do. Precise gene identification will depend ultimately on the development of a complete gene map of the human genome. It also will depend on use of genetic association studies (see below) that test the association of alcoholism with specific alleles of genes lying within chromosomal regions identified by these and other linkage studies.

Findings From Genetic Association Studies

Genetic association tests measure whether a particular allele of a gene occurs more frequently in individuals affected by a disease than in unaffected individuals. A finding of genetic association can indicate that the gene under study influences the disease. Although such tests require prior knowledge of the gene under study (unlike genetic linkage tests), they are statistically much more powerful than linkage tests for detecting genes exerting only small effects on predisposition to a disease (Broman et al. 1998; Schuler et al. 1996). They are also easier to perform than linkage tests, requiring ascertainment only of disease cases (and sometimes their parents) and controls rather than the entire nuclear families or large, multigenerational families required for linkage studies. However, since an apparent association between an allele and a disease can arise for reasons other than the influence of that allele on the disease, association studies can be highly prone to artifact and need to be carefully designed. Well-designed genetic association studies have the following characteristics (Broman et al. 1998; Schork and Schork 1998; Schuler et al. 1996):

- In case-control studies comparing unrelated affected individuals (cases) with unrelated individuals who are unaffected by the disease (controls), the controls need to be ethnically matched to the cases. Ideally, both cases and controls should come from a population that has arisen from a relatively small number of originating ancestors (Finns, French Canadians, Amish, and so on). This matching is necessary because different populations can have very different allele frequencies for reasons totally unrelated to presence or absence of disease. Comparisons of unmatched samples can thus result in artifactual associations between alleles and disease.

- An alternative approach to avoiding the ethnic matching problem is to use a family-based study design, which compares alleles transmitted to affected offspring by their parents with the parental alleles that were not transmitted, thereby avoiding use of a separate control group. Several analytic methods have been developed for this type of study design, for example, the haplotype relative risk method (Knapp et al. 1993) and the transmission-disequilibrium test (Spielman and Ewens 1996).

- When possible, haplotypes (clusters of genetic polymorphisms, or variations in the DNA sequence, occurring within a small chromosomal region) should be analyzed rather than merely single polymorphisms (Kidd et al. 1996). Such analyses yield a more accurate picture of the relationship between the disease-causing polymorphism and the surrounding chromosomal region.

- The polymorphisms analyzed should cause demonstrated functional alterations in the proteins encoded by the genes under study. In

cases where several genes are known to lie close to the site of the polymorphism being studied, demonstration of functional alteration in the protein product of one of these genes can help decide which of these genes is actually related to the disease.

- Findings should be replicated in independent subject samples.

An excellent example of studies meeting many of the design criteria listed above was a group of seven that focused on the association of the alcohol dehydrogenase genes *ADH2* and *ADH3* with alcoholism. These studies, done in various ethnically matched Asian subject samples, were meta-analyzed in an effort to measure to what extent genetic variation in these genes affects the risk of alcoholism (Reich et al. 1998). Meta-analysis is an approach that involves the use of specialized statistical methods to pool data from several studies. The polymorphisms analyzed have been demonstrated to result in changes in the speed with which the enzymes metabolize alcohol to form acetaldehyde. The results are also consistent across the seven studies included in the meta-analysis. Thus, it can now be regarded as firmly established that alleles encoding faster metabolizing forms of *ADH2* and *ADH3* reduce the risk that carriers of these alleles will develop alcoholism.

As mentioned in the introduction of this section, many association studies of alcoholism with the dopamine receptor gene *DRD2* have been published (Feighner 1972), with strikingly conflicting results. Many of these studies do not meet the design criteria listed above. However, some do meet these criteria, and results of these best designed studies are consistently negative. Researchers studied the association with alcoholism of an allele of *DRD2* known to produce a receptor defective in intracellular signaling in a Southwestern American Indian tribe, analyzing haplotypes rather than just this single allele (Goldman et al. 1997). Their results—no association of the defective allele with alcoholism—were similar to those of another study analyzing the same allele in Germans (Finckh et al. 1996). A third group of investigators using the transmission-disequilibrium test (one of the analytic methods mentioned above developed for family-based studies) analyzed three different DRD2 polymorphisms in a large U.S. sample (principally Caucasian) from the COGA study and found no association of any of these polymorphisms with alcoholism (defined in any of three different ways) (Edenberg et al. 1998). These negative findings do not mean that the dopamine receptor D2 plays no role in the process of addiction to alcohol. Indeed, there is excellent evidence from pharmacologic studies in both humans and animals that this receptor (as well as the entire dopaminergic pathway) plays a major role in brain reward circuits, the function of which is altered by addiction. Rather, the results mean that genetic variants of this receptor do not explain why some people are more predisposed than others to become alcoholic.

Genes encoding other components of the brain dopaminergic pathway also have been tested for association with alcoholism. While none of the findings has been definitive, two studies have produced suggestive results especially worthy of further pursuit. In one, investigators studied the association with alcoholism of alleles of the tyrosine hydroxylase gene, which encodes an enzyme centrally involved in the synthesis of dopamine, by using cladistic analysis. This analysis makes use of the evolutionary history of the chromosomal region containing the gene under study to afford a more precise and powerful statistical test of association of alleles with the disease (Lobos and Todd 1997). Although the results of this study were ambiguous, the application of cladistic analysis to other association studies deserves further exploration. Other investigators have found an association of a functional variant of the dopamine receptor D4 (a receptor type distinct from D2) with alcoholism in a small sample of severely affected Japanese alcoholics (Muramatsu et al. 1996). Validation of this finding will require replication in a larger subject sample.

As can be seen from the above examples, most genes tested so far for association with alcoholism

have been those that, based on independent physiologic or pharmacologic evidence, have already been suspected to play a role in predisposition to alcoholism. The power of genetic studies to reveal the influence of previously unsuspected genes on predisposition to alcoholism, thereby affording insights into previously unrecognized disease mechanisms, thus remains to be exploited, at least in genetic association studies. The authors of a recent paper have demonstrated that once all of the genes in the human genome have been mapped, and the more common alleles of each of them characterized, it will become possible to conduct statistically powerful tests of all genes in the genome for association with diseases (Schuler et al. 1996). These tests will have greater power than linkage tests to detect genes having small effects on disease predisposition. To hasten the day when such tests become possible, the National Human Genome Research Institute is leading a trans-National Institutes of Health (NIH) initiative to catalogue, as quickly as possible, a large fraction of the common polymorphisms in the human genome (Collins et al. 1997). NIAAA, along with other NIH Institutes, is providing funding for this initiative.

In Closing

The greatest value expected to accrue from genetic studies toward the improvement of treatment and prevention of alcoholism will come from identification of the predisposing genes and the proteins they encode. Since mapping genes that influence genetically complex diseases like alcoholism presents difficult challenges for investigators, progress on such diseases, including alcoholism, has been much slower than progress in gene mapping for single-gene disorders. Despite the difficulty of the problem, NIAAA-supported researchers have taken important steps during the last 3 years by identifying human chromosomal regions possibly containing relevant genes. Twin studies, which explore the relationship between alcoholism and other traits, continue to contribute to the formulation of a more biologically valid definition of the disease and to resolving disease subtypes that may ultimately prove to have differing genetic bases. Achievement of these objectives would greatly expedite the gene search. Further progress toward precise identification of genes influencing predisposition to alcoholism will depend on the development of improved tools for the gene-discovery enterprise. Foremost among these tools will be more sophisticated statistical methods, a complete human gene map, and a catalogue of the major human genetic polymorphisms. Once genes influencing predisposition to alcoholism have been identified, a major new challenge confronting genetic epidemiologists will be to understand how such genes (many of which will have been discovered in families specially selected to be densely affected by alcoholism) interact with environmental factors to influence the development of alcoholism in the general population.

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Psychosocial Factors in Alcohol Use and Alcoholism

There is no single, simple explanation for why some individuals develop problems with alcohol. One of the central findings of the large body of research that has examined the psychosocial causes, or etiology, of alcohol use is that there are multiple pathways to behavior that involves alcohol consumption (Cloninger et al. 1996; Sher et al. 1997; Zucker et al. 1994). Multiple biological and psychosocial factors mutually influence each other in causing alcohol abuse; it would be incorrect to view psychosocial causes as either independent from, or competing with, biological causes. Rather, alcohol use and alcoholism are best viewed as end products of a combination of biopsychosocial influences.

Researchers face the challenge of explaining diverse alcohol-related behavior ranging from simple alcohol experimentation to severe alcohol dependence. Clearly, different factors may influence different aspects of drinking, such as initial experimentation, later maintenance of regular drinking, and the decision to stop drinking. Not only is alcohol use different from alcoholism, but alcoholism itself takes different forms; researchers have suggested that different subtypes of alcoholism may have different etiologies (Cloninger et al. 1996; Zucker et al. 1996).

This section is not intended as a comprehensive overview of psychosocial research, but instead focuses on research that has been conducted since the *Ninth Special Report to the U.S. Congress on Alcohol and Health* (National Institute on Alcohol Abuse and Alcoholism [NIAAA] 1997) in four areas: family history of alcoholism, developmental issues, motivations, and alcohol-related cognitions (beliefs about alcohol). Recent research into the causes of alcoholism emphasizes the links between biological and psychosocial variables rather than studying each in isolation. Researchers hypothesize, for example, that in childhood, biologically based vulnerabilities in emotional and behavioral regulation (temperament or personality) interact with poor parenting to create emotional distress and exposure to negative peer influences, both of which create risk for alcohol misuse.

Finally, environment encompasses a wide range of influences, including not only family and peers, but also culture, social forces, advertising, and economics. Other sections of this report discuss these issues.

Family History of Alcoholism

It has long been recognized that alcoholism "runs in families." A family history of alcoholism is a well-established risk factor for the development of alcoholism (Cotton 1979; McGue 1994). Nonetheless, the majority of children of alcoholics do not develop alcohol use disorders. In fact, there is great variation among children of alcoholics with regard to their use of alcohol, and recent research has been directed at explaining this variation.

The *Ninth Special Report to the U.S. Congress on Alcohol and Health* (NIAAA 1997) identified several ways in which children of alcoholics have been found to differ from children without a family history of alcoholism. These findings include a higher prevalence of psychopathology (mental and behavioral disorders), more adverse family environments, and physiologic responses to alcohol that are known to be associated with risk—in particular, a lack of sensitivity to alcohol's intoxicating effects or an increased sensitivity to its anxiety-reducing effects. It is important to note that these characteristics are not unique to children of alcoholics, and that the same factors that mediate risk of developing alcohol problems in children with a family history may also explain the risk faced by those without a family history (Molina et al. 1994). Models that seek to explain how these risk factors interact

to lead to alcohol-related problems suggest that children of alcoholics are exposed to higher levels of these risk factors than are other children. Nonetheless, research aimed at clarifying why children of alcoholics are more likely than others to develop alcohol problems can reveal much about how the same risk factors are at play in children without a family history.

Effects of Parental Psychopathology Other Than Alcoholism

One source of the variation in the outcomes of children of alcoholics—that is, whether they develop alcohol-related problems themselves—is that familial alcoholism occurs in different forms. Scientists have identified subtypes of alcoholism that are characterized by the type and degree of psychopathology associated with the alcohol abuse—in particular, antisocial personality and affective (mood) disorders such as depression. Recent studies suggest that the type of alcoholic syndrome present in the family influences the child's risk of having psychological characteristics associated with risk for alcoholism.

Recently, for example, a research team identified three subtypes of familial alcoholism risk: one with familial alcoholism but low levels of other psychopathology; one with high levels of both familial alcoholism and familial antisocial personality and violence; and one with high levels of familial alcoholism along with depression, mania, and anxiety disorders (Finn et al. 1997). Predictably, young adult offspring from the families with alcoholism had elevated levels of alcohol problems compared with peers with no family history of alcoholism. In addition, other differences in offspring among the families were noted; for example, offspring of the families with alcoholism and antisocial personality themselves had the highest levels of antisociality and negative affect (anxiety, depression, and neuroticism) compared with offspring in the other (alcoholic) families.

Similar findings emerged from a community sample of younger children (preschool through age 8) (Zucker et al. 1996). In a comparison of children of families without alcoholism, families with alcoholism, and families with coexisting alcoholism and antisocial personality disorder, children whose families showed both alcoholism and antisociality had the highest levels of risk factors for developing alcohol problems—poor family environments and conduct problems—and were also most likely to maintain this risk over time.

Explaining the Effects of Parental Alcoholism: Mediational Models

Early research on risk factors in alcoholism tended to examine each one in isolation. A study might, for example, focus on one risk factor and attempt to identify differences between children of alcoholics and other children, the hypothesis being that the presence or absence of this single risk factor might explain why children of alcoholics themselves develop alcoholism.

A more recent trend has been the attempt to understand the mechanisms or processes that underlie the effects of parental alcoholism—and the associated risk factors—on children. An important approach involves the development and testing of mediational models, such as those described below, that provide an overall conception of how particular risk factors play out in the lives of the individuals affected to result in alcohol use or abuse. A test of the validity of a mediational model must include a demonstration that the risk factor is a feature of parental alcoholism; that individuals who show the highest level of the risk factor are most likely to develop drinking problems; and that this risk factor accounts for the effects of parental alcoholism on the development of drinking problems in their children (for more detail on mediational models, see Sher 1991). Recent advances in statistical methods allow tests of these models.

There have been three broad groups of theoretical models that provide platforms for exploring the transmission of alcoholism from parent to child: "deviance proneness," "negative affectivity" (or emotionality), and "sensitivity to the effects of alcohol." These hypothetical models, discussed below, are not mutually exclusive, but are interrelated and interacting.

Deviance Proneness. The deviance proneness model focuses on deficits in children in behavioral self-regulation and socialization and on the cascade of effects that result from and interact with these deficits. According to this model, children of alcoholics have difficult temperaments and experience poor parenting, both of which place them at risk for failure in school and emotional distress. This, in turn, raises risk for affiliation with a deviant peer group likely to promote alcohol use and misuse. Thus, according to this model, risk for alcohol misuse is part of a larger context of poor socialization and adolescent problem behavior.

Recent data are consistent with this model. For example, one study found that offspring of alcoholic fathers were more likely to abuse substances, in part because paternal alcoholism increased the likelihood of a child's having early conduct problems (Cadoret et al. 1995). Similarly, having an alcoholic father was found to be related to poor parental monitoring of adolescent behavior, which, in turn, was associated with membership in a drug-using peer group and escalating substance use over time. However, in both studies, the effect of paternal alcoholism could not be completely explained by these mediators, suggesting that other variables also must be considered.

Negative Affectivity. The negative affectivity model focuses on the importance of stress and negative affect in explaining the transmission of alcoholism from generation to generation. According to this model, children of alcoholics are exposed to high levels of life stress and are, as well, temperamentally hyperreactive to stress. These children develop high levels of emotional distress and drink to relieve these feelings. Again, recent tests of this model provide supportive data. In one study, researchers found that the environments of adolescent children of alcoholics were more stressful than those of other children, and that greater emotional reactivity was part of their temperaments. Both factors predicted more negative affect—self-reported crying and tension, for example—among these children than among children without a family history of alcoholism (Chassin et al. 1996). In turn, children in the study with high levels of negative affect were more likely than other children to join a drug-using peer group and to increase their substance use over time.

Another study found paternal alcoholism to be strongly associated with childhood stressors (for example, disrupted family rituals, embarrassment, neglect, or abuse). However, these stressors were only moderately and inconsistently related to the development of an alcohol use disorder in young adulthood (Sher et al. 1997). In both studies, the stressors only partly explained the effects of paternal alcoholism on the outcomes for children, again suggesting that other mediators must be considered.

Sensitivity to the Effects of Alcohol. "Alcohol effects" mediational models are based on the hypothesis that children of alcoholics have greater sensitivity to the stress response-dampening effects of alcohol (Pihl and Peterson 1995) and less sensitivity to the negative effects of alcohol (such as body sway and intoxication). Few tests of these mediational models have been performed. However, in one study, young men with a family history of alcoholism who had not yet developed drinking problems reacted less to alcohol than men from nonalcoholic families did (Schuckit and Smith 1996). The men with the lowest reactions—those in the bottom 15 percent—were more likely to be diagnosed 8 years later as having alcohol dependence. In another study, young men with a family history of alcoholism showed smaller responses as measured by an electroencephalogram (EEG) than others to a dose of alcohol (Volavka et al. 1996). Those men with the smaller EEG responses were more likely to eventually develop alcohol dependence.

The Role of Executive Functioning

Some theorists suggest that early conduct problems—which evolve according to the deviance proneness model into a broad set of "undercontrolled" behaviors, including alcoholism—are related to neuropsychological deficits in "executive functioning." Executive functioning encompasses the capacity for

sustained attention, concentration, abstract reasoning, goal setting, anticipation and planning, and the ability to monitor one's own behavior, inhibiting what is inappropriate and shifting to behavior that is adaptive (Moffitt 1993).

Recent studies of the executive functioning of children of alcoholics have produced conflicting results. Researchers conducted neuropsychological tests in a sample of 12-year-old boys with a multigenerational family history of alcoholism. These boys had poorer executive functioning than did boys with no familial alcoholism (Harden and Pihl 1995). However, other researchers found no significant differences in executive functioning between children in families with and without parental substance abuse (Giancola et al. 1996). Conflicting findings may be the result of differences among the groups participating in these studies. Alternatively, deficits in executive functioning may be found only among boys whose families are characterized by transmission of alcoholism from male to male over several generations (Pihl and Peterson 1995) or among children of fathers whose alcoholism is severe and persistent (Ozkaragoz et al. 1997).

Recent data suggest that poor executive functioning predicts increases in alcohol consumption among young adults with a family history of alcoholism (Deckel and Hesselbrock 1996). Poor executive functioning may lead to alcohol problems in several ways. Children with poor executive functioning are harder to parent, evoke more punishment, and thus may develop poorer bonds to parents and poorer socialization (Dobkin et al. 1997; Ge and Cadoret 1996). Moreover, children with poor executive functioning are likely to experience more failure in school (Moffitt 1993), and recent data suggest that executive functioning partially mediates the impact of parental alcohol dependence on academic achievement (McGrath et al. 1999). School failure increases the risk that children will make friends with deviant peers, which increases the risk of escalating alcohol use in adolescence (Curran et al. 1997), a sequence of effects hypothesized in the deviance proneness model.

Finally, investigators have suggested that individuals with deficits in executive function also are unable to regulate their own mood, making them more sensitive to stress. These individuals would be particularly vulnerable to the stress response-dampening properties of alcohol (Pihl and Peterson 1995).

The Role of Parenting and the Family Environment

Researchers have examined parenting and family environment in an attempt to understand both the transmission of alcoholism from generation to generation and the causes of alcohol use and misuse in the wider population (Barnes et al. 1994; Wills and Cleary 1996). In general, the same parenting factors that are linked to adolescent alcohol abuse—low levels of parental emotional support and a lack of control and monitoring of child behavior—are linked to other adolescent problem behaviors, such as smoking and early sexual activity (Jacob and Leonard 1994; Jessor and Jessor 1977; Stice and Barrera 1995).

Evidence suggests that children of alcoholics grow up in homes in which parenting and the family environment are poor (Jacob and Leonard 1994; Zucker et al. 1996). These conditions may improve when parents recover from alcoholism (Moos and Billings 1982). Moreover, the effects of parental alcoholism are not confined to parent-child interactions that involve the alcoholic parent. In families with heavily drinking fathers, researchers have found disturbances in attachments between mothers and infant children (Eiden and Leonard 1996).

Some of the parenting deficits in alcoholic families are associated with the development of early conduct problems and early onset of alcohol use, a risk factor itself for later problems with alcohol use. For example, in alcoholic families, parents show less monitoring of adolescent behavior (Chassin et al. 1996), more family conflict (Barrera et al. 1995; Webb and Baer 1995), and poorer parent-child relationships (Blanton et al. 1997; Curran et al. 1997). Children of these families may not learn

emotional and behavioral self-regulation and may lack social skills, which also increases the likelihood of rejection by mainstream peer groups and association with substance-using peers (Webb and Baer 1995). All of these findings support the hypothesis that poor parenting and poor socialization create a high risk of alcohol problems, not only for children of alcoholics, but also for adolescents from nonalcoholic families.

However, poor parenting may be a product as well as a cause of behavioral difficulties in children. Some researchers have noted that children with conduct disorders may evoke poor parenting (Ge and Cadoret 1996). Another study showed that boys from alcoholic families who themselves were not disruptive had interactions with their mothers that were not disturbed and that were similar to the interactions between mothers and sons in a group of nonalcoholic families (Dobkin et al. 1997).

Moreover, it is not yet clear to what extent correlations between parenting practices and adolescent alcohol involvement may be due to shared genetic influences. In a study of more than 650 families with adopted adolescents, poor family functioning had only a slight effect on whether the adopted child drank, while the effect was substantial for birth offspring (McGue et al. 1996*a*). On the basis of these findings, the investigators suggested that research may overestimate the importance of family environment and underestimate the role of genetic factors. Another finding of this study was that the adopted children were significantly more likely to drink if another sibling in their adopted family used alcohol. If the sibling was of the same gender and similar age, it increased further the likelihood that the adopted child would drink, suggesting that sibling influence may be an important and understudied form of family influence on adolescent drinking (McGue et al. 1996*a,b*). The recognition that siblings as well as parents can influence adolescent drinking will broaden the inquiry into the effects of family environment on the development of alcohol problems.

Protective Factors

Most children of alcoholics do not develop alcohol dependence. According to the mediational models described earlier, this would be partially due to these children not experiencing mediators of risk such as difficult temperaments or poor parenting. It is also possible that even children of alcoholics subject to these risk mediators may have good outcomes—avoiding problems with alcohol—because their risk is buffered by exposure to a protective factor.

Some recent evidence is available on protective factors. One 3-year study of adolescents in alcoholic families found that these children were less likely to begin using substances if they perceived that they had control over their environment, if they had good cognitive coping skills, and if they reported that their families were highly organized (Hussong and Chassin 1997). Other investigators have found that in alcoholic families that preserve family rituals, such as keeping to established daily routines and celebrating holidays, the young adult offspring are less likely to report problem drinking (Hawkins 1997).

Although only a few studies of protective factors have looked specifically at alcoholic families, some broader studies have found evidence of risk buffers among children. Important recent findings come from the National Longitudinal Study on Adolescent Health, in which nearly 12,000 students in grades 7 through 12 completed two extensive interviews 1 year apart (Resnick et al. 1997). On the basis of the interview data, the investigators identified children who were less likely to take risks in four health areas: substance abuse (cigarettes, alcohol, and marijuana), emotional health, violence, and sexuality. Two factors were found to protect children from taking risks in all four areas: parent-family connectedness and school connectedness. Children who experienced parent-family connectedness said they felt close to their mother or father or both, they perceived that either or both of their parents cared about them, they expressed satisfaction with their relationship with either or both of their parents, and they felt loved and wanted by family

members. School connectedness was experienced as a feeling that teachers treated students fairly and a feeling of being close to people at school and being part of one's school.

Other studies have found parental support to be protective, particularly in terms of children's mental health (Barrera et al. 1995). In a study of more than 1,700 adolescents, those who received more emotional support from their parents were found to drink less; the parental support seemed to work by enabling these adolescents to cope better with life stresses, which prevented them from turning to heavy drinking (Wills and Cleary 1996).

However, parental support may be less protective for children's alcohol and drug use in the context of parental alcoholism. In a study of nonalcoholic families, adolescents who reported good relationships with their parents were more likely to imitate their parents' patterns of substance use than were adolescents with less positive relationships with their parents (Andrews et al. 1997). If such imitation were to occur in an alcoholic family, then receiving support from an alcoholic parent might increase a child's risk of drinking.

Developmental Issues

Alcohol use and alcoholism can best be studied within the context of psychosocial development throughout the life span (Tarter and Vanyukov 1994), and research interest in applying a developmental perspective to alcohol problems is increasing. Findings suggest that early developmental antecedents to alcoholism can be seen even in the preschool years in the form of deficits in self-regulation, emotional reactivity, and conduct problems (Tarter and Vanyukov 1994; Zucker 1994). In one study, observers rated the temperaments of 3-year-old children; 18 years later the same individuals underwent diagnostic interviews (Caspi et al. 1996). The boys whose temperaments were rated as undercontrolled at age 3 (impulsive, restless, distractable) were more likely than other children to be diagnosed at age 21 as alcohol dependent or as having alcohol-related problems. Boys rated as having inhibited temperaments at age 3 (shy, fearful, and easily upset) also were more likely to have alcohol-related problems at age 21.

Developmental researchers also look at age-related peaks and declines in alcohol use. Drinking usually begins in adolescence. National epidemiologic data show that the prevalence of alcohol use increases greatly after eighth grade. For example, the Monitoring the Future Study reported that in 1999, 9.4 percent of 8th graders, 22.5 percent of 10th graders, and 32.9 percent of 12th graders reported being drunk in the past month (Johnston et al. 1999). Escalation of drinking during adolescence is a risk factor for alcohol-related problems in adulthood (Hawkins et al. 1997; Schulenberg et al. 1996*b*), and in subgroups of children, drinking does escalate during this time.

Recently, researchers have been able to predict which subgroups of adolescents will increase their alcohol use. In general, the factors that predict alcohol involvement among adolescents are similar to those that predict other forms of adolescent problem behavior, such as delinquency and risky sexual behavior. Current work has identified several predictors of increased adolescent substance use. In addition to paternal alcoholism and affiliation with substance-using peers (Chassin et al. 1996), the predictors include high life stress, nonadaptive coping styles, parental and peer substance use, little parental support, a low level of academic competence, and poor behavioral control (Wills et al. 1996).

For young adults, alcohol use peaks in age-related patterns and then declines after the mid-20's (Chen and Kandel 1995; Gotham et al. 1997; Johnstone et al. 1996; Schulenberg et al. 1996*a*). The stronger evidence in more recent studies for this age-related decline in drinking may reflect changes in social norms regarding the acceptability of using alcohol (Johnstone et al. 1996). Research suggests that developmental changes in older adolescents and young adults as they experience the freedoms and responsibilities of this age period influence drinking behavior (Bachman and Wadsworth 1997). From the developmental perspective, the heavy drinking

often seen in late adolescence is linked to adolescents' moving away from parental restrictions and living in college environments, including fraternities and sororities (Cashin et al. 1998). At this stage, alcohol use is a relatively accepted norm.

Studies show that when young adults take on the responsibilities of work and marriage, they reduce their drinking (Gotham et al. 1997; Schulenberg et al. 1996*a*) and are less likely to report symptoms of alcohol abuse and dependence (Chilcoat and Breslau 1996). One interpretation is that these individuals drink less during this period because drinking is incompatible with the obligations of adult roles (Yamaguchi and Kandel 1985). These findings are consistent with past research indicating that a subtype of alcoholism may be developmentally limited; that is, some people may drink heavily and have alcohol-related problems in young adulthood but not in later years (Zucker 1994).

Indeed, investigators are finding more evidence to support the idea that different subtypes of alcoholism start at different ages, and that they have different causes. Alcohol problems that begin in adolescence and young adulthood are often part of broader problems of undercontrolled behavior. In a subtype that tends to have its onset in later adulthood, individuals drink to self-medicate negative emotions such as anxiety and depression (Cloninger et al. 1996; Zucker et al. 1996). Establishing classification schemes for alcoholics is not an abstract pursuit; the treatment needs of these groups are likely to differ.

Motivation To Drink

One area of psychosocial research on alcohol use focuses specifically on what motivates individuals to drink. Perhaps the most commonly studied motivation involves alcohol's ability to reduce anxiety, thus making it a way to cope with stress (Cappell and Greeley 1987; Sher 1987; Wills and Filer 1996). The *Ninth Special Report to the U.S. Congress on Alcohol and Health* (NIAAA 1997) reviewed the literature on the relationship between stress and alcohol use and concluded that the relationship was complex, varying with the nature of the stressor, the characteristics of the individual, and the context within which the drinking occurs. This report also suggested that the strength of the relationship between stress and alcohol consumption varies across the life span, being weaker in adolescents and more pronounced in older adults.

Stress Reduction

Evidence that some people use alcohol to reduce stress is complex and inconsistent for a number of reasons, not least of which is that there are multiple determinants of alcohol use. Only subgroups of individuals use alcohol to cope with stress. One model proposes that experiencing negative emotions such as anxiety or depression, expecting that alcohol will relieve these feelings, and having a coping style characterized by avoiding rather than confronting life issues all combine to make it more likely that an individual will be motivated to drink to cope with stress. Data support this model in adolescents and adults, and across racial/ethnic groups. Individuals with these characteristics show the strongest correlation between stress and drinking (Cooper et al. 1992; Cooper et al. 1995; Kushner et al. 1994).

Other individuals who might be vulnerable to "drinking to cope" are those with a family history of alcoholism. Laboratory data suggest that male children with multigenerational family histories of alcoholism are hyperreactive to stress and derive greater stress response-dampening benefits from alcohol (Conrod et al. 1995, Harden and Pihl 1995).

The effect of protective factors that reduce the impact of stress on drinking also complicates the evidence for the relationship between stress and drinking. For example, a 3-year study of more than 1,000 people examined the relationship between financial stress and drinking (Peirce et al. 1996). Financially stressed individuals who reported that they had tangible support, such as help with transportation and chores, were less likely to have drinking problems than were other financially stressed people without this support.

Finally, problems in study methods may result in inconsistent findings. For example, there may be a time lag between the occurrence of a stressful event and resulting alcohol use. One study found, using daily diaries, that women consumed less alcohol on high-stress weeks, perhaps because alcohol impaired their ability to cope with stressors. However, these women then consumed more alcohol after the stressful event was over. Thus, variations in the time lag between the measurement of the stressor and alcohol consumption are likely to produce different findings (Breslin et al. 1995).

Mood Enhancement

Another reason for the modest relationship between stress and drinking is that other motives and determinants of alcohol use can overshadow stress-reduction motives. Alcohol, for example, can be used to enhance positive mood, a motive that has received recent research interest (Cooper et al. 1995). In both adolescents and adults, and in different racial/ethnic groups, data support a model in which individuals characterized by high levels of sensation seeking, and those who expect that alcohol use will enhance positive mood, will be more strongly motivated to drink for this effect (Cooper et al. 1995). Such a model does not imply that using alcohol to reduce stress or enhance positive mood (including its use for celebratory reasons) are mutually exclusive motivations to drink, or that they cannot be observed in the same person. The most severe alcohol problems have been reported in individuals who are characterized by both high levels of negative affect and low levels of constraint (including high sensation seeking [McGue et al. 1997]).

Alcohol's Effect on Emotional State

Questions remain as to exactly how alcohol affects emotional state. Laboratory data show that alcohol dampens responses to stress, but this effect of alcohol differs in individuals; alcohol can increase anxiety in some cases (Sayette 1993; NIAAA 1997).

Recently, investigators used a "startle probe" method to determine whether alcohol produced a specific decrease in negative affect or whether it simply reduced emotional arousal across the board, muting the intensity of any emotion. The startle probe method involves showing individuals slides with pleasant, unpleasant, and neutral subjects and observing the watchers' responses to a sudden noise while viewing different slides. Studies have repeatedly shown that a person viewing an unpleasant slide—intended to evoke an unpleasant emotional state—will have a quicker, stronger startle response to a sudden noise than when viewing pleasant or neutral scenes. In this study, alcohol dampened the startle reflexes of viewers of both pleasant and unpleasant scenes (Stritzke et al. 1995). The data suggest that alcohol generally reduces emotional arousal, rather than specifically diminishing responses occurring during positive emotional states evoked by pleasant slides. In contrast, in similar studies, diazepam (Valium) blocked the startle response during exposure to aversive stimuli, but not during exposure to neutral stimuli (Patrick et al. 1996).

If the effect of alcohol consumption is generally to lower emotional arousal, then it is unclear how alcohol acts to enhance emotional state. However, more research must be conducted using these investigators' methods with different doses (they administered roughly three standard drinks to each person), placebo conditions (comparing the effect of alcohol with a nonalcoholic beverage), and a wider range of participant groups. These investigators suggest that alcohol's effects on emotional reactivity may be the result of alcohol's effects on cognition and information processing, rather than on motivational systems involving affect and emotion. Cognitive factors, such as those discussed below, may account for the role in motivating alcohol consumption of the positive effects of alcohol on emotion.

External Motivations To Drink

Finally, it is important to note that regulation of emotional state—reducing stress or lifting or enhancing mood—is not the only motive for alcohol consumption. External motives to drink include the social rewards of projecting a particular image, as well as the avoidance of social

rejection by complying with perceived social norms that include consuming alcohol in social settings (Cox and Klinger 1988). Thus, social influences, norms, and contexts also play a role in the motivation to drink.

The Role of Cognition: Beliefs About Alcohol

Most of the previous discussion has focused on the impact of alcohol on emotional tone. Another active research area involves cognition, or conscious and unconscious knowledge or beliefs about alcohol and the role of these beliefs in shaping alcohol-related behavior. As a result of direct experience with the pharmacologic effects of alcohol and vicarious learning—from parents, peers, and the broader culture and media—individuals develop expectancies about what will happen to them when they consume alcohol. These expectancies then influence their decisions to drink.

Theorists have suggested that cognition may in some cases be a bridge between the primary reinforcing effects of alcohol—the sense that alcohol reduces stress, for example—and individuals' decisions to use alcohol in a particular situation. For example, expectancies about alcohol's effects may be the mediator between the neurobiological reinforcing effects of alcohol and the decision to drink (Stacy 1997; Stacy et al. 1994). As someone makes the decision to drink, expectancies about alcohol's effects may be the common pathway mediating the effects of many other psychosocial variables that set the stage for the decision (Smith et al. 1995).

Explicit Beliefs and Expectations

If asked, most people can describe many of their beliefs and expectations about alcohol. These beliefs are conscious or "explicit." As noted in the *Ninth Special Report to the U.S. Congress on Alcohol and Health* (NIAAA 1997), expectations about alcohol's effects begin developing early in life, even before a person drinks any alcohol (Zucker et al. 1995). Recent studies continue to confirm earlier work showing that expectations about alcohol predict future alcohol use. For example, young adolescents who told researchers that they believed alcohol makes it easier to socialize were shown in later years to have increased their drinking over time to higher rates than their peers without this belief (Smith et al. 1995). More general expectancies may not be predictive; in another study, responses to such general questions as whether alcohol had "positive" or "negative" effects did not predict increased alcohol use over time in a group of adolescents, many of whom were from families with alcoholism (Colder et al. 1997). Data suggests that expectancies and the experience of drinking have reciprocal effects. Not only do expectancies predict later drinking, but drinking experiences shape later expectancies about alcohol's effects (Sher et al. 1996; Smith et al. 1995).

Recent data have been less supportive of the hypothesis that expectancies by offspring about alcohol can explain the effects of family history of alcoholism on drinking. Researchers have found differences in expectations about alcohol between children of alcoholics and children of nonalcoholics (Sher et al. 1996). Even in preschool, children of alcoholics have more knowledge about alcohol than their peers. For example, they are better able to identify alcoholic beverages visually (Zucker et al. 1995). However, recent data suggest that expectations about alcohol explain only a modest amount of the influence of familial alcoholism on alcohol use among college students (Sher et al. 1996). College students are a select group, however, and live in an environment that strongly promotes drinking, a factor that may mask the role of expectations. As noted above, a study of younger adolescents showed that their general expectations about alcohol did not account for differences in the increase of heavy alcohol use over time among children of alcoholics versus those of nonalcoholics (Colder et al. 1997).

Recent studies have identified a role for expectancies about alcohol as moderators of the effects of other risk factors on alcohol consumption. For example, as noted in the earlier discussions of motivational factors, individuals will be motivated to drink to reduce anxiety only if they believe that

alcohol consumption actually produces this effect (Cooper et al. 1995; Kushner et al. 1994).

Implicit Beliefs and Expectations

In the studies described so far, researchers directly asked individuals to report their beliefs and expectations about the effects of drinking. This approach best measures "explicit cognition": what individuals consciously think and report to be their attitudes and beliefs. In other studies, researchers attempt to identify (and investigate) the beliefs, memory associations, and emotional states that are activated more spontaneously, without a person's conscious awareness—termed "implicit cognition" (Greenwald and Banaji 1995). Recently, alcohol researchers have begun to study the role of implicit alcohol-related cognition in drinking behavior (Dunn and Goldman 1996; Stacy 1997; Stacy et al. 1996; Weingardt et al. 1996).

These associative memory processes have been measured in diverse ways, including investigating how individuals at various ages mentally organize associations between alcohol and its effects (Dunn and Goldman 1996), measuring free associations to alcohol-related words and pictures (Stacy et al. 1996; Stacy 1997), and priming memory activation (observing how exposure to an alcohol-related concept affects a participant's responses to later stimuli) (Roehrich and Goldman 1996; Weingardt et al. 1996).

Data from these studies suggest that while late elementary school children resemble adults in how they process memory associations related to alcohol, there are also age-related changes. Older children activate impressions about the positive and arousing effects of alcohol, and this may reflect a form of preparation for alcohol use (Dunn and Goldman 1996). Children in the early years of elementary school are apt to have mostly negative alcohol-related associations, describing drinkers with words such as "sleepy," "dizzy," "goofy," and "rude" (Dunn and Goldman 1998). As children get older, their associations turn to the positive and arousing effects of alcohol, and they begin to use words such as "outgoing," "relaxed," "wild," and "funny."

Recent studies using similar methods have shown that high school students who drink are more likely than those who do not drink to have these positive and largely unconscious memory associations about alcohol (Stacy et al. 1996); similar results have been found among college students (Weingardt et al. 1996).

Little is yet known about the relationship between implicit and explicit beliefs about alcohol and the potential differences in the way that the two types of knowledge influence alcohol use. One hypothesis suggests that conscious, explicit expectations influence alcohol use through deliberate, conscious decision making (Stacy 1997). In contrast, unconscious memory associations may influence alcohol use more spontaneously, when the expectations are triggered in an immediate situation. A recent study that measured conscious beliefs and expectations about alcohol (by direct questions) and unconscious beliefs and expectations (by free association) in a sample of college students showed that both predicted later alcohol use (Stacy 1997).

In Closing

Research on psychosocial factors in alcohol consumption and alcoholism encompasses a broad range of investigations, all aimed at understanding how multiple biological and psychosocial risk factors interact to influence alcohol-related behavior. Research on familial transmission of alcoholism in particular focuses on how genetic vulnerabilities are translated in the context of the family and social environment into alcoholism.

Recent research traces the evolution of the disorder of alcoholism along the life span and teases out the motivational factors—both emotional and cognitive—that induce individuals to drink. By constructing models of how the risk factors identified interact, then testing these models empirically—seeing to what extent the models can predict who will drink and to what extent—scientists are identifying risk factors for alcohol misuse, as well as potential mediators and moderators of this risk. The ultimate goal of this research is to develop preventive interventions

that target these risk and protective factors in order to reduce the prevalence of alcohol-related illness and death.

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Medical Consequences

Underlying the spectrum of potential health consequences of alcohol is an array of mechanisms that encompasses not only the direct toxic harm by alcohol and its metabolites, but a variety of more complex changes. This chapter describes some of the newest insights into the nature of these mechanisms, in particular how alcohol can disrupt the normal balance of systems with which cells communicate with each other in the regulation of such functions as cell growth, muscle contraction, and the immune response. The understanding being gained is helping to explain the variety of alcohol's effects and why individuals can differ so dramatically in how they respond to the same cumulative amount of alcohol over time.

Research suggests, for example, that alcohol may alter the balance of protective and destructive responses of the immune system, particularly in the liver where most ingested alcohol is metabolized. Changes in immune regulation appear to be at the root of some of the liver damage resulting from drinking, and the inborn genetic tailoring of each individual's immune profile may help shape vulnerability to alcohol-induced damage. Similarly, research findings suggest that alcohol-related disruption of cell membrane function—and with it the ion exchange that is at the base of heart muscle contraction—contributes to heart arrhythmias. Studies also are examining the impact of alcohol on a variety of substances that shape the normal development and proliferation of cells, functions that could help to explain changes in bone mass or breast cancer risk. At the most fundamental level, there is evidence to suggest that alcohol can perturb molecular regulators of gene expression, with the potential for consequences that are both broad and lasting.

For reasons as yet largely unexplained, gender plays an influential role in vulnerability to alcohol's health effects. Three sections that follow, on alcohol and women, bone disease, and breast cancer, examine current research aimed at understanding this differential vulnerability and how alcohol could contribute to the risk of two major diseases that predominantly affect women.

Finally, the sections on heart and bone disease discuss suggestions in epidemiologic research that alcohol in no more than moderate amounts (up to one drink per day for women and two drinks per day for men) may have benefits for some groups, reducing the risk of heart disease and possibly contributing to increased bone mass, an important factor in protection from fractures. Much remains to be learned about the magnitude and mechanism of these effects and their meaning in terms of personal health.

Alcohol-Induced Liver Injury

The liver is a vital organ, involved in the processing of fats, sugars, proteins, and vitamins and in the regulation of blood clotting. It plays a central role in the body's defenses, filtering toxins and microbes from the blood and marshaling an array of responses to trauma, stress, or inflammation (Hill et al. 1997).

Although the liver is capable of regeneration and repair, severe liver disease must be viewed as life threatening. Long-term heavy alcohol use is the leading cause of illness and death from liver disease in the United States. The number of persons with alcoholic liver disease is conservatively estimated at more than 2 million (Dufour et al. 1993).

There are three phases of alcoholic liver disease: fatty liver, which is usually reversible with abstinence; alcoholic hepatitis, or liver inflammation; and cirrhosis, or scarring of the liver. Patients frequently have more than one type of liver disease, such as coexisting fatty liver and alcoholic hepatitis or alcoholic hepatitis together with cirrhosis. Patients with both cirrhosis and alcoholic hepatitis have a death rate of more than 60 percent over a 4-year period, with most of those deaths occurring within the first 12 months of diagnosis (Chedid et al. 1991). This prognosis is bleaker than the outlook for many types of cancer.

The major problem in developing new therapies for alcoholic liver disease has been a lack of understanding of the mechanisms for liver injury. While many people who drink heavily do not develop liver disease, others seem to be highly susceptible to the disease, suggesting a probable role for nutritional, environmental, and hereditary factors.

This section examines current research on one class of potential initiators of liver cell injury and repair, the cytokines. It also discusses recent studies on nutritional variables associated with liver disease and on three other liver disorders that may affect the course of alcoholic liver disease. Researchers are hopeful that these current investigations will lead to new insights into the mechanisms of alcoholic liver disease and will provide a basis for the development of new forms of therapy.

Alcoholic Liver Disease

The Role of Cytokines

One of the liver's most important responses to trauma or stress is the production of cytokines. These small molecules act as chemical messengers, regulating cellular interactions and functions. Cytokines play an important role in cell-to-cell communication during normal metabolism, and they are the primary chemical messengers during periods of inflammation or infection. The signaling pathways are extremely complex, but current studies are progressing toward a better understanding of these pathways.

Cytokines are produced by many different cell types. Specialized cells within the liver, the Kupffer cells, are major producers of certain cytokines. Other types of liver cells, producing different cytokines, are the hepatocytes, stellate cells, and endothelial cells. The Kupffer cells are macrophages, one of several types of phagocytic white blood cells that engulf and destroy foreign substances; stellate cells are fat-storing cells; hepatocytes are the major functional cells of the liver, acting to process and store nutrients, secrete bile, and remove toxins from the blood; and endothelial cells line the liver's blood vessels.

The Kupffer cells produce the cytokines interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α, or TNF), and interleukin-6 (IL-6), all of which promote inflammatory responses (Hill et al. 1997). The stellate cells produce and are activated by transforming growth factor beta (TGF-β), which plays an important role in production of collagen (a connective tissue

protein) and in liver fibrosis (the formation of scar tissue) (Hill et al. 1997). This process leads to the scarring of the liver in cirrhosis. Hepatocytes produce the cytokine interleukin-8 (IL-8), which attracts neutrophils to the site of an infection, where they adhere to cell surfaces. Neutrophils, which circulate in the blood, are another type of phagocytic white blood cell. Endothelial cells produce adhesion molecules, which act by increasing the adhesion of phagocytes to the outer surface of cells (Hill et al. 1997). These phagocytes eventually enter liver tissue and injure hepatocytes.

Cytokine Imbalance

In response to injury or infection, cytokines can initiate a variety of responses, including attracting and activating phagocytes, promoting fibrosis, and stimulating the production of additional chemical messengers, including more cytokines. However, if the increased levels of cytokines do not subsequently return to normal, they can cause chronic inflammation. Even though cytokines probably evolved as protection against injury, infection, or inflammation, overproduction can lead to cell injury or cell death. For example, if there is overproduction of the cytokine TNF or if defenses against TNF are inadequate, liver injury can occur and, in fact, elevated levels of TNF appear to correlate with increased mortality (Rodriguez-Rodriguez et al. 1995).

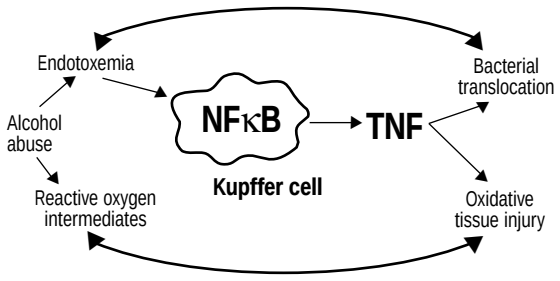
Alcoholic liver disease is marked by increased levels of cytokines. Increases in IL-1 and TNF were first noted a decade ago in patients with alcoholic hepatitis (McClain et al. 1986, 1989). Investigators initially suspected that these cytokines played a role in the development of hepatitis because of a similarity in metabolic effects: both cytokines and alcoholic hepatitis cause symptoms of fever, increased levels of neutrophils, anorexia (loss of appetite), muscle wasting, and altered mineral metabolism (McClain et al. 1993). As mentioned previously, elevations in TNF levels are correlated with mortality, as are blood levels of neopterin, a macrophage product that is an indicator of macrophage activation (Rodriguez-Rodriguez et al. 1995).

Recent studies have reported that a rare genetic polymorphism (genetic variant) associated with increased production of TNF is also associated with susceptibility to steatohepatitis, or fatty liver (Grove et al. 1997). This suggests that genetic abnormalities in cytokine metabolism may predispose certain individuals who drink alcohol to the development of alcoholic liver disease.

One stimulus for the excessive production of potentially toxic cytokines seen in alcoholic liver disease is endotoxin, or lipopolysaccharide, a complex molecule found in the cell wall of many bacteria. Heavy alcohol consumption has been reported to increase intestinal permeability to endotoxin, allowing endotoxin produced in the intestine to leak into the blood vessels that carry blood to the liver. In the liver, endotoxin is taken up by the phagocytic Kupffer cells. Endotoxin then activates nuclear factor kappa B (NFκB), a regulatory complex of molecules that, when activated, initiates gene-directed synthesis of specific proteins. NFκB causes the production of certain pro-inflammatory cytokines, such as TNF (Schreck et al. 1992). TNF further increases gut permeability, thus creating and perpetuating a destructive cycle (figure 1).

Another stimulus for excessive cytokine production is the generation of reactive oxygen species (ROS) as a by-product of alcohol metabolism in the liver (Hill et al. 1997). ROS are highly reactive molecular fragments capable of inflicting serious damage on cells. Normally, ROS are quickly inactivated by antioxidants,

Figure 1: Mechanisms of alcohol-related cytotoxicity



NFκB, nuclear factor kappa B; TNF, tumor necrosis factor alpha.

protective molecules such as glutathione and vitamins A and E. However, if these defenses are impaired or if there is an overproduction of ROS, the result is oxidative stress, which can result in cell death. Lipid peroxidation is a reaction between ROS and components of cell membranes, which results in membrane injury and eventual cell death. ROS also can activate the transcription factor NFκB (Sen and Packer 1996), causing a further increase in production of the cytokine TNF.

The cytokine IL-8, generated by hepatocytes and Kupffer cells, attracts and activates neutrophils (Strieter et al. 1996). The neutrophils contribute to liver cell injury by releasing toxic substances (ROS, cytokines, and proteases, enzymes that break down proteins). Researchers have noted increased levels of chemoattractant cytokines such as IL-8 and growth-related oncogene alpha in alcoholic liver disease, with the highest levels in patients with acute alcoholic hepatitis (Huang et al. 1996; Maltby et al. 1996). Levels were highest in patients who died, and levels correlated with biochemical and histologic evidence of liver disease (Huang et al. 1996). Patients with alcoholic liver disease also had increased levels of cell adhesion molecules, which may explain why certain cells "stick" in the liver and release toxic products that can lead to liver injury (Diez-Ruiz et al. 1996).

Recent studies have found that alcoholic cirrhosis is associated with elevated levels of cytokines that induce inflammation, but at the same time there is an underproduction of the cytokine interleukin 10 (IL-10), which has anti-inflammatory effects (Le Moine et al. 1995). This decreased secretion of IL-10 may play a role in the imbalance of cytokine levels seen in alcoholic liver disease.

Apoptosis: Cell Suicide

Traditionally, injured liver cells have been thought to die by necrosis, a process in which the cells swell and break open, releasing their contents, thereby initiating inflammation that further damages the liver (Hetts 1998). However, a second mechanism called apoptosis, or programmed cell death, has recently been the subject of intense investigative attention. In this type of cell suicide, the cell shrinks and the entire cell, including the nucleus, breaks into numerous fragments, called apoptotic bodies. These bodies are then ingested and digested by macrophages or by neighboring cells. Apoptosis is considered "physiologic" and is important both in cell development and in removal of senescent cells (Hetts 1998). A disruption in the balance between apoptosis and cell proliferation, however, can cause harm. Initial studies suggest a role for apoptosis in liver cell death in animal models of alcoholic liver disease as well as in human alcoholic liver disease (Goldin et al. 1993; Kawahara et al. 1994; Nanji 1998; Yacoub et al. 1995; Zhao et al. 1997).

Apoptosis may be initiated by a receptor-ligand interaction. Hepatocytes have docking sites, or receptors, on the cell surface. Each specific type of receptor interacts with a corresponding molecule or ligand. The Fas receptor, a member of the TNF receptor family, is normally found in modest levels on hepatocytes (Galle et al. 1995; Muschen et al. 1998); Fas ligand is also present on hepatocytes in alcoholic liver disease (Galle et al. 1995). The Fas receptor-ligand interaction, as well as the interaction between TNF and TNF receptors, can activate pathways leading to cell death by apoptosis (Baichwal and Baeuerle 1997; Galle et al. 1995; Tewari and Dixit 1996).

Recent research indicates that mitochondria are involved in apoptosis (Kroemer et al. 1997; Zamzani et al. 1996). Mitochondria are intracellular bodies that generate energy for the cell's metabolic processes. They respond to specific signals by releasing two proteins, cytochrome c and apoptosis-inducing factor (AIF), which in turn are involved in the activation of caspases (Kroemer et al. 1997). Caspases are substances that play a role in activating the apoptotic death pathway (Salvesen and Dixit 1997). The mitochondrial release of cytochrome c and AIF and the subsequent interaction of these proteins with caspases represent critical steps in the control of apoptosis.

Alcohol has long been known to influence mitochondrial function. Several recently reported effects of alcohol on mitochondria may be relevant to mitochondrial involvement in apoptosis. Among these alcohol effects are a decrease in the activity of ATP synthase (Marin-Garcia et al. 1995, 1996), an enzyme involved in the production of adenosine triphosphate (ATP), a critical component of the cell's metabolic processes. Other effects of alcohol on mitochondria are reduction in antioxidant levels (Colell et al. 1997; Kurose et al. 1996), enlargement of mitochondria (Mateos et al. 1995), and changes in mitochondrial membranes (Garcia-Ruiz et al. 1995). TNF is thought to mediate at least part of its toxicity through oxidative stress and alteration of mitochondrial function (Stadler et al. 1992).

Experimental Models

Studies in rats, mice, and tissue culture are evaluating the role of cytokines, especially TNF, in experimental models of liver disease. TNF has been shown to play a role in many forms of experimental liver disease, including that induced by a variety of toxins (Hill et al. 1997). The liver is normally resistant to the toxic effects of TNF. However, as noted previously, when TNF is produced in excess or when defenses against TNF are inadequate, liver injury may result.

Because mice and rats have a natural aversion to drinking alcohol, researchers developed a method of alcohol feeding by infusing it directly into the stomach (gastric infusion) (Tsukamoto et al. 1986). With this experimental model, researchers were able to produce blood alcohol levels high enough to cause liver injury. Research using this animal model demonstrated that liver damage coincided with increased levels of TNF messenger ribonucleic acid (mRNA) in the liver (Nanji et al. 1994*d*), indicating an increase in the message level directing synthesis of TNF. Other work with the same feeding model in rats showed that isolated Kupffer cells had increases in secretion of TNF, both spontaneously and after endotoxin administration, as well as increases in TNF mRNA (Kamimura and Tsukamoto 1995).

A decade ago, studies showed that the livers of chronically alcohol-fed rats, compared with controls, were more sensitive to the toxic effects of injected bacterial endotoxin (Bhagwandeen et al. 1987). Subsequent studies showed that alcohol-fed rats had much higher levels of TNF than did controls after exposure to endotoxin, but that liver injury could be lessened by administration of a prostaglandin-like drug that decreased TNF production (Honchel et al. 1992). Prostaglandins, substances that have diverse physiologic effects, have a protective effect on liver cells, partly as a result of their ability to control inflammation.

Rats fed alcohol by gastric infusion had high blood endotoxin levels and evidence of induction of cytochrome P450 2E1, an enzyme that metabolizes alcohol and causes the generation of ROS (Koop et al. 1996; Nanji et al. 1994*c*). Indeed, markers for oxidative stress and for lipid peroxidation were noted in these animals, confirming the probable presence of ROS (Li et al. 1997; Nanji et al. 1997*a*).

An animal model for liver regeneration is provided by surgically removing a portion of the liver in rats. Researchers have noted elevated levels of TNF and IL-6 in rats following such partial hepatectomy. They also showed that anti-TNF antibody inhibited regeneration (Akerman et al. 1992; Diehl and Rai 1996). Other studies showed that regeneration was inhibited in IL-6 knockout mice, a strain of genetically engineered mice in which the gene for IL-6 has been inactivated (Cressman et al. 1996). Although hepatectomized rats chronically fed alcohol had increased levels of TNF, signaling was depressed in important liver regeneration pathways (Zeldin et al. 1996). It appears that these rats have an impaired regenerative response to a TNF signal. This impairment may partially explain the depressed liver regeneration seen in patients with alcoholic liver disease and in rats chronically fed alcohol. These studies demonstrate the complexity of cytokine signaling in alcoholic liver disease: excessive amounts of TNF can result in liver injury, whereas insufficient levels can result in an impaired healing response. The fine line

between injury and health highlights some of the important issues that will have to be resolved concerning potential anticytokine therapy for liver injury in alcoholic liver disease.

Preventing Liver Injury

In an attempt to prevent or minimize liver injury, researchers devised several strategies to decrease oxidative stress, decrease endotoxin levels, or decrease cytokine production and activity. In one set of experiments, researchers fed antibiotics to rats in an attempt to sterilize the intestine and thus decrease the source of endotoxin. These experiments were successful in reducing alcohol-induced liver injury (Adachi et al. 1995). Other workers attempted to decrease endotoxin levels by changing the intestinal flora, feeding the rats a "good" strain of bacteria, *Lactobacillus* (Nanji et al. 1994*a*). This strategy was also successful at lessening liver injury.

Another approach was to administer gadolinium chloride to rats in an attempt to destroy the Kupffer cells in the liver, which are a likely source of toxic cytokine production (Adachi et al. 1995; Koop et al. 1997). This strategy was also successful, significantly diminishing alcohol-induced liver injury. In an attempt to decrease the generation of ROS, researchers administered agents to decrease cytochrome P450 2E1 (Nanji et al. 1994*b*). This approach also decreased alcohol-induced liver injury in rats. More recently, anti-TNF antibody prevented liver injury in alcohol-fed rats, providing compelling evidence of the relationship of TNF to alcohol-induced liver injury (Iimuro et al. 1997*b*).

The concept of anticytokine therapy is not unique to alcoholic liver disease. It is, in fact, the current focus of many biotechnology companies. Successful human clinical trials are already under way in other disease processes, such as rheumatoid arthritis and inflammatory bowel disease, where there are increased levels of proinflammatory cytokines such as TNF (MacFarlane et al. 1994; McSweegan 1997; van Dullemen et al. 1995).

Nutritional Factors

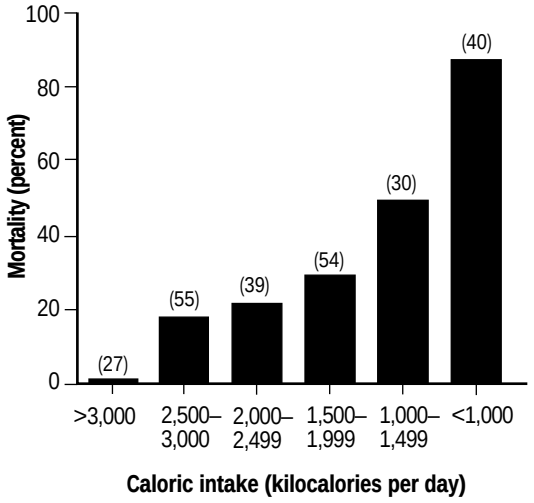
Changes in nutritional status and nutrient metabolism are associated with the development and progression of alcoholic liver disease. Researchers have used specific nutrients as well as total nutritional improvement in an attempt to reduce alcohol-induced liver injury in both humans and experimental animals. Results have shown that individual nutrients can either improve or aggravate liver injury.

Malnutrition

The most compelling evidence for a relationship between nutritional status and alcoholic liver disease comes from two large studies undertaken by the U.S. Department of Veterans Affairs. The subjects of these studies were inpatients with liver injury serious enough to cause symptoms of jaundice. All of them suffered from malnutrition (Mendenhall et al. 1995). The degree of malnutrition correlated with the development of serious liver complications such as ascites (fluid retention); encephalopathy (brain injury or damage causing abnormal mental function), which causes changes in mental status; and impaired kidney function. Malnutrition also correlated with death rate. The controls for these studies were patients who were alcoholics but had not yet developed detectable liver disease. However, the control patients also showed some evidence of malnutrition, which suggests that malnutrition might precede serious liver injury.

There was an inverse correlation between caloric intake and mortality. Almost all patients who consumed more than 3,000 calories a day survived, while more than 80 percent of those who took in less than 1,000 calories a day died (figure 2). Patients were strongly encouraged to increase their food consumption, with a goal of 2,500 calories a day. In spite of this, 67 percent of patients consumed insufficient calories, many of them because of severe anorexia. The cause of this anorexia is not clear, but it could be related to elevated levels of the cytokine TNF or to abnormalities in the metabolism of leptin, a hormone that controls appetite.

Figure 2: Six-month mortality associated with 1-month daily caloric intake in 245 patients



Numbers in parentheses denote number of patients. A highly significant relationship was observed ($p = 0.0001$; χ^2 test).

Source: Mendenhall et al. 1995. Reprinted with permission from *Alcoholism: Clinical and Experimental Research*, Vol. 19, pp. 635–641, 1995. Copyright 1995, Lippincott Williams & Wilkins, Baltimore, MD. Publisher web site: http://lww.com.

In one of the two Veterans Affairs studies, patients were given an anabolic steroid along with a nutritional support product designed specifically for patients with liver disease. Those with only moderate malnutrition improved significantly. However, those who were severely malnourished did not benefit from this regimen, possibly because their condition had already progressed beyond the point at which they could be helped by nutritional therapy (Mendenhall et al. 1993*a*, 1995).

A frequent complication of alcoholic liver disease is hepatic encephalopathy (brain disease), in part due to the effects of waste products that the liver is not able to detoxify. Traditionally, the condition has been treated by restriction of protein intake, a treatment designed to reduce toxin production. However, long-term protein restriction inevitably leads to more serious malnutrition. Indeed, these studies showed that low protein intake was associated with a worsening of encephalopathy (Mendenhall et al. 1993*a*). Recent studies showed that most patients could be treated successfully with antiencephalopathy medications, obviating the need for protein restriction.

Fats and Fatty Acids

Investigators have long believed that fat intake correlates with the development of cirrhosis, and that increased body weight may be a risk factor for alcoholic liver disease. Recent research on more than 1,600 alcoholic patients in France has confirmed that obesity is indeed a risk factor for the development of alcoholic liver disease (Naveau et al. 1997). In those patients who had been overweight for 10 years, there was an increased risk of developing fatty liver, alcoholic hepatitis, and cirrhosis. These observations are supported by animal studies. When rats were fed alcohol by gastric infusion and also received a diet high in polyunsaturated fats from fish oil, the severity of liver injury was increased (Nanji et al. 1994*c*, 1997*b*). On the other hand, a diet high in saturated fats protected the rats against liver injury (Nanji et al. 1995). These studies suggest that not all fats are alike; some are clearly harmful in the development of alcoholic liver disease, while others may actually have a protective effect. Other diseases, especially autoimmune disorders in animal models, have been accelerated by consumption of high-fat diets (Leitinger et al. 1999; Shimabukuro et al. 1997).

Iron

There is an association between increased iron in the liver and alcoholic liver disease. Alcohol intake generally increases the iron content in hepatocytes and Kupffer cells (Valerio et al. 1996), and supplemental iron intake exacerbates alcoholic liver injury (Tsukamoto et al. 1997). One effect of iron is that it promotes alcohol-induced injury by ROS (Tsukamoto et al. 1997).

Recent experiments have used cultured stellate cells to study the effects of iron. Stellate cells play a major role in the production of the tissue protein collagen, a step in fibrosis, or scarring. Iron appears to prime Kupffer cells for their role in stimulation of cultured stellate cells. Kupffer cells are a source of the cytokines TNF and IL-6 in liver injury (Kamimura et al. 1995). These cytokines stimulate stellate cells and their activity is regulated by NFκB, which is iron dependent (Lin et al. 1997). Indeed, Kupffer cells of rats

with alcohol-induced injury contain 70 percent more iron and have a two- to threefold increase in NFκB activity (Lin et al. 1997). Treatment of the cells with an iron chelator, a substance that binds the iron, resulted in a return of iron content and NFκB activity to normal levels (Lin et al. 1997). Future studies will attempt to determine the exact roles of iron and iron chelator in the development of injury and fibrosis in alcoholic liver disease.

Other Nutrients

Experiments with a soybean extract, polyenylphosphatidylcholine (PPC), showed that it can prevent fibrosis and cirrhosis in alcohol-fed baboons. It also stimulates the activity of collagenase, an enzyme that breaks down collagen, in cultured stellate cells (Li et al. 1992; Lieber et al. 1994). These observations led researchers to the conclusion that PPC prevents alcohol-induced fibrosis by way of its anticollagen activity (Lieber et al. 1994). Researchers then studied the effects of several related compounds but found only one, dilinoleoylphosphatidylcholine (DLPC), that had the same anticollagen effect. Experiments with DLPC showed that it not only decreased the severity of liver fibrosis, it actually accelerated its regression (Ma et al. 1996). Other observations of the action of DLPC in alcohol-fed baboons led to the conclusion that it may have antioxidant properties (Lieber et al. 1997). These properties could help prevent fibrosis and protect cells from injury. Because of these encouraging results with DLPC, a current Veterans Affairs study is now evaluating the effects of this drug in humans with early alcoholic liver disease.

Abnormal metabolism of the amino acid methionine is well documented in alcoholic liver disease (Marchesini et al. 1992). An enzyme, methionine adenosyltransferase (MAT), is responsible for conversion of methionine to *S*-adenosyl-L-methionine (SAM) (Lu 1998). SAM is important for its role in a variety of cellular processes. Recent studies have indicated that oxidative stress and depletion of the antioxidant glutathione play a role in MAT inactivation (Sanchez-Gongoro et al. 1997). Low oxygen levels in the liver also can cause a decrease in MAT activity (Avila et al. 1998). Both oxidative stress and low oxygen levels are prominent features of alcoholic liver disease (Chawla and Jones 1994). A reduction in levels of the products of methionine metabolism, such as SAM, thus may be associated with alcoholic liver disease. Depletion of mitochondrial glutathione appears to be an important factor in the development of alcoholic liver disease in rats (Hirano et al. 1992), but other studies have shown that therapy with SAM lessens this depletion (Colell et al. 1997).

Choline is a substance derived from methionine and SAM metabolism in the liver. Choline deficiency causes severe fatty deposits in the liver that are similar to the fatty liver seen in alcoholic liver disease. Recent studies showed that rats fed a diet low in methionine and choline developed SAM deficiency and a marked fatty liver (Chawla et al. 1998). Choline-deficient rats also showed increases in cytochrome P450 2E1 activity, which is believed to play a role in the development of liver injury (Weltman et al. 1996). Rats deficient in methionine and choline were highly susceptible to endotoxin-induced liver injury and had elevated levels of the cytokine TNF. Antibodies to TNF helped protect against endotoxin-induced liver injury in choline-deficient rats (Eastin et al. 1997). Administration of SAM before injection with endotoxin reduced liver injury and decreased TNF levels, an observation that supports the concept that SAM may have protective effects on the liver. Studies are currently under way in both animal models and human subjects with alcoholic liver disease to determine the effectiveness of supplementation with products such as SAM.

Other Liver Diseases

Recent work has highlighted three liver diseases that may be important in understanding the mechanisms of alcoholic liver disease. Acetaminophen toxicity may be enhanced by alcohol consumption. Hepatitis C has important and complex interactions with alcohol abuse. Fatty liver, often associated with obesity, can mimic alcoholic liver disease and may provide important clues to the mechanisms involved in alcoholic liver disease.

Acetaminophen Liver Toxicity

Acetaminophen is a widely used over-the-counter pain medicine that until recently had been marketed as an entirely safe product. It is sold in more than 200 formulations in the United States, including brand names such as Tylenol. Two decades ago, reports described an association between chronic alcohol consumption and acetaminophen liver toxicity (Goldfinger et al. 1978; McClain et al. 1980). Acetaminophen overdose can cause very acute, sudden liver failure, and death can occur in less than 1 week (Makin et al. 1995). If the patient survives the severe acute phase of toxicity, the liver will eventually return to normal. One means of maintaining patients through the period of acute toxicity is the use of an artificial liver system, which can keep patients alive until they either recover spontaneously or obtain a liver transplant (Watanabe et al. 1997).

Researchers reviewed cases of 67 patients who regularly consumed alcohol and who developed liver injury after taking acetaminophen for therapeutic reasons (Zimmerman and Maddrey 1995). Acetaminophen doses were within what is generally considered a nontoxic range in 60 percent of the patients and were within the recommended range for the other 40 percent. Patients developed severe liver damage, and 18 percent of them died. In another study of 71 patients hospitalized for acetaminophen liver toxicity, 21 had taken an accidental overdose of acetaminophen as a pain reliever and 50 had taken it in a suicide attempt (Schiodt et al. 1997). Sixty-three percent in the accidental overdose group and 25 percent in the suicidal group were chronic alcohol abusers. The accidental overdose group had much more severe liver injury (52 vs. 14 percent) and a greater number of deaths (19 vs. 2 percent). Acetaminophen ingestion accounted for approximately 40 percent of patients with acute liver failure during the study period. This study highlights the importance of accidental acetaminophen overdose as a major cause of acute liver failure. Patients with sudden and severe liver failure may go to the hospital too late to benefit from the only currently available antidote, *N*-acetylcysteine. Both of these reports stress the need for greater awareness of the risks of acetaminophen liver toxicity, both in the medical community and among the general public. Acetaminophen itself does not cause liver toxicity. Instead, a highly reactive metabolite, *N*-acetyl-*p*-benzoquinonimine (NAPQI), generated through the alcohol-metabolizing cytochrome P450 2E1 system, is believed to be the cause of liver cell death. Activity of 2E1 is greatest in the area of the liver in which acetaminophen toxicity is most severe (Cohen et al. 1997). NAPQI normally binds to a protective substance, glutathione. However, if liver glutathione stores are depleted, this reactive metabolite is free to cause liver cell injury. Alcoholics are more predisposed to glutathione depletion for several reasons, including poor nutrition.

Animal studies have confirmed the link between alcohol intake and increased risk for acetaminophen toxicity. Cytochrome P450 2E1 is increased in the hepatocytes of alcohol-consuming rats, and recent studies show that it is also increased in Kupffer cells, where inflammatory cytokines and ROS are generated (Koivisto et al. 1996). Investigators found that cytochrome P450 3A, another enzyme system, can be induced by alcohol in humans and in rats (Hoshino and Kawasaki 1995; Kostrubsky et al. 1997*a*). An important additional finding was that an inhibitor of cytochrome P450 3A protected against alcohol-enhanced acetaminophen liver toxicity in rats (Kostrubsky et al. 1997*a,b*).

Researchers have reported the presence of activated macrophages at the site of injury in acetaminophen toxicity. Also, increased levels of the cytokines IL-1 and TNF are present in acetaminophen liver toxicity in mice (Blazka et al. 1995). The same symptoms, Kupffer cell activation and cytokine production, are caused by chronic alcohol consumption. Recent research demonstrated that blocking Kupffer cell function totally prevented acetaminophen liver toxicity (Laskin et al. 1995).

The studies reported here tend to confirm the interaction between alcohol consumption and the

risk of developing acetaminophen liver toxicity. Acetaminophen liver toxicity has been established as the major cause of sudden and severe liver failure in the United States and in many European countries. Fortunately, warning labels are now being placed on acetaminophen-containing products concerning alcohol intake and risk of liver injury.

Hepatitis C

Hepatitis C virus (HCV) is an RNA virus that causes about 30,000 new infections each year (National Institutes of Health [NIH] Consensus Statement 1997). In the United States, almost 4 million people are infected with hepatitis C, four times the number infected with the human immunodeficiency virus (HIV). This infection is more prevalent in minority populations. About 85 percent of HCV-infected individuals do not become virus free within 6 months and are highly likely to develop chronic hepatitis.

There are usually few symptoms during the first 20 years of infection, and therefore the United States is currently entering an era in which individuals infected decades ago are beginning to show symptoms. The disease may be fatal and is, in fact, the leading cause of liver transplantation in the United States. Between 1 and 5 percent of patients with chronic HCV for 20 years will develop liver cancer (NIH Consensus Statement 1997).

A recent study of 100 alcoholics in a rehabilitation program found that 23 percent were positive for antibodies to HCV (anti-HCV). Of those who had liver disease, 43 percent tested positive for anti-HCV, while only 10 percent of those without clinically apparent liver disease tested positive (Coelho-Little et al. 1995). Thus, data from this and other studies strongly suggest that, for as yet unknown reasons, actively drinking alcoholic patients are more likely to have HCV infection.

Patients with alcoholic liver disease are at very high risk of having hepatitis C. A study of 288 patients with alcoholic hepatitis found that 18 percent of them had anti-HCV (Mendenhall et al. 1993*b*). Previous intravenous drug abuse was a risk factor, but more than 40 percent of these patients had no known risk factor for hepatitis C other than alcohol abuse. Another study of patients with alcoholic liver disease showed that those who were HCV positive had more severe liver disease and were younger than HCV-negative patients (Befrits et al. 1995). A study of individuals with chronic HCV found not only that those individuals developed the disease at a younger age but that those who drank alcohol heavily had higher liver enzyme levels, a clinical marker for liver disease (Cromie et al. 1996). Although abstinence from alcohol is associated with a decrease in liver enzyme levels, the presence of HCV interferes with this improvement (NIH 1997).

There are several possible mechanisms for the association of alcohol consumption with greater severity of HCV. The interaction of alcohol and HCV may impair immune responses to the virus (Geissler et al. 1997; NIH 1997; NIH Consensus Statement 1997). Iron levels in the liver are higher in HCV patients who drink alcohol heavily, and iron accelerates several forms of liver injury (Geissler et al. 1997). In addition, the inflammatory response in the liver is greater in individuals with HCV who drink alcohol. A further complication is that alcohol depresses the response to interferon therapy, which is the therapy of choice for HCV (Izumi et al. 1996). Interferons are proteins that provide an important defense against viral infections by making noninfected cells virus resistant.

Nonalcoholic Steatohepatitis

Nondrinkers may develop a disease that is virtually indistinguishable from alcoholic fatty liver (Pinto et al. 1996; Sheth et al. 1997). As in alcoholic liver disease, nonalcoholic steatohepatitis (NASH) results in inflammation, fibrosis, and cirrhosis. Most studies show that NASH is more frequent in women, although one study reported a higher frequency among men. Most patients are in their 40's and 50's, and most are obese (Sheth et al. 1997). NASH is generally present in greatly obese patients who have abdominal surgery for weight reduction.

Complications of NASH include non-insulin-dependent diabetes, hyperglycemia, and hyperlipidemia, a risk factor for heart disease. Often the liver is enlarged. Up to one-sixth of NASH patients eventually develop cirrhosis (Sheth et al. 1997). Recent studies show that increased iron content or changes in drug metabolism in the liver may play a role in the development of NASH (Bacon et al. 1994; George et al. 1998; Weltman et al. 1998). Nearly one-third of patients have, or carry a gene for, hemochromatosis, a disorder of iron metabolism.

No established therapy currently exists for treating NASH patients, although some physicians recommend use of the drug ursodeoxycholic acid (Laurin et al. 1996). However, because the disease is so closely associated with obesity, a frequent recommendation is simply that patients gradually lose weight (Sheth et al. 1997).

Researchers have developed strains of rats and mice that become obese due to a disruption in the action of leptin, the hormone that controls appetite. Both of these strains develop severe fatty liver. These animals are highly sensitive to endotoxin, developing severe fatty liver after exposure (Yang et al. 1997). Animals chronically fed alcohol exhibit a similar reaction following endotoxin injection (Honchel et al. 1992). In the obese animal strains, females are more sensitive than males to endotoxin injury. Females are also more sensitive to alcohol-induced liver injury, and endotoxin may play a role in that injury (Iimuro et al. 1997*a*). The obese animals showed abnormalities in the levels and actions of cytokines as well as impaired immune function (Loffreda et al. 1998). Further studies with these genetically obese rodents, as well as with obese humans, may provide new insights into the mechanisms of fatty liver in alcoholic liver disease.

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Alcohol and the Immune System

One of the least appreciated medical complications of alcohol abuse is its effect on the immune system. Excess alcohol consumption may lead to immune deficiency, causing increased susceptibility to certain diseases. Life-threatening complications of alcoholism such as liver disease and liver failure may have a component of autoimmunity, in which the immune system turns on the body's own tissues. This section describes current research that is providing new insights into the regulation of the immune system in people who drink alcohol heavily by examining alcohol-related alterations in the cells and molecules that shape the immune response. It also describes some of the exciting new techniques that are being designed to improve or restore immune function by manipulation of these cells and molecules. Although much remains to be learned, researchers are making rapid progress in understanding alcohol-related immune disorders.

Alcohol and Diseases Related to the Immune System

Physicians have long observed that excessive alcohol consumption can lead not only to liver damage but also to increased illness and death from infectious diseases such as pneumonia. (See, for example, the writings of Philadelphia physician Benjamin Rush [1745–1813] [Rush 1943]). We now regard this increase in disease as the result of immunodeficiency caused by alcohol abuse. Further, there is reason to suspect that the organ damage, such as alcoholic liver disease, observed in people who drink alcohol heavily is at least partially caused by alcohol-triggered autoimmunity in which the immune system attacks the body's own tissues. A number of reviews in the literature provide an overview of current knowledge concerning alcohol's effects on the human immune system (Baker and Jerrells 1993; Cook 1995, 1998; Frank and Raicht 1985; Ishak et al. 1991; Johnson and Williams 1986; Kanagasundaram and Leevy 1981; MacGregor and Louria 1997; Mendenhall et al. 1984; Mufti et al. 1989; Palmer 1989; Paronetto 1993; Watson et al. 1986).

Diseases Related to Immunodeficiency

Pneumonia

In the early part of this century, researchers noted that alcoholics were more than twice as likely as nonalcoholics to die from pneumonia (Capps and Coleman 1923). Despite the availability of antibiotics in the modern era, alcohol abusers still suffer from increased susceptibility to bacterial pneumonia (Chen et al. 1992; Chomet and Gach 1967; Cortese et al. 1992; Esposito 1984; Kuikka et al. 1992; Kuo et al. 1991). Further, a study of all patients with pneumonia has shown that a high percentage were alcohol abusers, even though they may not have been diagnosed previously as alcoholics (MacGregor and Louria 1997). Clearly, the effects of alcohol abuse on illness rates and treatment costs for pneumonia are considerable.

Tuberculosis

The incidence and severity of pulmonary tuberculosis (TB) is greater in alcoholics than in nonalcoholics (MacGregor and Louria 1997). In the overall population, 16 percent of TB patients are alcohol abusers; the percentage ranges up to more than 35 percent in some populations (Centers for Disease Control and Prevention [CDC] 1996). For example, long-term studies of drug and alcohol abusers who were followed for many years showed that these individuals had TB incidence rates from 15 to 200 times the rates for control populations (Friedman et al. 1987, 1996). In recent years, the incidence of TB has been increased by the presence of human immunodeficiency virus (HIV) in drug and alcohol abusers. However, even after this added risk is taken into account, it is still clear that drug and alcohol abusers have increased rates of illness and death from TB (CDC 1996; White and

Portillo 1996). The recent rise of drug-resistant strains of the TB bacillus (CDC 1996) gives even greater urgency to the need for effective intervention among populations at risk of TB, both nationally and worldwide.

HIV

Infection with HIV, which leads in its later stages to acquired immunodeficiency syndrome (AIDS), has become one of the great epidemics of our time, with millions infected worldwide. Transmission is primarily through sexual contact or the sharing of used needles by drug abusers. Alcohol abusers may be at increased risk for infection due to risky sex practices compared with nonabusers (MacGregor and Louria 1997), but two questions remain unanswered. The first question is whether alcohol consumption, either before or at the time of exposure, increases susceptibility to infection. The second question is whether alcohol use hastens the progression from asymptomatic HIV infection to full-blown AIDS. Studies of alcohol effects on HIV using isolated white blood cells have produced conflicting results. One research group reported an increased HIV growth rate after prior alcohol consumption by donors of the cells (Bagasra et al. 1989, 1993, 1996). A second group found no consistent effect (Cook et al. 1997*b*). A recent clinical study of HIV-positive drug abusers who were followed for several years showed that those who drank alcohol heavily had significantly more abnormalities in the T-lymphocytes (T-cells; see the discussion in this section on the immune system) than did those who were light alcohol drinkers or abstainers (Crum et al. 1996). Since both HIV-infected individuals and noninfected alcohol abusers have compromised immune systems, the question of interactions between these two conditions remains important for investigation.

Hepatitis C and Hepatitis B

Many recent studies have attempted to determine the relationship between alcohol abuse and hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. The most recent studies have determined that, after correction for nonalcohol-related risk factors such as intravenous drug abuse and unsafe sexual practices, alcoholics do not have an increased incidence of HBV but do have an increased HCV incidence of about 10 percent compared with nonalcoholics (Rosman et al. 1996). If alcoholics are considered as a group without excluding other risk factors for infection, the prevalence of either HBV or HCV is in the range of 10 to 50 percent (French 1996; Grellier and Dusheiko 1997; Rosman et al. 1996). These hepatitis-positive patients are suffering from two diseases, alcoholism and nonalcoholic viral hepatitis, that may have additive or synergistic effects on the development of liver disease. Both conditions may affect the immune system to produce immunodeficiency and autoimmunity.

Other Infections

Alcohol abusers are more susceptible than nonabusers to other infections, such as septicemia, which is an infections of the circulating blood. In some cases, septicemia is caused by bacterial spread from pneumonia. Other infections that may lead to septicemia in the alcohol abuser include urinary tract infections and bacterial peritonitis, an infection of the lining of the abdominal cavity (Chen et al. 1992; Cortese et al. 1992; Esposito 1984; Kuikka et al. 1992; Kuo et al. 1991).

Alcoholics appear to be more susceptible than nonalcoholics to several less common infections, such as lung abscess, empyema (an accumulation of pus in the chest), spontaneous bacterial peritonitis, diphtheria, cellulitis (an inflammation of connective tissue), and meningitis (an inflammation of the membranes of the brain and spinal cord) (MacGregor and Louria 1997). It is clear that the increased incidence of infectious diseases in alcohol abusers represents a significant toll of individual suffering and of medical expense to society.

Diseases Related to Autoimmunity

A disastrous medical complication of chronic alcohol abuse is alcoholic liver disease with eventual liver failure. Alcoholic liver disease,

which includes alcoholic hepatitis, cirrhosis, and fatty liver, is discussed in the section "Alcohol-Induced Liver Injury" earlier in this chapter and in the *Ninth Special Report to the U.S. Congress on Alcohol and Health* (National Institute on Alcohol Abuse and Alcoholism 1997). Several extensive reviews present an overview of published research (Lieber 1994; Mendenhall et al. 1984, 1995).

Alcoholic hepatitis is characterized by acute liver inflammation and cell death. In severe cases, death of the patient occurs in one to several weeks after admission to the hospital. There is evidence that the immune system may cause some of the injury. One indication is that alcoholic hepatitis continues to worsen after withdrawal from alcohol, suggesting that the damage is not due solely to the presence of alcohol. A second indication of immune system involvement is that alcoholics who recover from alcoholic hepatitis but then resume drinking alcohol typically suffer new episodes of hepatitis. These recurrent episodes are more severe and occur at a lower level of alcohol consumption. This suggests a possible autoimmune process in which immunity to some component of the patient's own liver has developed and is exacerbated by a resumption of alcohol drinking.

In alcoholic cirrhosis, the structure of the liver is distorted by scarring due to the deposition of fibrous tissue, and the functional units of the liver—the lobules—are damaged. Eventually, this process may result in liver failure and death. Many cirrhosis patients also suffer from alcoholic hepatitis and may have autoantibodies against the liver, which would contribute to cell damage and scarring. Involvement of the immune system in alcoholic cirrhosis is currently under study.

Several other conditions with probable autoimmune origin have been noted in alcohol abusers. Kidney disease is increased in alcohol-abusing individuals in some racial groups or isolated populations, suggesting a possible genetic component (Smith et al. 1993). The presence of autoantibodies in a wide range of tissues in alcohol abusers supports the possibility that other illnesses in the alcoholic are of autoimmune origin. Possible involved molecules include white blood cells, brain cells, deoxyribonucleic acid (DNA), and various proteins (Cook et al. 1996; Laskin et al. 1990; Paronetto 1993; Wehr et al. 1993).

The Immune System

The effects of alcohol on the immune system involve various types of immune cells and their interactions. These interactions are partly mediated by cytokines, chemical messengers that are described in some detail in the previous section, "Alcohol-Induced Liver Injury." The following discussion provides some background on the immune system and its components.

Two broad categories of immune cells are phagocytes and lymphocytes. Phagocytes are white blood cells that act by engulfing and destroying bacteria and other foreign substances. They include monocytes, neutrophils, and macrophages. Monocytes may circulate in the blood, or they may migrate into the tissues where they develop into fixed macrophages, such as the Kupffer cells in the liver. Neutrophils circulate in the blood and are among the first cells to arrive at the site of an injury or infection.

Lymphocytes are white blood cells produced in the lymphoid organs, mainly the bone marrow, thymus, lymph nodes, and spleen. Two of the main types of lymphocytes are T-cells, which are produced in the thymus, and B-lymphocytes (B-cells), which are produced in the bone marrow. There are several subtypes of T-cells. Helper T-cells respond to infection by secreting cytokines that stimulate other immune system cells. Cytotoxic T-cells recognize foreign substances, or antigens, on the surface of infected or transplanted cells and act by destroying these cells. Suppressor T-cells alter other immune responses in order to prevent overreaction of the immune system.

The B-cells are stimulated by antigens to produce antibodies, or immunoglobulins. Each B-cell is specific to one particular antigen. Most activated B-cells develop into plasma cells, which secrete

large numbers of antibodies into the blood stream. Specialized B-cells are the memory cells, long-lived cells that continue to circulate in the blood. If memory cells are re-exposed to the original antigen, they respond even more vigorously than in the initial response.

Another type of lymphocyte, the natural killer (NK) cell, provides an important defense against cancer and viral infections. NK cells can recognize, bind directly to, and destroy cells infected by viruses and, possibly, cancerous cells. They do not require previous exposure in order to recognize target cells.

Immune responses may be broadly classified as either cell mediated or humoral. Cell-mediated immunity refers to direct cell-to-cell immune response, such as that provided by the phagocytes and T-cells. Humoral immunity is provided by antibodies that circulate in the blood and lymph. The term refers to the body's fluids, or "humors." B-cells are the source of humoral immunity. T-cells play a central regulatory role, inhibiting or stimulating production of antibodies by B-cells, producing many different cytokines, interacting with monocytes, and interacting with and regulating other subclasses of T-cells. Monocytes interact with T-cells by presenting antigen to the T-cells, which leads either to stimulation of the production of antibody by B-cells or to cell-mediated responses by the T-cells themselves.

One of the most important developments in immunology in recent years has been the discovery of a vast network of regulatory molecules called cytokines. Many different types of these protein molecules are secreted by cells of the immune system, and changes in their balance have profound effects on the function of the immune cells. Some cytokines induce inflammation, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α, or TNF). Interleukin-10 (IL-10), on the other hand, has antiinflammatory effects. Interleukin-8 (IL-8) attracts neutrophils to the site of an infection. Interleukin-12 (IL-12) activates NK and helper T-cells and induces the cell-mediated immune response.

Changes in the Immune System of Alcoholics

Alcoholics often have greatly increased blood levels of immunoglobulins (Cook et al. 1996; Sheron 1994). The major classes of these antibodies are immunoglobulins A, G, and M (IgA, IgG, and IgM), each of which has a specialized role in the immune response. Typically, IgA is elevated in the blood of alcoholics both with and without alcoholic liver disease, while IgG is elevated in those with liver disease. IgM is elevated only in patients with active liver disease, such as alcoholic hepatitis. IgA also may be found as tissue deposits in the skin, liver, and kidney of alcoholics (Paronetto 1993). Although an increase in a given antibody is usually associated with a specific immunity, such as the immunity resulting from a vaccination, alcoholics with these greatly increased antibody levels are often immunodeficient. These higher antibody levels may be due to abnormal regulation of the production of antibodies, or they may be a manifestation of autoimmunity.

Changes in the cell-mediated immunity of alcoholics include reduced response to tuberculin and fungal skin tests. Isolated lymphocytes taken from alcoholics also demonstrate a reduction in the immune response. Several recent reviews summarize studies on cell-mediated immunity in alcoholics (Cook 1995; MacGregor and Louria 1997; Paronetto 1993).

Alcoholics without liver disease typically have normal numbers of lymphocytes in their peripheral blood, while those with liver disease have a wide range of abnormalities. In patients with alcoholic hepatitis (an earlier stage of alcoholic liver disease), there is a mild reduction in lymphocyte numbers, with a return to normal levels after several weeks of recovery. However, patients with alcoholic cirrhosis (a later stage of alcoholic liver disease) may have lymphopenia, a severe reduction in lymphocyte numbers.

Abnormalities of immune function can be accompanied by changes in the percentages of different types, or subsets, of lymphocytes or by

changes in cell surface markers. Investigators have compared lymphocyte subsets in alcoholics and in nonalcoholic controls (Cook 1995). They have shown that, in alcoholics, the ratio of helper T-cells (designated CD4) to cytotoxic and suppressor T-cells (designated CD8) is normal or elevated. This finding is in sharp contrast to patients with AIDS, who have a greatly decreased CD4-to-CD8 ratio. Alcoholics also show changes in various molecules on the surface of T-cells that, taken together, may be considered a chronic activation of the T-cells. Recent studies have shown that T-cell activation is apparent for considerable periods of time after alcohol withdrawal (Laso et al. 1996, 1997).

Alcoholics without liver disease tend to have normal numbers of B-cells, the antibody-producing lymphocytes. However, in patients with alcoholic liver disease, B-cells often are decreased in number, in spite of the fact that these cells produce abnormally large amounts of immunoglobulins. B-cells also show changes in their subset patterns (Cook et al. 1996; Laso et al. 1996), but these changes appear to be more short-lived than the T-cell changes (Laso et al. 1997). Together, the changes in both T-cells and B-cells suggest that there may be alterations in the interactions between the two types of cells that are important for understanding many of the defects of immune regulation in alcoholics.

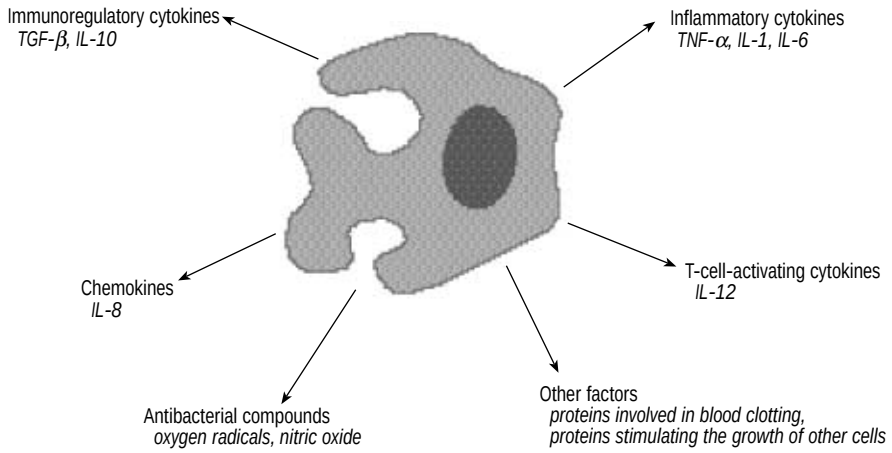
Although results have been inconsistent, some investigators have reported that the NK cells have reduced functional activity in alcoholics (Charpentier et al. 1984). Recent work has shown that alcoholics without liver disease may have normal NK cell activity and numbers, but that some patients with alcoholic liver disease have greatly reduced NK cell numbers and loss of NK cell activity (Cook et al. 1997*a*; Kronfol et al. 1993). Interestingly, normal NK cells are mildly stimulated by overnight exposure to alcohol if activity is measured after alcohol removal (Li et al. 1997). This finding indicates that NK cell loss in alcoholics with liver disease is probably not a direct result of alcohol consumption but is an indirect consequence of other immune changes resulting from chronic alcohol exposure.

Neutrophils not only form one of the first lines of defense against invading bacteria, they also react to other stimuli, such as one's own tissues after damage by various agents. In alcoholic hepatitis, there often is an increase in the number of neutrophils in the blood, and microscopic examination of the liver shows infiltration of the liver by neutrophils. Since these cells typically release powerful enzymes that damage tissue, an abnormal number of neutrophils in the liver of alcoholics is one possible mechanism for liver damage. In some alcoholics with late-stage disease, neutrophil numbers in the blood may be significantly reduced, apparently because of bone marrow suppression, a situation that contributes to immunosuppression. Other neutrophil abnormalities associated with alcohol include reduction in the movement of neutrophils to sites of inflammation and decreased antibacterial activity (Cook et al. 1990).

Monocytes circulate in the blood and also have counterparts residing as fixed macrophages in many tissues, including the liver and lungs. These cells not only have the ability to engulf bacteria, they also produce chemicals that are toxic to bacteria. These and other functions can be altered by alcohol in cultured cells (Zuiable et al. 1992) and in the monocytes of alcoholic patients (Silvain et al. 1995), as can the substances derived from monocytes and macrophages (figure 1).

Cytokine balance is disrupted in alcoholic liver disease (McClain et al. 1993). The monocytes in the bloodstream and the fixed macrophages, such as the Kupffer cells in the liver, produce an excess of the proinflammatory cytokines IL-1, IL-6, and TNF in response to alcohol. These same cells are sensitive to stimulation by a lipopolysaccharide, known as LPS or endotoxin, a toxic substance produced in the cell walls of bacteria that commonly reside in the intestine. LPS is a powerful activator of many immune system cells. It can potentiate the effects of alcohol in activating macrophages, particularly the Kupffer cells. One result of this combined activation is to increase liver damage under experimental conditions. Since alcoholics can have increased

Figure 1: Monocyte- and macrophage-derived substances potentially affected by alcohol



Monocytes and macrophages produce numerous substances that initiate and regulate inflammatory reactions; attract other immune cells (chemokines); stimulate T-cells; help in the elimination of pathogens, such as bacteria; and perform other functions throughout the body. Alcohol may interfere with the production and secretion of all these substances, thereby impairing the body's immune response.

IL, interleukin; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

Source: Szabo 1997.

levels of LPS in their blood, and their isolated monocytes may respond more strongly to LPS, it is possible that liver damage in alcoholics is accentuated by the interaction of alcohol and LPS (Schenker and Bay 1995). Stimulation by LPS causes the monocytes and macrophages to secrete more TNF (Schafer et al. 1995). Since TNF is toxic to many cells, excessive production of this cytokine contributes to cell death. Patients with acute alcoholic hepatitis have a poorer outcome if they have markedly elevated TNF levels in the blood, which seems to confirm this concept (Bird et al. 1990; Felver et al. 1990). Some researchers report that alcoholics produce lower than normal amounts of the anti-inflammatory cytokine IL-10, thus failing to inhibit the excessive production of pro-inflammatory cytokines such as TNF (Le Moine et al. 1995).

Experimental Models

In order to properly evaluate clinical observations and immune system changes found in human alcoholics, it is necessary to compare immune functions in animals and cell cultures. Mice and rats are fed alcohol in the diet or by direct infusion into the stomach so that levels of intake can be controlled carefully. The levels of alcohol mimic the approximate amount consumed by human alcoholics: 15 to 40 percent or more of total caloric intake. In some experiments, researchers administer larger amounts of alcohol in a single exposure to mimic the effect of human binge drinking. In most of these experiments, researchers then examine lymphocytes and other immune system cells for alterations in function, growth, and cell development. Other experimenters use isolated immune system cells grown in culture. After exposing the cells to alcohol for periods of up to a few days, they are able to

evaluate the direct effects of alcohol on specific functions. In addition to the research outlined below, several recent reviews describe other aspects of work in this area (Baker and Jerrells 1993; Jerrells and Sibley 1995; Jerrells et al. 1994).

Infectious Diseases

Animal models of infections in the presence or absence of alcohol have demonstrated a number of important findings (Jerrells et al. 1994). Bacterial pneumonia initiated by *Klebsiella* or *Streptococcus pneumoniae* causes increased mortality in alcohol-fed rats and mice (Lister et al. 1993*b*; Nelson et al. 1991). Several other infections are more severe or prolonged in these animals, including the systemic infection listeriosis and the gastrointestinal infections caused by *Salmonella* and by intestinal parasites such as *Nippostrongylus* (Jerrells et al. 1994).

Researchers have studied TB organisms both in mice and in cell cultures of macrophages, the cells that ordinarily provide a first line of defense against this organism. Alcohol exposure increased the number of TB organisms in both cases and caused changes in the TB organism that lessened the effectiveness of the macrophage response (Bermudez et al. 1992, 1994). Some investigators have produced limited data suggesting that, in contrast to the worsening of TB infections after standard chronic alcohol exposures, low-dose alcohol exposure in experimental animals may actually improve the response to the TB organism (Mendenhall et al. 1997*b*). Other factors that may be involved in these alcohol-TB interactions have been reviewed recently (Nelson et al. 1995).

Immune System Cells

Cells of the Lymphoid Organs. Both chronic and acute alcohol administration can produce loss of lymphocytes from the thymus, spleen, and lymph nodes of experimental animals (Ewald 1989; Ewald and Shao 1993; Jerrells et al. 1994; Pruett et al. 1994). The cell types lost include B-cells, NK cells, and thymocytes, which are the developing T-cells in the thymus. The mechanisms of these cell losses appear to include a form of cell suicide known as apoptosis (programmed cell death). This phenomenon is discussed in detail in the section "Alcohol-Induced Liver Injury" earlier in this chapter. Under normal conditions, apoptosis helps to maintain the balance of cell numbers throughout the body. It is currently thought that alcohol may affect this process by disturbing the balance between cell increase through cell division and cell loss through apoptosis. One possible alcohol-induced disturbance in the thymus would be a selective apoptosis that would fail to delete self-reactive cells, resulting in a predisposition to autoimmunity. Recent research tends to discount this possibility (Livant et al. 1997). However, several investigators are actively pursuing the study of alcohol-induced apoptosis in other organs and cells, and new insights are anticipated.

T-Cells. Experimenters have exposed isolated lymphocytes of alcohol-fed animals to various agents in order to evaluate T-cell responsiveness to these agents. Results from one study indicated that stimulation by nonspecific agents or stimulation in the presence of mixed-cell populations caused a reduced response by the T-cells of alcohol-fed animals (Baker and Jerrells 1993). However, there has been some doubt as to whether the reduction was actually due to a T-cell alteration by alcohol. More recent work has used stimulation of T-cells by antibody to the T-cell receptors, mimicking the stimulation by antigen specific for the receptor. These studies have suggested that the inhibition produced by alcohol consumption may indeed be due, at least in part, to an alcohol-associated T-cell defect (Domiati-Saad and Jerrells 1993). In addition to reductions in T-cell proliferation, there appear to be alterations in the amount or pattern of cytokine production by T-cells in alcohol-fed animals.

Monocytes. Researchers have shown that exposure of cultured normal human monocytes to alcohol concentrations similar to those seen in binge drinkers reduces the ability of these monocytes to present antigen to T-cells (Szabo et al. 1993). (It is necessary for an "antigen-presenting" cell to process and display antigen in a way that the

T-cell will recognize it.) Researchers attributed this reduction to an alcohol-induced imbalance of cytokines. Experiments with cultured cells from alcohol-fed animals also showed a reduction in antigen presentation (Mikszta et al. 1995). Other animal research found genetic variation in the degree of alcohol-induced reduction in T-cell responses (Schodde et al. 1996). When cells were exposed to alcohol after antigen presentation, the effectiveness of the T-cell response was not diminished (Waltenbaugh and Peterson 1997). The reduction in cell-mediated immunity so commonly seen in chronic alcoholics thus appears to be partly due to the loss of an early step in antigen presentation. This could be a result of a functional change in monocytes and/or a change in T-cell-monocyte interactions.

Natural Killer Cells. Some alcoholics, especially those with cirrhosis, may have considerably reduced NK cell activity as measured in their isolated lymphocytes (Charpentier et al. 1984). Studies in alcohol-fed mice and rats have generally shown that the effect of alcohol on NK cell activity depends greatly on such factors as nutritional state, specific genetic strain, age, exercise, and amount and timing of alcohol administration (Cook et al. 1997*a*; Li et al. 1997). Nevertheless, chronic alcohol ingestion clearly inhibits NK cell activity in some mouse strains (Gallucci et al. 1994). A binge-equivalent single administration also can temporarily reduce both NK cell numbers and activity (Wu et al. 1994).

Indirect clinical evidence implicates NK cells in immune system protection from various cancers. Since alcohol can reduce NK cell numbers and activity, several studies have compared the spread of experimental tumors in animals both with and without continuous alcohol exposure. Some experiments suggested enhancement of tumor spread by alcohol, presumably mediated by alcohol-induced NK cell suppression (Yirmiya et al. 1992). Other studies, using a different tumor model, reported suppression of tumor spread (Meadows et al. 1993). Some data indicate that both the exact site of the tumor and previous exposure of the cells to alcohol are important in predicting whether alcohol will accelerate or retard tumor spread (Blank and Meadows 1996).

Neutrophils. More than half a century ago, an investigator observed that alcohol prevented the neutrophils of intoxicated rabbits from reaching the skin and lungs in response to the administration of pneumococcal bacteria (Pickrell 1938). Later investigators confirmed that alcohol inhibited neutrophil migration in humans (Brayton et al. 1970; Gluckman and MacGregor 1978) and in experimental animals (Astry et al. 1983; Avaria et al. 1981; Nelson et al. 1991).

A critical factor in the migration of immune cells across capillary walls is the presence of certain proteins, known as adhesion proteins, on the cell surface (Gallatin et al. 1983; Lewinsohn et al. 1987). Some researchers have reported that alcohol reduces the expression of adhesion molecules, with the result that fewer immune cells arrive at sites of infection (MacGregor et al. 1988; Zhang et al. 1997*b*). On the other hand, other researchers have reported increases in the levels of adhesion molecules in human alcoholics (Cook et al. 1994; Santos-Perez et al. 1996) and in animals (Bautista 1995, 1997; Nanji et al. 1995*b*). These increases could be a partial explanation for the infiltration of neutrophils into the liver that is observed in alcoholic hepatitis. A complicating factor is the observation that the migration of neutrophils to infection sites is altered after acute alcohol ingestion similar to binge drinking (Nelson et al. 1991) but not after chronic alcohol exposure (Lister et al. 1993*a*). This observation suggests that chronic exposure may lead to adaptation in adhesion molecules, a situation that makes predictions extremely difficult.

Since chronic alcohol exposure in experimental models may not reduce neutrophil migration to the lung, researchers evaluated the effectiveness of other neutrophil functions, such as phagocytosis and killing of pneumococcal bacteria. Experiments with alcohol-fed rats showed that their neutrophils phagocytosed bacteria efficiently but

did not kill all strains of pneumococcal bacteria with normal effectiveness (Jareo et al. 1995, 1996). It is interesting that one study of alcohol-fed rats reported changes in pulmonary surfactant, a lung secretion, that resulted in a lessening of antibacterial activity (Rubins et al. 1996).

Cytokines

Acute exposure to alcohol in LPS-stimulated normal rats can produce rapid changes in the production of several cytokines (Nelson et al. 1995). Experiments with isolated human monocytes show the same effects (Mandrekar et al. 1996; Szabo et al. 1992, 1996*a*,*b*; Verma et al. 1993). The changes reported include increases in some cytokines and decreases in others. These changes have important implications for immunity because cellular immune reactions are dependent on different cytokines for their initiation and continuation. Other experiments have shown that changes in cytokine balance in alcoholics may be due to a reduction in a process known as endocytosis, in which the cytokine is taken up by the cells and degraded (Deaciuc et al. 1996; Tuma et al. 1996*b*).

Animal research supports the concept of increased levels of proinflammatory cytokine production after exposure to alcohol. Animal studies also confirm the additive effects of LPS and alcohol in producing liver injury (Kamimura and Tsukamoto 1995; Pennington et al. 1997). In the lung, however, the LPS-stimulated secretion of proinflammatory cytokines actually may be reduced in alcohol-fed animals (Standiford and Danforth 1997) and in human alcoholics (Gosset et al. 1995). This reduction in cytokines could increase susceptibility to pneumonia. Consistent with this finding, researchers have reported a loss of TNF receptors on lung macrophages (D'Souza et al. 1994).

The cytokine IL-8 causes an increase in the number and activity of neutrophils. IL-8 is elevated in patients with alcoholic hepatitis, and this elevation may be one mechanism for the increased infiltration of the liver by neutrophils in this disease (Bird 1994; Hill et al. 1993; Huang et al. 1996). Recent work with rats indicates that the stimulation of IL-8 production in alcoholics may be indirect, involving interactions of alcohol metabolism, liver cells, and Kupffer cells (Maher 1995).

Current Directions

In the past several years, research in immunology has shown that there is a dramatic degree of interaction and mutual regulation among the different types of immune system cells. The insights from this work have led to many new avenues for investigation.

TH1/TH2 Immunity

One of the most fascinating and useful developments in immunology in the past several years has been the description of polarized responses of the immune system according to the offending agent, the type of immune cell encountered, and the cytokine environment in which the response occurs (Fitch et al. 1993; Medzhitov and Janeway 1997; O'Garra and Murphy 1994; Romagnani 1995). As noted earlier, the cells of the immune system respond to infectious agents along two broad pathways—cell-mediated immunity and humoral immunity. Within these pathways are further distinctions based on the type of infectious agent and the cytokine environment that stimulates the response most strongly.

TH1 (referring to a subset of T-helper cells) responses are predominantly cell mediated and are stimulated most strongly by the cytokines IL-12 and interferon gamma (IFN-γ). TH2 (an alternate subset of T-helper cells) responses are predominantly humoral, or antibody mediated, and are stimulated most effectively by the cytokines interleukin-4 (IL-4), interleukin-5 (IL-5), and IL-10. If the TH1/TH2 balance is skewed too far in one direction, immunologic disease may result. Autoimmunity is often associated with TH1 reactions, while immunodeficiency and allergies may be polarized toward a TH2 response (Romagnani 1995).

The responses tend to be mutually inhibitory. For example, the maturation of T-cells in a TH2 environment results in a preponderance

of TH2-type T-cells, with inhibition of TH1 development. It is of great interest to determine what factors in the infectious agent or in the environment influence the direction of the initial immune response toward TH1 or TH2. Current evidence points toward monocytes and other antigen-presenting cells as critical in the initial interpretation of the offending agent and the production of the cytokines that will stimulate either a TH1 or TH2 response (Medzhitov and Janeway 1997). This innate, first-responding component of the immune system is distinguished from the adaptive immune system consisting of T-cells and B-cells. This adaptive system produces cells that respond to specific antigens and that confer specific long-term immunity to those antigens.

The immune abnormalities seen with alcohol abuse, including elevated immunoglobulin levels and immunodeficiency, may be the result of polarization toward excess TH2 function (Cohen 1995). However, the TH1/TH2 balance in alcoholics with late-stage cirrhosis may be different from that of alcoholics with early acute alcoholic hepatitis. It is important to determine whether TH1/TH2 imbalance is caused by acute or chronic alcohol abuse and, if so, whether this imbalance could account for immune abnormalities.

Results of recent work with cultured normal human monocytes acutely exposed to alcohol indicate an increase in IL-10 and a decrease in IL-12 (Girouard et al. 1998), which would shift the TH1/TH2 balance toward TH2. Another recent study showed that the cells of alcohol-fed mice tend to shift toward a TH2 response, with a decrease in TH1 response (Peterson et al. 1998*b*). This second report offers a possible mechanism for the shift. Glutathione, a protective antioxidant, is known to be depleted by heavy alcohol consumption; in the cell cultures used for this research, reduction of glutathione also caused a shift toward TH2 cytokine production (Peterson et al. 1998*a*). The observations reported by these two groups represent an exciting new direction for analysis of the immunologic abnormalities caused by alcohol abuse. TH1/TH2 balance must now be evaluated in the human alcoholic whose innate and adaptive immune systems have had many years of high-level exposure to alcohol.

Molecular Regulation

Transcriptional Control. When an agent that influences cell behavior, such as an antigen stimulating an immune response, interacts with the cell, its influence on the cell occurs through an elaborate sequence of molecular events. The first such event is binding to a cell surface receptor. That receptor then conveys a signal to the cell's interior. This signal is interpreted in the cell's cytoplasm, and a new signal is transmitted to the nucleus, where interaction with cellular DNA occurs. The DNA transcribes the message to a strand of ribonucleic acid (RNA), which then directs the synthesis of new proteins, such as cytokines. These proteins are transported out of the cell, where they influence the original agent or other cells in the vicinity.

Although there are no specific cell receptors for alcohol, alcohol does influence this sequence of events in several ways. Both potassium and calcium ion concentrations change rapidly in the cell's interior during various types of cell activation events, and they often are measured as indirect indicators of changes within the cell. After short-term alcohol exposure, potassium conductance is increased (potassium channels in the cell membrane are opened) in T-cells (Oleson et al. 1993), and intracellular calcium concentrations are shifted in neutrophils (Nilsson et al. 1992; Patel et al. 1996) and in Kupffer cells (Hijioka et al. 1993). Although there has been little research on alcohol's direct effects on specific signaling pathways in immune system cells, studies of liver cells and tumor cells show that alcohol can cause alterations in receptor molecules and other molecules in the signal cascade leading to cell activation (Saso et al. 1996; Thurston and Shukla 1992; Zeldin et al. 1996). It is clear from these and other results that alcohol alters the molecular mechanisms that control cell responses to normal stimuli. An understanding of the consequences of these changes will require further study.

One of the cytoplasmic elements involved in the activation of cellular responses is a transcription factor called nuclear factor kappa B (NFκB). This molecular complex is activated by signaling events. It is then transported to the nucleus, where it binds to DNA and initiates the synthesis of RNA. Researchers have examined the effect of acute alcohol exposure on this process in Kupffer cells of experimental animals (Fox et al. 1996) and in normal human monocytes (Mandrekar et al. 1997). Both studies reported disturbances of LPS-induced NFκB activation. The study of human cells reported that alcohol disturbed the NFκB complex in such a way that the signal to the nucleus was inhibitory rather than stimulatory (Mandrekar et al. 1997).

Mediators of Inflammation. Cells of the innate immune system produce reactive oxygen species (ROS), toxic substances that kill bacteria and cause inflammation. These species include nitric oxide (NO), hydrogen peroxide, and other highly reactive chemicals. Since the cells that produce ROS are ubiquitous, abnormally increased or persistent activation of the pathways leading to production of these chemicals could cause tissue destruction and inflammation.

Studies of liver injury find that alcohol-fed animals have higher levels of ROS resulting from increased NO production after LPS stimulation (Chamulitrat and Spitzer 1996). The effect of NO in causing liver damage may depend on the type of liver cell producing the increase (Nanji et al. 1995*a*). Protective mechanisms within the liver are themselves affected by alcohol and also are influenced by cytokines whose balance, in turn, is affected by alcohol (Perera et al. 1995). These and other recent studies (Higuchi et al. 1996) have emphasized the complexity of interactions between factors regulating the immune system and tissue injury caused by ROS produced by the immune system.

If production of ROS were inhibited by alcohol, the effectiveness of the immune system cells in killing bacteria and other infectious agents would be reduced, leading to immunodeficiency. In rats, several days of alcohol feeding caused a reduction in the release of ROS from their cultured neutrophils when challenged by pneumococcal bacteria (Jareo et al. 1996). Acute administration of alcohol to rats reduced NO production by isolated lung macrophages after challenge with TB organisms (Greenberg et al. 1995). Further work with the regulatory enzyme for NO production showed that its induction by LPS is suppressed by both acute and chronic alcohol exposure. However, other ROS may differ in their response to acute versus chronic exposure (D'Souza et al. 1996). It is clear that investigation of the production of NO and other ROS has significant potential for contributing to knowledge of alcohol-induced tissue injury and immunodeficiency.

Acetaldehyde-Protein Adducts. Acetaldehyde, the first product of alcohol metabolism, is reactive and combines chemically with proteins in the cells or blood of the person or animal consuming the alcohol (Crossley et al. 1986; Hoerner et al. 1986; Israel et al. 1986; Tuma et al. 1987). These chemical combinations are called adducts. The development of autoimmunity after alcohol exposure may be a result of the formation of these acetaldehyde-protein adducts. Many investigators have found antibodies to these adducts produced after chronic exposure to alcohol. Research has shown that new antigens may persist for up to 30 days after alcohol exposure in animals (Anthony et al. 1983), providing ample exposure time of the adducts to the immune system.

Later studies have found not only that acetaldehyde forms adducts to nonprotein molecules but that nonacetaldehyde products of alcohol metabolism form adducts to cellular or blood components (Chang et al. 1997; Clot et al. 1995; Trudell et al. 1991). For example, the alcohol-induced cytochrome P450 2E1 readily forms adducts with hydroxyethyl. More than 85 percent of alcoholics with cirrhosis have antibodies that react to this adduct (Clot et al. 1996). Further experimentation with this adduct, using rat liver cells and IgG antibodies from patients with alcoholic liver disease, resulted in an antibody-dependent cytotoxic effect in the cells (Clot et al. 1997). This finding clearly

demonstrated the potential cellular toxicity of the antibodies to this adduct.

There have been major efforts to determine the mechanisms of formation of acetaldehyde-protein adducts and to establish their clinical significance. One study of persons who drank heavily found high levels of IgA and IgM antibodies to acetaldehyde-albumin adducts, and that the IgA antibodies were correlated with alcohol intake (Worrall et al. 1996). A study of 140 alcohol drinkers and nondrinking controls found anti-acetaldehyde-adduct antibodies of each immunoglobulin class in these subjects (Viitala et al. 1997). The levels of antibodies were higher in drinkers than nondrinkers, including those with nonalcoholic liver disease, and antibody levels were positively correlated with several indicators of liver disease severity.

Determination of the immunologic relevance of acetaldehyde-protein adducts produced in cell cultures has been complicated by the fact that various products are formed depending upon the chemical environment (Klassen et al. 1994; Thiele et al. 1994). Therefore, antibodies with specificity for adducts prepared under different experimental conditions were developed for further analysis of the effects of these adducts in alcohol-fed animals. Researchers recently found that another aldehyde generated during alcohol metabolism, malondialdehyde, could react with coexisting acetaldehyde (Tuma et al. 1996*a*). The mixed adduct is called MAA. Antibodies specific for MAA did not cross-react with known acetaldehyde-only or malondialdehyde-only adducts. These antibodies were used to show that alcohol-fed rats have significant amounts of this mixed adduct in their livers.

This work with adducts and antibodies to them, with their clear potential for cellular cytotoxicity, represents exciting progress in understanding how alcohol may produce autoimmunity and tissue damage. It provides one possible explanation for the increasing severity of alcoholic hepatitis in successive episodes and may help explain the progressive damage that occurs for some time after alcohol withdrawal in many patients.

Therapeutic Measures

Alcohol has a great array of effects at the molecular, cellular, and organ levels. These effects may be produced by alcohol that is consumed in acute, bingelike episodes or in chronic excess. With so many variables to consider, therapeutic approaches must be based on a specific goal. Researchers must determine whether the immediate problem is restoration of TH1/TH2 balance, reduction of an autoimmune process, or repair of scarring produced by the autoimmune process. There are many possible approaches to preventing acute alcoholic liver injury (McClain et al. 1993), and the same principles apply to manipulations of the immune system. Some proposed therapies include administration of such substances as antibodies against endotoxin (LPS) or against specific cytokines, soluble cytokine receptor molecules that would absorb excess cytokines, cytokine receptor antagonists, drugs that block either cytokine production or specific responses, adhesion molecule antagonists, and drugs that have a widespread effect (such as improvement of gut integrity).

Most investigators have dealt with acute problems such as alcoholic hepatitis or pneumonia. In studies of pneumonia, several groups have used granulocyte colony-stimulating factor (GCSF) to improve neutrophil number and function (Nelson 1994). GCSF is a neutrophil-specific growth factor that stimulates the growth of neutrophils and enhances their activity. In alcoholic rats infected with *Klebsiella pneumoniae,* GCSF improved neutrophil influx and survival (Nelson et al. 1991). GCSF also increased migration of neutrophils into the lungs of alcohol-fed rats with pneumococcal pneumonia or after administration of LPS (Lister et al. 1993*a*; Preheim et al. 1996), but it did not always improve survival. Consistent with increased neutrophil migration to the lungs, adhesion molecule expression was improved in neutrophils after GCSF treatment (Zhang et al. 1997*a*). Although experimental results are encouraging, there have been few attempts at GCSF treatment in human alcoholics (Grimsley 1995).

If the TH1/TH2 balance is proven to be significant in immunologic disturbances of alcohol abusers, methods of correcting the imbalance will need to be found. Recent work with rats has shown that cell-mediated immunity (TH1) is reduced by 10 days of alcohol feeding but that certain TH2 functions are not changed. Administration of IL-12 restored both the TH1 functions and the ability of isolated lymphocytes to make IFN-γ, a critical TH1 cytokine (Peterson et al. 1998*b*). Other investigators, using a more direct route to TH1 enhancement, administered the IFN-γ by means of an experimentally altered virus, called an adenoviral vector, introduced into the trachea (Kolls et al. 1998). This procedure resulted in enhanced IFN-γ production by the lung, improved TNF responses after stimulation with LPS, increased recruitment of neutrophils into the lung, and reduced bacterial survival. It also reversed the effects of acute alcohol administration on these measures.

Another recent therapeutic approach involves attempts to improve overall protein balance and metabolic status in malnourished alcohol-fed rats. Hormonal therapy with insulin-like growth factor and growth hormone was successful in improving nutritional state, and it also improved some, but not all, measures of immune function (Mendenhall et al. 1997*a*).

These are exciting new approaches to specific types of therapy for the alcohol-damaged immune system. New discoveries in this rapidly developing field will lead to additional therapeutic measures based on specific or general immunotherapy.

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Glossary

Adaptive immunity: Also called adaptive immunity. Immunity that is activated after the body is exposed to a pathogen. The most important cells in acquired immunity are the T-cells and B-cells. See innate immunity.

Adduct: The product resulting from the attachment of one type of molecule to another. For example, an acetaldehyde molecule may attach to a protein molecule, forming an acetaldehyde-protein adduct.

Adenoviral vector: An altered adenovirus that can still invade cells but does not have the ability to produce disease. Genes purposely introduced into its structure are carried into the host cells.

Adhesion molecules: Several classes of protein molecules on the surface of cells and membranes that can bind to molecules on another surface, thus binding the surfaces together.

Antibody: A protein molecule produced by B-cells in response to an antigen. Its structural specificity allows it to bind the antigen.

Antigen: A molecule interpreted by the immune system as foreign (such as a surface component of a bacterium) and that elicits specific antibody production.

Antioxidant: A protective molecule that neutralizes reactive oxygen species.

Apoptosis: A process of cell "suicide" elicited by some specific signal such as a cytokine. It is a part of normal cell physiology necessary for maintaining a balance between cell growth and loss. In the immune system, apoptosis also rids the body of self-reactive (autoimmune) cells.

ATP: Adenosine triphosphate. An essential molecule involved in the cell's energy-consuming metabolic processes. It is necessary for normal cell function.

Autoantibody: An antibody that reacts with a self-antigen, which can be a normal or altered cell or tissue of the body.

Autoimmune reactions: Immune responses directed at the body's own cells and tissues. These inappropriate reactions can result in autoimmune diseases and disorders.

B-cell: A type of lymphocyte that produces antibody. B-cells are the primary source of humoral immunity.

CD4 and CD8 T-cells: CD4 T-cells are helper T-cells; CD8 T-cells are cytotoxic and suppressor T-cells. Changes in the ratio of CD4 to CD8 cells are considered to be indicators of abnormalities in immune function.

Cell-mediated immunity: Immunity provided by the direct action of immune system cells, primarily the T-cells. See humoral immunity.

Chemoattractant: A substance that attracts migratory cells, such as neutrophils, to a specific site.

Choline: A substance that prevents the deposition of fat in the liver. A deficiency of choline causes severe fatty deposits.

Collagen: The major protein constituent of connective tissue. It is the protein that forms scar tissue.

Cytochrome P450 2E1: An enzyme that metabolizes alcohol and causes the generation of reactive oxygen species.

Cytokines: Small molecules that act as chemical messengers, regulating cellular interactions and functions. They play an important role in cell-to-cell communication during normal metabolism and are the primary chemical messengers during periods of inflammation or infection.

DLPC: Dilinoleoylphosphatidylcholine. A protective substance that acts to prevent fibrosis and appears to have antioxidant properties.

Endothelial cells: Cells that line the interior of blood vessels.

Endotoxin: A lipopolysaccharide (LPS). A toxic molecule found in the cell wall of certain bacteria.

Fas: Also called CD95 or APO-1/Fas. A specific receptor, or docking site on a cell, that reacts with a corresponding molecule, Fas ligand. The joining of Fas with Fas ligand initiates chemical processes within the cell that can lead to cell death by apoptosis.

Fatty liver (steatohepatitis): Deposition of fat in the liver.

Fibrosis: Deposition of collagen in the form of scar tissue. It can lead to cirrhosis.

Glutathione: An antioxidant found in mitochondria.

Hepatitis: An inflammation of the liver with associated pain, fever, and jaundice. It may be induced by alcohol (alcoholic hepatitis) or by a virus, such as hepatitis B or hepatitis C.

Hepatocytes: The main functional cells of the liver. They process and store nutrients, remove toxins from the blood, and secrete bile, which is involved in the digestion of fats.

Humoral immunity: Immunity conferred by antibodies that circulate in the blood and lymph. Antibodies are produced by B-cells. See cell-mediated immunity.

IFN-γ: Interferon gamma. A cytokine that induces protection against viral infection and stimulates macrophages and neutrophils.

IL-1: Interleukin-1. A cytokine that induces inflammation, stimulates proliferation of helper T-cells, and promotes B-cell growth and differentiation.

IL-4: Interleukin-4. A cytokine that stimulates T-cell growth, induces B-cell activation and growth, and modulates antibody production by B-cells.

IL-6: Interleukin-6. A cytokine that induces inflammation and promotes the maturation of B-cells into plasma cells.

IL-8: Interleukin-8. A cytokine that attracts and stimulates neutrophils.

IL-10: Interleukin-10. A protective cytokine with anti-inflammatory effects. It inhibits T-cell proliferation, reduces the production of inflammatory cytokines, and promotes B-cell proliferation and antibody secretion.

IL-12: Interleukin-12. A cytokine that activates natural killer cells, activates a subtype of T-cell, and induces the cell-mediated (TH1) immune response.

Immunodeficiency: A condition in which some component of the immune system functions at too low a level to provide normal protection.

Immunoglobulins: Several classes of antibody proteins produced by B-cells. The major classes are immunoglobulins A, G, and M (IgA, IgG, and IgM).

Innate immunity: Immunity that does not require prior exposure to an antigen. The main components of innate immunity are the phagocytes, which attack any invading organism regardless of prior exposure, and the natural killer cells. See acquired immunity.

Interferon: A substance produced by cells that have been infected with a virus. It moves to noninfected cells, where it confers resistance to that virus.

Kupffer cells: Phagocytic cells resident in the liver. They engulf and destroy invading substances and secrete cytokines, such as tumor necrosis factor alpha.

Leptin: A hormone that controls appetite.

Lipid peroxidation: A reaction between reactive oxygen species and components of cell membranes. It is a destructive process that may degrade cell membranes and impair cell function.

LPS: Lipopolysaccharide. See endotoxin.

Lymphocyte: A class of immune cell that includes T-cells, B-cells, and natural killer cells.

Macrophage: A phagocytic cell found in the tissues, such as the liver (Kupffer cells) and lung. It develops from a monocyte.

MAT: Methionine adenosyltransferase. An enzyme involved in the production of *S*-adenosyl-L-methionine (SAM).

Methionine: An amino acid that is essential in the diet and necessary for normal metabolism.

Mitochondria: Small bodies within the cell, each enclosed in its own membrane. They generate energy for the cell's metabolic processes.

Monocyte: A phagocyte that circulates in the blood stream. Monocytes may migrate into the tissues, where they develop into macrophages.

mRNA: Messenger ribonucleic acid. A complementary copy of a gene in the DNA. It encodes proteins and participates in protein synthesis.

NAPQI: *N*-acetyl-*p*-benzoquinonimine. A highly reactive product of acetaminophen metabolism. If it is not bound by the antioxidant glutathione, it causes serious cell damage.

NASH: Nonalcoholic steatohepatitis, fatty liver not related to alcohol consumption. It is characterized by inflammation, fibrosis, and cirrhosis.

Natural killer (NK) cells: A type of lymphocyte that attacks virus-infected or cancerous cells without a requirement for previous exposure.

Necrosis: A type of cell death whereby the cell swells and breaks open, releasing its contents.

Neutrophil: A phagocytic cell that circulates in the blood and attacks bacteria without a requirement for previous exposure. Neutrophils react to chemoattractants such as interleukin-8 by moving to the site of inflammation, where they adhere to cell surfaces. When present in excess, they damage cells by releasing toxic metabolites.

NFκB: Nuclear factor kappa B. An oxidative stress-sensitive transcription factor involved in the production of certain cytokines. It is a regulatory complex of molecules that lies in the cell cytoplasm until activated by signals from the cell exterior. It then moves to the nucleus to initiate specific RNA synthesis.

Oxidative stress: A condition caused by an excess of reactive oxygen species and/or a deficiency of antioxidants. This imbalance causes cell damage and may end in cell death.

Phagocyte: A cell that engulfs and destroys bacteria and other foreign substances. This process is called phagocytosis. The phagocytes include monocytes, macrophages, and neutrophils.

Plasma cell: A large cell that develops from a B-cell after it encounters an antigen. The plasma cells produce large numbers of antibodies to that specific antigen.

PPC: Polyenylphosphatidylcholine. A substance extracted from soybeans. It acts to prevent the development of alcohol-induced fibrosis.

Prostaglandin: One of a family of compounds that affect various physiologic functions. Certain prostaglandins have protective effects on liver cells. Other prostaglandins affect other bodily functions, including smooth muscle contraction, blood pressure, body temperature, and blood clotting.

Reactive oxygen species (ROS): Also called free radicals. Highly reactive molecular fragments that are released during metabolic processes. If not promptly removed by antioxidants, they can interact with cell components and cause serious damage, such as lipid peroxidation.

Receptor: A specific docking site on a cell that connects with a corresponding molecule.

SAM: *S*-adenosyl-L-methionine. A precursor of glutathione. It has a beneficial effect on mitochondrial membranes, allowing normal transport of glutathione through the membranes.

Steatohepatitis: Fatty liver.

Stellate cells: Fat-storing cells in the liver. They produce collagen, which leads to fibrosis.

T-cell: A type of lymphocyte that produces cell-mediated immunity. Helper T-cells produce and secrete cytokines that stimulate the activity of other immune cells. Cytotoxic T-cells recognize antigens on the surface of virus-infected or transplanted cells and destroy those cells. Suppressor T-cells inhibit other immune responses, thereby preventing overreaction of the immune system.

T-cell receptor: A characteristic signaling molecule on the surface of T-cells. It has high molecular specificity for antigens.

TGF-β: Transforming growth factor beta. A cytokine that induces stellate cells to synthesize collagen. It can cause direct cell damage and increase liver inflammation.

TH1: A type of immune response that is primarily cell mediated.

TH2: A type of immune response that is primarily humoral, or antibody mediated.

Thymocyte: A cell that migrates from the bone marrow to the thymus, a lymphoid organ. In the thymus, the thymocytes develop into T-cells having the ability to recognize and respond to antigen.

TNF (TNF-α): Tumor necrosis factor alpha. A cytokine produced mainly in Kupffer cells. It induces inflammation, stimulates neutrophils, and induces the production of other cytokines, including more TNF.

Transcription: The enzymatic process by which the code for a specific gene in the DNA is transcribed into the same code in a strand of messenger RNA, which will later direct protein synthesis.

Alcohol's Effects on the Cardiovascular System

Over the last century, the medical and scientific communities have generally considered alcohol to be a toxin for the heart. Chronic heavy drinking is a leading cause of cardiovascular illnesses such as cardiomyopathy (degenerative disease of heart muscle), coronary artery disease, high blood pressure, dangerous heart rhythms (arrhythmias), and stroke.

However, as early as 1926, Raymond Pearl, one of the pioneers of modern epidemiology, noted that moderate drinkers had the longest life expectancy, followed by abstainers, then heavy drinkers (Pearl 1926). Some 70 years later, studies of mortality in widely disparate populations (Camargo et al. 1997; Keil et al. 1997; McElduff and Dobson 1997) have reported that moderate drinkers are 25 to 40 percent less likely to die from coronary heart disease (CHD) than abstainers are. An American Cancer Society prospective study (Boffetta and Garfinkel 1990) that followed more than 275,000 middle-aged men for 12 years found that men who consumed one drink daily had a lowered risk for CHD mortality (figure 1). Men who consumed three or more alcoholic drinks a day also had lower rates of CHD mortality compared with abstainers but increased rates of death from stroke, cancer, accidents, and violent crimes.

Alcohol in low to moderate amounts thus seems to have the potential for beneficial as well as toxic effects on the heart. The 1995 report of the Advisory Committee to the Secretaries of Health and Human Services and Agriculture on the *Dietary Guidelines for Americans* (U.S. Department of Agriculture [USDA] 1995*b*) acknowledges the evidence of an association between moderate drinking—defined in the guidelines as no more than two drinks a day for men and one drink a day for women—and lower risk of CHD in some groups. However, research has not confirmed that alcohol itself causes the lower risk. It is also plausible that the lower risk might result from some as yet unidentified factor or surrogate associated both with alcohol use and lower CHD risk, such as lifestyle, diet, exercise, or additives to alcoholic beverages (U.S. Department of Health and Human Services [USDHHS] 1999). This section highlights recent research examining the deleterious as well as the potentially beneficial effects of alcohol on the cardiovascular system, as well as the potential cellular mechanisms underlying these effects. An excellent summary of previous studies on the effects of alcohol on the heart can be found in the *Ninth Special Report to the U.S. Congress on Alcohol and Health* (National Institute on Alcohol Abuse and Alcoholism 1997).

The Heart

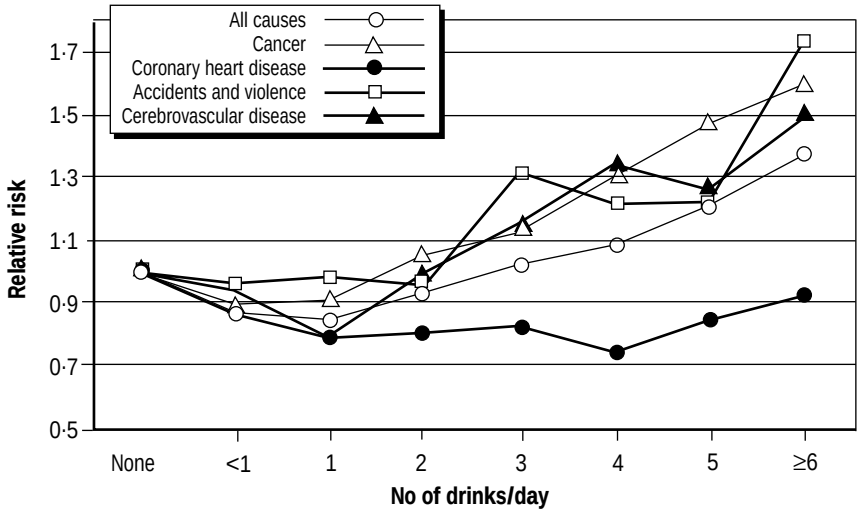
Alcoholic Cardiomyopathy

Long-term heavy drinking can cause the heart to become enlarged and lose some of its ability to contract, a condition known as alcoholic cardiomyopathy. This type of cardiomyopathy is nonischemic, meaning it is not the result of a loss of blood supply to the heart. Alcoholic heart disease is the most common cause of nonischemic cardiomyopathy in Western societies, responsible for up to 45 percent of cases (Kasper et al. 1994;

Definitions Related to Drinking

Studies investigating the health effects of alcohol vary in their definitions of "low," "moderate," and "heavy" drinking. According to the *Dietary Guidelines for Americans*, issued jointly by the U.S. Department of Agriculture and the U.S. Department of Health and Human Services, moderate drinking is no more than two standard drinks per day for men and no more than one per day for women (U.S. Department of Agriculture 1995). The National Institute on Alcohol Abuse and Alcoholism further recommends that people aged 65 and older limit their consumption of alcohol to one drink per day. Information on drinking levels as they are defined in the individual studies cited in this report can be found in the original references.

Figure 1: Alcohol consumption and relative risk of death over 12 years in American Cancer Society prospective study of 276,802 men aged 40–59



Mortality ratios are adjusted for age and smoking habits and for the four most common causes of death and death from all causes.

Source: Marmot and Brunner 1991. Reprinted with permission from *British Medical Journal*, Vol. 303, pp. 565–568, 1991. Copyright 1991, BMJ Publishing Group, London.

Sugrue et al. 1992). Alcoholic cardiomyopathy often leads to heart failure and death.

Most studies examining the prevalence of alcoholic cardiomyopathy have focused on male alcoholics. However, two recent studies found that women are more sensitive to alcohol's toxic effects on the heart and therefore have a greater risk than men of developing alcoholic cardiomyopathy (Fernandez-Sola et al. 1997; Urbano-Marquez et al. 1995). In both studies, alcoholic cardiomyopathy was as prevalent in female as male alcoholics, even though the mean lifetime dose of alcohol for women was only 60 percent that of male alcoholics. Why women are more sensitive to alcohol's toxic effects on the heart is unknown and should be a focus of future research (see the next section in this chapter, "Alcohol and Women: An Overview").

Interestingly, people survive longer with alcoholic cardiomyopathy than with other nonischemic cardiomyopathies, such as those caused by viral infection or pregnancy. A recent study showed that 81 percent of people with alcoholic cardiomyopathy were still alive after 5 years, while only 48 percent of people with other forms of cardiomyopathy survived that long despite comparable severity of symptoms and similar structural changes in the failing heart (Prazak et al. 1996).

Other researchers have found that alcoholic cardiomyopathy is totally or partially reversible with abstinence, unlike other nonischemic cardiomyopathies, in which irreversible heart damage and failure often occur (Francis et al. 1990). These findings suggest that disease progression is different in alcoholic cardiomyopathy than in other nonischemic cardiomyopathies. In a study of alcoholics with cardiomyopathy who were admitted to a detoxification unit, there was evidence that heart muscle damage was reduced or disappeared with abstention (Ballester et al. 1997). The researchers assessed damage to the heart muscle by measuring heart uptake of radioactively labeled antibodies to the muscle protein myosin. Over time, levels of

antimyosin antibodies decreased or disappeared, and cardiac ultrasound demonstrated that heart muscle function was improved. Alcoholics in the study with no evidence of heart disease did not have antimyosin antibody uptake even when they had been drinking a similar length of time and had similar total lifetime consumption as those with cardiomyopathy. This suggests that some people may be genetically predisposed to developing alcoholic cardiomyopathy.

Basic Mechanisms of Heart Muscle Damage

Researchers are exploring possible cellular and molecular mechanisms of alcohol's toxic effects on the heart, which may include alcohol-induced damage to the surface membrane of heart muscle cells, the myocytes; damage to important intracellular organelles and the apparatus that controls the cell's contractile machinery; or alteration of the myocyte's ability to synthesize proteins and enzymes. These alcohol-induced disruptions of myocyte integrity, contraction, or ability to self-repair can lead to cell death. Recent studies suggest at least two mediators of alcohol's toxic effects on myocytes: (1) production of oxygen-containing molecules, called reactive oxygen species (ROS), which damage cells (Husain and Somani 1997), and (2) detrimental changes in the receptors on the myocyte surface that regulate intracellular function (Strasser et al. 1996).

ROS, highly reactive molecular fragments produced as a by-product of alcohol metabolism, can cause serious harm to cells. Normally ROS are rapidly inactivated by antioxidants, but if the level of antioxidants is low or if ROS are over-produced, cell death can result. According to the ROS theory, chronic heavy alcohol consumption both increases the levels of ROS and decreases the levels of antioxidant enzymes that protect against cell damage by reducing ROS. Phospholipids, the backbone of cell membranes, are primary targets of the destructive process initiated by ROS, or peroxidation, and damage to the myocyte's membrane decreases cell integrity and intracellular functions, leading to cell death. Loss of myocytes, in turn, results in cardiomyopathy. A recent study of rats given large amounts of alcohol over long periods supports the ROS theory, finding that lipid peroxidation increased 149 percent, while levels of antioxidant enzyme activity decreased approximately 80 percent (Husain and Somani 1997).

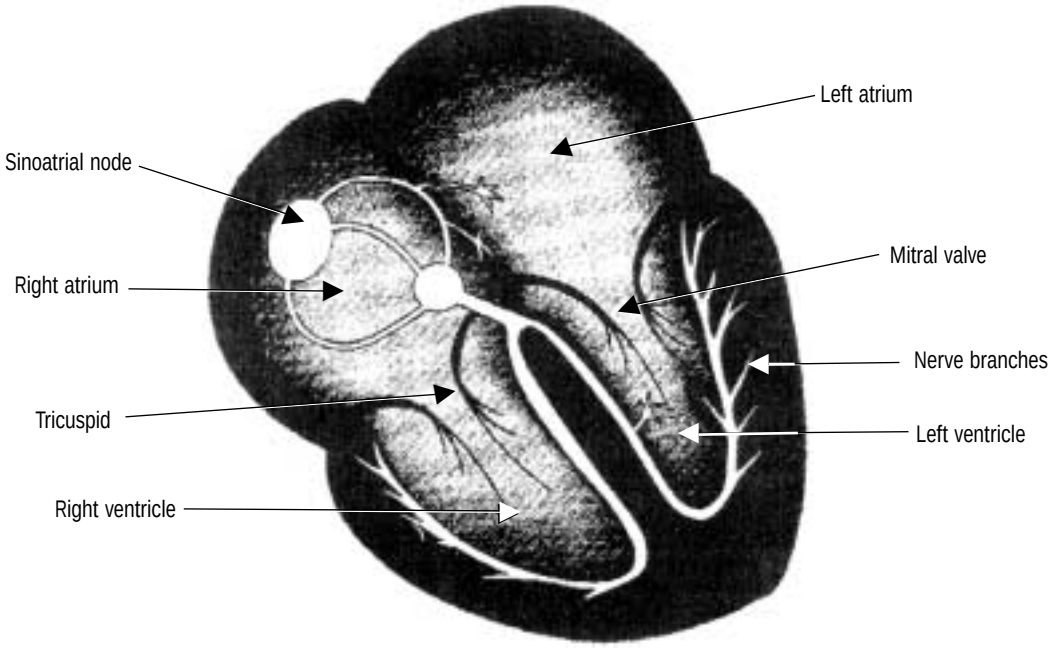
According to the myocyte surface receptor theory, alcohol causes harmful changes to signaling receptors—molecules on the cell surface that dock with signaling molecules outside the cell, causing corresponding changes inside—thereby damaging the ability of myocytes to maintain proper metabolism and contraction and leading to myocyte death and cardiomyopathy. A recent study in rats found that chronic alcohol consumption of up to 8 weeks reduced levels of two important classes of myocyte receptors, alpha-adrenergic receptors and muscarinic receptors (Strasser et al. 1996). When receptor activity is not normal, it can activate self-destructive mechanisms, leading to myocyte death. Future studies should focus on the intracellular consequences of alcohol's effects on increased ROS levels and myocyte receptor activity.

Arrhythmias

The heart's ability to function effectively as a pump depends on regular, synchronous contraction of the heart muscle (figure 2). Heavy drinking can disrupt the heart's own intrinsic pacemaker system and in this way increase the risk of abnormal changes in heart rhythm both acutely (during an episode of drinking) and chronically (due to long-term use).

The two most common types of irregularities, or arrhythmias, associated with heavy drinking are atrial fibrillation (rapid, irregular beating originating in the upper or atrial heart chambers) and life-threatening ventricular tachycardia (very rapid beating originating in the lower or ventricular chambers). Recent studies have aimed to identify the cellular mechanisms underlying alcohol's disruption of the heart's pacemaker system.

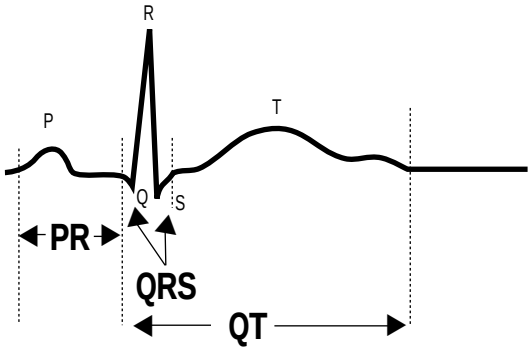
Figure 2: The heart's electrical system



The heart's electrical system stimulates the contraction of the muscle cells of the heart's four chambers, thereby causing blood to circulate through the heart chambers in a precise and sequential fashion. Electrical stimulation begins in the sinoatrial node, proceeds through the right and left atria, then moves through the ventricles.

Source: Chung and Rich 1990.

Figure 3: Sample electrocardiogram



The PR interval represents conduction from the sinoatrial node through the atria and into the atrioventricular chamber. The QT interval represents conduction through the ventricles and the return of conduction to baseline for the next heartbeat. Abnormalities in the segment between the S and T waves suggest heart injury.

Intoxication and Heart Rhythm

Intoxication can cause atrial fibrillation and other arrhythmias in both alcoholics and otherwise healthy persons. The development of arrhythmias with binge drinking—a condition seen most frequently around the holidays—is known as "holiday heart syndrome." Arrhythmias during intoxication result from alcohol-induced disturbances in the electrical discharge from individual myocytes and in the conduction of that electrical impulse through the heart muscle. A recent study demonstrated that in healthy intoxicated subjects, changes occurred in the electrocardiograms—surface recordings of the heart's electrical conduction (Cardy et al. 1996). In these subjects, the duration of electrical conduction through the atrial chamber of the heart—termed the P wave (figure 3)—was prolonged. A prolonged P wave increases the likelihood of developing atrial fibrillation.

Study of cellular transmission of electrical impulses provides clues to how alcohol disrupts the contraction of heart muscle. Electrical conduction through the heart muscle results when the movement of ions, including sodium, calcium, and potassium, across myocyte surface membranes changes the electrical potential of the

cells from negative relative to the exterior—the "resting" condition—to positive, a process called depolarization. This electrical impulse moves sequentially across myocytes in the heart muscle, resulting in synchronous contraction.

A recent study found that alcohol in concentrations within the range of what could be measured clinically in people who drink decreases calcium ion movement across myocyte membranes (Habuchi et al. 1995). This change could alter depolarization and conduction of the electrical impulse through the heart, leading to arrhythmias. These investigators also demonstrated that high doses of alcohol altered the movement of sodium ions across the myocyte membrane. Such changes could contribute to the increased incidence of death from arrhythmias among alcoholics who have engaged in binge drinking.

Alcohol Withdrawal and Heart Rhythm

Sudden death due to ventricular arrhythmias is one of the causes of mortality in alcoholics with or without preexisting heart disease (Wannamethee and Shaper 1992). Interestingly, blood alcohol levels in alcoholics who suffer sudden death due to cardiac causes often are low or undetectable (Clark 1988), suggesting that death occurred during abstinent periods. This finding supports the theory that sudden death due to cardiac causes in alcoholics may be related more to development of arrhythmias during alcohol withdrawal than to the toxic effects of alcohol during intoxication.

If the portion of the electrocardiogram called the QT interval (see figure 3) is prolonged, it signals delayed conduction and a predisposition to life-threatening ventricular arrhythmias. In a study of 62 alcoholics admitted for detoxification, researchers found that nearly half had a prolonged QT interval during withdrawal (Otero-Anton et al. 1997). When the symptoms of withdrawal were over, the QT interval returned to normal. Other researchers found higher than normal levels of adrenaline and noradrenaline among alcoholics undergoing detoxification (Denison et al. 1997). These hormones increase sensitivity to arrhythmias. Body stores of magnesium and potassium also were decreased, a change that can lengthen the QT interval and increase the chances of developing arrhythmias.

Heart ischemia—damage resulting from deficiency of blood flow due to narrowing or blockage of a vessel—also increases sensitivity for developing life-threatening arrhythmias. A recent study found that, during withdrawal, alcoholic men without clinical heart disease showed changes in the ST segment of the electrocardiogram, an indicator of ischemia (Denison et al. 1997). Twenty-four-hour continuous electrocardiograms revealed episodic ST segment depressions in more than a third of subjects. Such ST segment depressions in people with atherosclerotic heart disease reflect ischemia and are associated with increased risk of myocardial infarction—heart attack—and arrhythmia. This finding suggests that alcohol withdrawal should be considered a condition in which acute cardiac complications, such as ventricular arrhythmias, may be expected in susceptible alcoholics.

The Vascular System

Alcohol and Coronary Heart Disease

Detrimental Versus Beneficial Effects of Alcohol.

Heavy drinking increases the risk of heart attack due to CHD. Studies have shown that binge drinking increases episodes of angina (heart pain) in people with heart disease (Rossinen et al. 1996) and raises the risk of fatal heart attack (Kauhanen et al. 1997*a*; McElduff and Dobson 1997). Researchers in Finland recently reported that binge drinkers had six times the risk of fatal heart attack as moderate drinkers (Kauhanen et al. 1997*a*). In another study, this research group found that frequent hangovers were associated with a greater than twofold increase in death due to CHD (Kauhanen et al. 1997*b*). These studies underline the importance of preventive actions regarding not only the amount of alcohol consumed but also the way people consume it.

While it is clear that prolonged heavy drinking can damage the heart in the ways described above, numerous studies have shown an association

between drinking at more moderate levels and lower risk of CHD in some groups. Epidemiologic studies carried out over the past 25 years suggest that moderate drinking is associated with lower risk of CHD, the top killer in the Nation. A recent study among 22,000 U.S. male physicians, for example, demonstrated that moderate drinking lowers the risk for chest pain and heart attack in apparently healthy men (Camargo et al. 1997). Light-to-moderate drinkers among nearly 86,000 U.S. female nurses showed lower death rates, especially among those at increased risk for CHD, compared with women who did not drink (Fuchs et al. 1995). Data from the National Health Interview Survey (Hanna et al. 1997) and studies in Germany (Keil et al. 1997), China (Yuan et al. 1997), Australia (McElduff and Dobson 1997), and Sweden (Hammar et al. 1997) also found that moderate drinking was associated with lower risk of CHD.

In studies looking specifically at alcohol and heart disease, the term "moderate drinking" has encompassed a wide range of consumption levels, sometimes more than the amount defined by the *Dietary Guidelines for Americans* as moderate: two or fewer standard drinks per day for men and one or less per day for women (USDA 1995*a,b*). However, the apparent benefits of moderate drinking on CHD mortality are offset at higher drinking levels through increasing risk of death from other causes (USDHHS 1999).

Mechanisms. Recent research has suggested several possible mechanisms by which alcohol may protect against CHD. One possibility is that alcohol may impede the accumulation of fatty deposits, or atherosclerotic plaques, in the arteries of the heart by causing changes in a person's cholesterol profile. Researchers have found that alcohol reduced the development of atherosclerotic plaques in the coronary arteries of mice genetically altered to have high levels of LDL-cholesterol—a form of cholesterol that has been found to be associated with increased risk of heart disease (Dai et al. 1997). Furthermore, these animals showed increased levels of HDL-cholesterol, high levels of which are associated with lower risk of CHD.

Other studies have indicated that alcohol consumption increases HDL-cholesterol by decreasing the activity of cholesteryl ester transfer protein (CETP), which transfers cholesterol molecules from HDL particles to LDL or VLDL particles (another form of cholesterol associated with increased risk) (Fumeron et al. 1995). Drinking alcohol was found to alter, at the gene level, the production of two variants of CETP with different activity levels. The change resulted in decreased CETP activity and increased HDL-cholesterol.

These findings provide evidence that one way moderate drinking may lower the risk of CHD is by altering the cholesterol profile. Researchers have confirmed the association between alcohol consumption and increased HDL-cholesterol in people who participated in studies in the United States (such as the Framingham Heart Study) (Sonnenberg et al. 1996), France and Ireland (Marques-Vidal et al. 1995), and Finland (Huijbregts et al. 1995).

However, these changes in HDL-cholesterol and LDL-cholesterol levels contribute only about half of the observed protection against CHD with alcohol consumption. Researchers are therefore investigating alcohol's anti-blood clot (anti-thrombotic) effect. Blood platelets and clotting factors cause blood clots or thrombi to form in coronary arteries narrowed by atherosclerosis, thereby precipitating heart attacks. Researchers have found that alcohol consumption is associated with antithrombotic effects, such as reduced platelet activation and clotting factor activity (Rubin and Rand 1994).

Several studies suggest that alcohol acts on clot-related proteins in the blood. For example, one study found that drinking 30 grams of alcohol (about two and one-half drinks) per day for 4 weeks caused reduced platelet aggregation and decreased blood levels of fibrinogen, which stimulates clot formation (Pellegrini et al. 1996). Another study of more than 600 physicians found a positive association between moderate alcohol intake and blood levels of tissue plasminogen activator (tPA), an enzyme that breaks down blood clots (Ridker et al. 1994). In a laboratory

study, cultured endothelial cells, which line the artery walls, produced increased levels of tPA with exposure to low levels of alcohol (Aikens et al. 1997). In another recent study, exposure of endothelial cells to low levels of alcohol suppressed the production of substances that promote clotting and stimulated the production and activity of substances (such as tPA) that inhibit clotting (Booyse 1999).

Moderate alcohol consumption may also lower CHD mortality by improving survival after a heart attack (Dufour et al. 1996; Wannamethee et al. 1995). For example, a recent analysis of more than 14,000 subjects followed over 20 years in the National Health and Nutrition Examination Survey Epidemiologic Followup Survey found that regular drinkers are more likely to survive myocardial infarction than abstainers are (Dufour et al. 1996). Although epidemiologic data regarding the association between alcohol consumption and improved heart attack survival are still limited, researchers are already discovering some of the cellular mechanisms by which alcohol may have such an effect.

Researchers have known for some time that alcohol increases blood levels of the chemical adenosine, which protects or "preconditions" heart cells against damage. Transient blockage of a coronary artery can induce this preconditioning by adenosine; administering compounds known to increase adenosine—alcohol is one—also has this effect. Investigators recently found that hearts from guinea pigs fed alcohol for 3 to 12 weeks had less damage and greater recovery of their ability to contract after an experimentally induced heart attack (Miyamae et al. 1997). They also found that blocking adenosine docking sites or receptors on the surfaces of myocytes inhibited alcohol's protective effect. Another recent study demonstrated that hearts from rats already preconditioned by brief ischemia prior to an experimental heart attack could be further protected if the animals had been chronically consuming alcohol (McDonough 1997).

The intracellular mechanisms of alcohol's apparent protective effect against heart attack injury activated by adenosine remain unclear. Researchers are examining several possibilities, such as activation of the myocyte enzyme protein kinase C, which may beneficially alter movement of ions (electrolytes) through the myocyte surface that are key to cell function and contractility (Rodriguez et al. 1998); increased production of protective compounds such as nitric oxide by endothelial cells (Davda et al. 1993); and activation of molecules (transcription factors) that turn on genes responsible for producing protective enzymes and proteins (Zeldin et al. 1996). Further studies will be needed to understand these intracellular mechanisms and to determine their applicability in humans.

Alcohol and Stroke

The relationship between alcohol consumption and stroke is similar to that seen with CHD. Studies have found that while moderate alcohol consumption is associated with lower incidence of ischemic strokes, in which the blood supply to the brain is blocked, heavy drinking may increase the risk of both ischemic and hemorrhagic strokes (Palomaki and Kaste 1993; Stampfer et al. 1988). The mechanisms behind any apparent protection by moderate alcohol intake against ischemic stroke are likely to be the same as with CHD—for example, improved cholesterol levels and antithrombotic effects, which decrease the likelihood of atherosclerosis and thrombus formation in the arteries of the brain. Future studies should also consider the potential detrimental effects of alcohol withdrawal, since stroke may occur in alcoholics during the withdrawal period.

Alcohol and Blood Pressure

An association between heavy alcohol consumption and increased blood pressure (hypertension) has been observed in more than 60 studies in diverse cultures and populations (recent studies include Ascherio et al. 1996; Seppa et al. 1996; York and Hirsch 1997). It is clear that heavy alcohol consumption elevates blood pressure, causing or exacerbating hypertension. However, controversy remains as to whether moderate

alcohol consumption has any beneficial effects on blood pressure.

Deleterious Effects of Alcohol on Blood Pressure. Heavy alcohol consumption reversibly increases blood pressure in people with and without hypertension (Puddey et al. 1995; Ueshima et al. 1993). It is estimated that one drink a day can chronically increase blood pressure 1 millimeter mercury in middle-aged individuals, and even more in the elderly and in people who already have high blood pressure (Beilin et al. 1996). This raises the possibility that regulating alcohol intake might be one means of reducing blood pressure in people with hypertension. A 2-year study found that hypertensive drinkers could reduce their blood pressure after educational intervention and through self-regulation of alcohol intake (Lang et al. 1995). Given the abundance of data associating alcohol with hypertension, the World Health Organization and the International Society of Hypertension have jointly recommended reducing daily alcohol intake to treat high blood pressure (World Health Organization 1996).

Recently, the Prevention and Treatment of Hypertension Study looked at the effectiveness of a 6-month behavior intervention program to reduce both alcohol intake and blood pressure among drinkers who consumed at least three drinks daily and who had normal to slightly elevated blood pressure (Cushman et al. 1998). After 6 or more months, individuals in the behavioral intervention group consumed approximately 1.3 fewer drinks per day than those in the control group. This reduction in alcohol consumption did not result in a significant effect on blood pressure. The authors concluded that although greater reductions in alcohol intake might have led to greater reductions in blood pressure, the study results did not strongly support reducing alcohol consumption below two drinks daily as a sole means of preventing or treating hypertension.

Despite the well-recognized association between alcohol and hypertension, the cellular mechanisms of alcohol's effect on blood pressure remain uncertain. Especially confusing is the fact that, initially, drinking alcohol dilates blood vessels, which lowers blood pressure. Studies looking to explain how long-term, heavy alcohol consumption reverses this lowering and leads to elevated blood pressure suggest effects by alcohol on the autonomic nervous system, an important regulator of blood pressure. For example, heavy alcohol consumption has been associated with increased release of the stress hormones adrenaline and noradrenaline (reflecting activation of the sympathetic component of the autonomic nervous system). This release causes constriction of blood vessels—and hence increased blood pressure—and decreased sensitivity of sensory neurons called baroreceptors, which send signals from the heart and large arteries to the brain to regulate blood pressure.

In addition to its effects on central regulation of blood pressure, heavy alcohol consumption also may alter peripheral regulation of blood pressure by affecting smooth muscle cells in the walls of the blood vessels (summarized in Altura and Altura 1996). Chronic alcohol exposure may inhibit the function of endothelial cells, which normally release chemicals to relax the smooth muscle cells in the vessel walls. These vascular cells regulate blood vessel tone and, as a result, blood pressure. Chronic alcohol exposure appears to reduce cellular magnesium levels, which can cause increased calcium fluxes in vascular smooth muscle cells, producing constriction of the blood vessels and increasing blood pressure.

Two studies suggest that increased blood pressure results not from alcohol consumption but from alcohol withdrawal. Investigators found that a single drink of alcohol depressed the blood pressure of patients with hypertension for several hours (Kawano et al. 1996). However, in a related study, the research team found that if patients consumed one drink each evening for 7 days, their blood pressure seesawed, sinking in the evening and rising in the morning (Abe et al. 1994). The studies suggest that regular consumption of alcohol can raise blood pressure during the hours that alcohol is not consumed. These findings are consistent with observations

that sympathetic nerve activity—a regulator of blood pressure—increases during alcohol withdrawal (Denison et al. 1997).

Possible Beneficial Effects of Alcohol on Blood Pressure. Some studies have shown a linear relationship between alcohol and blood pressure at all levels of consumption, whereas other studies have found a J- or U-shaped association, with the lowest levels occurring in people who consumed one to three drinks a day. Most of these studies examined blood pressure among middle-aged people, but a recent study of young adults—aged 18 through 26—found a similar J-shaped relationship between alcohol and blood pressure (Gillman et al. 1995). Taken together with previous data in middle-aged individuals, this suggests that moderate alcohol consumption is associated with a slight reduction in blood pressure or may protect against age-related development of hypertension.

How moderate alcohol consumption might chronically lower blood pressure remains unclear. A recent study found that rats consuming moderate amounts of alcohol for 8 months had lower age-related increases in blood pressure than did animals not given alcohol (Guillaume et al. 1997). The researchers found beneficial changes in kidney receptors for the hormone atrial natriuretic peptide (ANP), which regulates sodium and water levels in the body, and, in turn, blood pressure. Other researchers have found that ANP levels increase with acute alcohol intake (Gianoulakis et al. 1997), promoting water loss and lowering blood pressure. Eight months of moderate alcohol consumption altered kidney ANP receptors in a way that appeared to protect against increasing blood pressure. Future studies will need to clarify the importance of alcohol's influence on ANP in modulating blood pressure, including determining how heavy alcohol consumption may affect ANP receptors and lead to increases in blood pressure.

In a recent study of more than 6,000 people with hypertension, moderate alcohol consumption was associated with lowered mortality due to stroke and heart attacks (Palmer et al. 1995). However, heavy alcohol consumption offsets these effects by increasing the risk of death from causes unrelated to cardiovascular disease. Future studies will be necessary to confirm this finding.

In Closing

Recent research has significantly increased knowledge of how alcohol acts on the heart and the cardiovascular system. Future research will direct the development of therapies to protect against the cardiovascular complications of heavy drinking, although abstinence remains the most likely cure. As important, future studies will elucidate the mechanisms underlying the apparent protective effects of moderate drinking on the heart. Understanding these mechanisms may lead to therapies for patients at risk for myocardial infarction and other cardiovascular events.

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Alcohol and Women: An Overview

Inborn differences shape each individual's response to alcohol, including the risk of developing complications from alcohol abuse. Some of these inborn differences may be related to gender: women seem to be more vulnerable than men to alcohol-related liver disease, cardiovascular disease, and brain damage.

The reasons for this vulnerability are not well understood. Women, on the average, are less likely than men to consume alcoholic beverages or to drink heavily or even moderately (Dawson and Archer 1992). Among women who do consume alcohol, their drinking patterns tend to be quite different from those of men. Men's drinking often is characterized by infrequent "binge" episodes, whereas women tend to drink more frequently but ingest smaller amounts of alcohol on each occasion (Dawson 1996). As the studies described below illustrate, however, women develop alcohol-related complications after drinking smaller cumulative amounts of alcohol than men do.

Health Consequences of Alcohol for Women

Women develop alcoholic hepatitis and alcoholic cirrhosis after the ingestion of smaller daily amounts of alcohol than men do (Mezey et al. 1988*a*). A recent large prospective study followed 13,000 adults for 12 years to determine the association between self-reported alcohol intake and the risk of future liver disease (Becker et al. 1996). The study found that the level of drinking above which there was a risk of alcohol-induced liver disease and alcoholic cirrhosis was 7 to 13 drinks (84 to 156 grams of alcohol) per week for women but 14 to 27 drinks (168 to 324 grams of alcohol) per week for men. Intake of 28 to 41 drinks (336 to 492 grams of alcohol) per week increased the risk of developing cirrhosis of the liver during the 12-year period 17 times for women and 7 times for men (compared with the minimal risk experienced by women or men drinking one to six drinks per week). Women, in addition, were found to be at higher risk of developing liver disease at any given level of alcohol intake.

Alcoholic women are more susceptible than alcoholic men to the development of myopathy (degenerative disease of skeletal muscle) and cardiomyopathy (degenerative disease of heart muscle). In a study of alcoholic women and men who had no symptoms of muscle disease, myopathy—indicated by clinical muscle weakness and evidence on microscopic examination of biopsy tissue—and cardiomyopathy were present in half of the women. These conditions were at least as common in women as in men, although the lifetime alcohol consumption for alcoholic women was only 60 percent that of alcoholic men (Urbano-Marquez et al. 1995). For both women and men, the severity of the deficiencies in muscle function was correlated to the total lifetime dose of alcohol, but the threshold dose for women for the development of cardiomyopathy was much lower. In alcoholics with a diagnosis of alcoholic cardiomyopathy, the women reported a lower daily dose of alcohol, shorter duration of alcoholism, and lower lifetime consumption (Fernandez-Sola et al. 1997).

Alcoholic women perform worse on neuropsychological tests of immediate recall and psychomotor speed than do alcoholic men with similar drinking histories (Acker 1986). Computer tomography scans showed decreases in brain volume in alcoholic women after a shorter length of excessive drinking compared with alcoholic men (Mann et al. 1992). In a more recent study using magnetic resonance imaging scans, the area of the corpus callosum (the primary nerve fiber bundle connecting the two cerebral hemispheres) was smaller in hospitalized alcoholic women than either control women or hospitalized alcoholic men (Hommer et al. 1996). In this study, alcoholic women and men had similar lifetime alcohol consumption. This study suggests an

increased sensitivity to alcohol-induced brain damage among women who drink. Although alcohol-induced decreases in brain volume are sometimes reversible following sobriety (Carlen and Winkinson 1987), the effect of long-term sobriety on the reduced corpus callosum size in alcoholics is unknown.

Finally, mortality rates are higher among women than men who drink heavily. The most frequent causes of mortality among alcoholic women are alcoholic liver disease, pancreatitis, accidents or violence, suicide, cancer, and cardiovascular disease (Lindberg and Ågren 1988; Smith et al. 1983). Heavy alcohol ingestion places young women (up to 55 years old) at increased risk of death from cardiovascular disease. In a study that compared causes of death among drinkers versus abstainers, 11.2 percent of women who consumed more than two alcoholic drinks per day died of cardiovascular disease, compared with 3.5 percent of women who abstained. For men in the same age group, 11.6 percent of those who consumed at least two alcoholic drinks per day died of cardiovascular disease, versus 8.4 percent of nondrinkers (Hanna et al. 1992).

Physiologic Mechanisms

Current research provides hints, but not by any means a complete picture, of the differences in the metabolism of alcohol between women and men, and at a finer level, hormonal and cellular differences that may lie behind differences in health consequences.

As a first step in determining why women seem particularly vulnerable to alcohol-induced damage, scientists have investigated whether there are differences between women and men in the way alcohol is absorbed into the bloodstream and metabolized. Making such comparisons is difficult. Physical characteristics such as body size and weight can influence the processing of alcohol, and genetically determined factors result in sizable differences in alcohol metabolism rates among individuals. Individuals' drinking history and how they consume alcohol—moderate amounts over time or binges, and in the context of what health history and age—can affect alcohol metabolism. Finally, differences in how the effects of alcohol are studied—how it is administered, over what time course, with or without food, and at what time of day—also can influence the resulting observations (Thomasson 1995).

One uniformly observed difference between women and men is that women attain higher peak blood alcohol levels than men when ingesting the same dose per kilogram of body weight. The higher peak blood levels are principally related to the distribution of alcohol—a water-soluble substance—in the smaller body water content of women compared with men (Jones and Jones 1976; Marshall et al. 1983).

Accounting for the difference in body water content is one of the difficulties in documenting the presence of other gender-related differences in alcohol metabolism and to what extent they contribute to the higher postconsumption blood alcohol level in women, and ultimately, alcohol-related health consequences. In particular, the extent to which there are differences between women and men in alcohol metabolism in the stomach—before alcohol reaches the liver, which is the primary site of alcohol processing—remains unclear (Thomasson 1995).

Studies also have differed on whether alcohol elimination rates—a reflection of how quickly the enzyme alcohol dehydrogenase (ADH) in the liver processes alcohol—are different in women and men (Arthur et al. 1984; Marshall et al. 1983; Mishra et al. 1989; Thomasson 1995). One approach to investigating this issue is examining whether sex hormones can influence elimination rates. No consistent changes in rates of alcohol elimination have been found during the various phases of the menstrual cycle (Gil 1997). However, higher levels of acetaldehyde—a toxic by-product of alcohol metabolism—were evident after alcohol ingestion in women during high estradiol phases of the menstrual cycle or in women taking oral contraceptives (Ericksson et al. 1996). Removing the ovaries of female rats has no influence on liver ADH or on rates of alcohol elimination (Mezey et al. 1981). Removal of the testes in humans with metastatic prostate cancer,

however, decreased plasma testosterone levels and increased rates of alcohol elimination (Mezey et al. 1988*b*), and, in another study, administration of dihydrotestosterone each day for 14 days decreased alcohol elimination in healthy men (Varbourdolle et al. 1991), suggesting that testosterone may have a measurable influence on alcohol elimination rates.

Finally, recent studies indicate that women have larger liver volumes per unit body weight than men do, which could result in higher rates of alcohol elimination when expressed per kilogram of body weight in women than in men (Kwo et al. 1997). The implication is that a larger liver will have more ADH available to metabolize alcohol. Additional research is needed to clarify the relative alcohol metabolic rates in women and men and the mechanisms behind gender-related differences.

Liver Injury

Similarly, the mechanism for the increased susceptibility of women to alcoholic liver disease is uncertain. One possibility is that higher relative rates of alcohol elimination in women than in men—a difference that has been noted in rodent studies but remains to be confirmed in humans—would result in more rapid formation of toxic metabolites such as acetaldehyde. Acetaldehyde is a very reactive compound that has been implicated in liver injury by stimulating the formation of free oxygen radicals, by-products of metabolism that can cause tissue damage.

Some research suggests that there may be gender-related differences at the cellular level that make women more susceptible to alcohol-related liver disease. One of the important contributors to alcoholic liver injury is activation of Kupffer cells, a type of immune cell that is resident in the liver, by alcohol. This activation is enhanced further in the presence of endotoxin, a component of the cell walls of bacteria found in the gut. The Kupffer cells are then stimulated to produce chemical mediators of the inflammatory process that can have either protective or destructive effects (see the section "Alcohol-Induced Liver Injury" earlier in this chapter). One group of investigators reported that Kupffer cells of acutely intoxicated female rats produced higher levels of tumor necrosis factor alpha (TNF-α or TNF, one of the proinflammatory mediators) than did Kupffer cells of intoxicated male rats (Spitzer and Zhang 1996). The actual amounts of TNF appeared to vary according to the phase of the estrus cycle. Interestingly, the females exhibited an attenuated, and thus less destructive, response to endotoxin by neutrophils, another immune cell. This may be a compensatory protective mechanism to reduce the potential for tissue injury by TNF. Finally, a recent finding suggests the involvement of estrogen in the greater sensitivity of female alcoholics to liver injury. Serum TNF levels and TNF messenger ribonucleic acid in the liver of female rats after endotoxin treatment were twice as high if the animals were pretreated with estrogen (Ikejima et al. 1998).

Many of the advances in our understanding of liver disease have resulted from the development of a clinically relevant animal model where continuous intragastric (directly to the stomach) feeding over a period of weeks mimics the progression of liver injury (the so-called French-Tsukamoto model) (French et al. 1986; Tsukamoto et al. 1985). This model recently was tested in female rats (Iimuro et al. 1997). Male and female rats were continuously given alcohol equivalent to 28 to 35 percent of total calories in a liquid high-fat diet for up to 4 weeks. Even though blood alcohol concentrations and rates of alcohol elimination were the same for the two genders under these conditions, female rats developed steatosis (abnormal fat deposition in the liver), inflammation, and necrosis (tissue death) more rapidly and to a greater extent than the males did, a picture that mimics the clinical situation. Other indicators of liver injury, including elevated plasma endotoxin levels, also were higher for females. The use of this model will facilitate investigations into the underlying mechanisms for greater female sensitivity to alcohol-induced liver injury and possibly other forms of tissue injury.

In Closing

As with liver disease, the mechanisms for the differential impact of alcohol on heart disease and mortality and on neurologic function in women and men are still unclear. There remain possibilities at every level of alcohol processing—its metabolism by enzymes in the stomach and liver, its absorption into the bloodstream, and its actions on the physiology of end organs—for mechanisms that could contribute to gender-related differences in the health consequences of drinking. The fact that adverse effects have been observed at levels of consumption that many would regard as low—7 to 13 drinks per week (Becker et al. 1996)—bespeaks the importance of research aimed specifically at identifying why women are so vulnerable to alcohol. The next two sections in this chapter discuss the impact of alcohol on two diseases—osteoporosis and breast cancer—that predominantly affect women.

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Alcohol and the Skeletal System

As long ago as ancient Egypt, alcohol abuse was observed to confer a high risk for skeletal fracture (Conn 1985; Mathew 1992; Seller 1985). While an association between alcoholism and accidental injury is well recognized (Lucas 1987), there is evidence to suggest that alcoholics may also suffer from a generalized skeletal fragility that makes their bones more liable to fracture. Basic science studies have identified processes that shape bone that are disrupted by alcohol.

Even more provocative, some recent studies find that moderate intake of alcohol may actually protect against the loss of bone mass that characterizes the disease osteoporosis. Despite the difficulty of establishing with certainty how and to what extent alcohol affects bone and the risk of fracture, this issue is an important one for public health. At some time in their lives, 30 to 50 percent of U.S. women and 10 to 25 percent of U.S. men will suffer an osteoporosis-related fracture (Melton and Riggs 1983). Approximately one in five people will die within 6 months after suffering a hip fracture, and many more will become disabled and will not be able to return to their previous lifestyle (Avioli 1991).

Research Challenges

The study of the effects of alcohol on bone disease is complex for several reasons. First, it is extremely difficult to define and accurately quantify lifetime alcohol exposure, a problem compounded further when studying elderly individuals with impaired recall. Second, studies may obscure the immediate and delayed effects of alcohol, which can be markedly different. Third, individuals vary in many ways other than alcohol consumption that can affect their health. Confounding factors such as diet, exercise, smoking, and overall health must be taken into account in analyses.

Finally, any association (either positive or negative) between drinking and fracture rates is difficult to demonstrate because fractures are relatively uncommon events. Fracture incidence peaks at 3 to 4 percent per year in women over 75 years of age, while in younger women the incidence can be as low as 0.02 percent to 0.1 percent per year depending on the age group studied. Sample sizes (the number of people in the study) must be large to convincingly demonstrate an effect. Attention to these and other serious methodological issues is lacking in most published studies and may result in a distorted estimation of the true consequences of alcohol on the skeleton. Even when these factors are accounted for, current studies document associations but do not prove causality.

The majority of available data on the impact of social drinking on skeletal integrity comes from "case-control studies" and "cohort studies" designed to identify general risk factors for osteoporotic fractures, not to explore specifically the effect of alcohol consumption on fracture prevalence. In case-control studies, researchers identify individuals with a particular characteristic or condition they wish to study, such as past fractures. They then match these individuals with others without fractures and compare other features in their health history, such as alcohol use, to detect any pattern linking fracture risk to alcohol consumption. Cohort studies focus on a cohort or population not selected for any particular disease or condition, and either look back at that population's health history (retrospective studies) or follow them through a time period and measure the frequency of events such as fractures (prospective studies). However, to demonstrate that a particular health practice is beneficial, a randomized intervention study—in which similar numbers of participants are randomly assigned to a health intervention or to no such intervention, and the long-term outcome

is compared—is usually required to prove a cause-and-effect relationship. A study of the relationship between (moderate) alcohol intake and fracture risk would be a formidable undertaking, but would be likely to have important public health implications, considering the prevalence of osteoporosis and the prominence of drinking in the United States.

Alcohol-Induced Fractures

Modern-day scientific research on fracture prevalence in alcoholic subjects is based for the most part on small, inadequately controlled studies composed mostly of men, perhaps reflecting the more modest levels of alcohol consumption by women. While men hospitalized for alcohol-related problems are four times more likely to have experienced a rib fracture than similar individuals with no drinking problems (Lindsell et al. 1982) and up to 14 times more likely to exhibit spinal crush fractures (Crilly et al. 1988; Israel et al. 1980), the effect of more moderate alcohol consumption on the bones of healthy men and women has not been well explored. Evidence from epidemiologic studies is inconsistent, with some reporting a positive association between alcohol intake and fracture occurrence, and others detecting no such association.

A prospective, population-based study of 3,140 perimenopausal women found alcohol intake to be higher among women who experienced fractures during the study than among those without fractures (Tuppurainen et al. 1995). Among women who drank alcohol, the risk of a fracture was increased about 50 percent over the risk among women who did not drink. In another study, osteoporotic fracture risk was higher with increased weekly alcohol intake in postmenopausal women (Paganini-Hill et al. 1981). In this study, women drinking more than eight standard drinks per week were almost twice as likely as nondrinkers to have an osteoporotic fracture. (A standard drink is defined as 0.5 ounces [oz] or approximately 15 grams of pure alcohol consumed as either 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof distilled spirits.) A survey of 84,500 U.S. women between the ages of 34 and 59 found that daily consumption of 25 grams of alcohol (one to two drinks) was associated with a 133-percent increase in risk for hip fractures and a 38-percent increase for wrist fractures (Hernandez-Avila et al. 1991). Although osteoporotic fractures are generally less common in nonwhite women, consumption of seven or more standard drinks per week was associated with a twofold increased risk of hip fracture in a cohort study of Japanese women (Fujiwara et al. 1997) and a 4.6-fold increased risk in a case-control study of black women (Grisso et al. 1994).

In the Framingham Heart Study, for those younger than age 65, both moderate (two to six drinks per week) and heavy (more than seven drinks per week) current drinking substantially and significantly increased the risk of fracture compared with the risk of fracture associated with light drinking (less than two drinks per week). For example, male heavy drinkers younger than age 65 experienced almost 10 times the risk of hip fracture as men who drank lightly (Felson et al. 1988).

In contrast, other studies of similar size and design have not identified any significant association between alcohol intake and fracture risk. Two separate case-control studies of risk factors for hip fracture in women—one in Europe (Johnell et al. 1995) and the other in Australia (Cumming and Klineberg 1994)—found no significant effect of alcohol intake. Similarly, a prospective cohort study of 2,513 women who participated in the first National Health and Nutrition Examination Survey found that self-reported alcohol use was not related to subsequent hip fracture (Huang et al. 1996). Finally, no association was detected between frequency of alcohol intake and either vertebral deformity in a population-based survey of over 14,000 participants in Europe (Naves Diaz et al. 1997) or distal forearm fracture in a case-control study in the United Kingdom (O'Neill et al. 1996).

Thus considerable—though not unanimous—evidence suggests that excessive alcohol intake increases the risk of fracture. Further, the

consequences of smaller amounts of alcohol consumption on the skeletal integrity are not clear. Because of the much larger number of people at risk from moderate alcohol consumption, it is crucial that the impact of social drinking on skeletal integrity be better assessed.

Alcohol-Induced Osteopenia

Epidemiologic studies that find a relationship between alcohol and fracture risk do not reveal to what extent the increase is due to a greater risk of trauma. Alcohol intoxication creates conditions that favor accidents and falls, facilitating bone fractures (Lucas 1987). In a study comparing the blood alcohol concentration (BAC) (see the box "The ABC's of BAC's" in the chapter on prevention) of people who had had falls (and had come to a hospital emergency room) with that of pedestrians identified for comparison, the risk of falling was tripled in those with a BAC of 0.1 to 0.15 percent and 60 times higher in those with a BAC of 0.16 percent or higher, compared with people whose BAC was 0.1 percent or lower (Honkanen et al. 1983). In addition to the effects of intoxication, the impaired muscle control that can accompany withdrawal seizures, hypoglycemic (low blood sugar) attacks, and alcohol-associated neuromuscular disabilities probably also contributes to the increased fall frequency.

Beyond the risk of falls, however, emerging evidence suggests that alcoholics may also suffer from a generalized skeletal fragility that makes their bones more liable to fractures. Bone density is an important determinant of bone strength and is a predictor of fractures. As measures of bone strength are neither well defined nor clinically available, osteoporosis, for all practical purposes, is currently synonymous with low bone density (or osteopenia). Saville (1965) was the first to demonstrate the association of osteopenia with alcohol abuse. Using postmortem material from 198 cadavers, he observed that fat-free bone mass was markedly reduced in the 39 samples from individuals with a history of alcoholism. He noted that the bone mass of young alcoholic males was comparable to that of elderly, postmenopausal females.

Subsequent studies over the past quarter century have clearly demonstrated clinically relevant reductions in bone mass in alcoholics, especially in the heel bone, vertebral column, and hip (Peris et al. 1995; Spencer et al. 1986). In a recent prospective case-control analysis of risk factors for the development of osteoporosis, average alcohol consumption was two to three times higher in both osteoporotic males and osteoporotic females than in age-matched controls (Blaauw et al. 1994). In another study, premenopausal women who consumed more than two standard drinks per day exhibited 13 percent lower bone density of the hip compared with women who consumed less than one standard drink per week (Gonzalez-Calvin et al. 1993).

Reduced bone density is not universally reported, however. In one study of 142 men and 220 women, bone density was measured 12 years after documentation of alcohol intake by questionnaire (Holbrook and Barrett-Connor 1993). Increasing alcohol consumption was associated with higher bone density at the hip in men and in the spine in women. A small study of 19 premenopausal alcoholic women found no difference in spine, hip, or forearm bone density (Laitinen et al. 1993), but a larger cross-sectional study of postmenopausal women by this research group did observe a positive correlation between alcohol intake and bone density (Laitinen et al. 1991*c*). The Study of Osteoporotic Fractures (7,963 ambulatory, nonblack women aged 65 and older) has also found that moderate alcohol intake is associated with higher bone density (Orwoll et al. 1996). However, less than 15 percent of this cohort consumed more than one standard drink per day.

The degree to which alcohol contributes to osteopenia in the entire population is not yet known. Intriguing data at lower levels of consumption, however, suggest that more modest alcohol consumption is less likely to be associated with low bone density and may even be associated with higher bone density. Moderate alcohol intake may affect endogenous hormone levels, as discussed below, to indirectly augment skeletal mass. However, the evidence for a protective

effect of moderate alcohol consumption is not entirely compelling and should be interpreted with caution. Although the results of the epidemiologic studies were adjusted for known confounding factors, the association may not be causal, and moderate alcohol intake may merely be a marker for relative affluence (resulting in better nutrition and lifestyle during peak bone mass acquisition earlier in life). Moreover, no study of osteoporotic fracture risk in women has thus far identified any corresponding protective effect of social drinking.

Bone Histomorphometry

Epidemiologic data on alcohol and bone mass are not entirely consistent, yet studies of the cellular, hormonal, and molecular processes involved in the formation of bone have identified mechanisms by which alcohol consumption could be a determinant of bone mass. Microscopic examination of bone (bone histomorphometry) from alcoholic subjects has provided important insight into the specific nature of the skeletal disorder induced by alcohol. Adult bone mass is regulated by a remodeling cycle that is composed of an initial period of bone breakdown (resorption) by cells called osteoclasts, coupled with a proportionate amount of new bone formation by cells called osteoblasts. Skeletal remodeling is a continuous process with approximately 10 percent of bone undergoing the process at any given time. Bone formation and bone resorption rates are tightly coupled, allowing for large amounts of bone to be replaced throughout adult life without significant alterations in total bone mass.

Over the past 20 years, scientists have found in both animals and human subjects that alcohol can disrupt this cycle. Clues that this is happening include the finding that the fibrous matrix on which calcium is deposited—trabecular bone—was reduced and resorption was enhanced in rats exposed to alcohol for more than 8 weeks (Baran et al. 1980). Trabecular bone in the hip bone or femur of rats fed alcohol has also been found to be thinner, with overall mechanical strength of the bone substantially compromised compared with rats not fed alcohol (Peng et al. 1988). Another study found that bone matrix synthesis and mineralization rates were reduced in rats fed intoxicating amounts of alcohol for 3 weeks (Turner et al. 1987).

Similar alcohol-induced histomorphometric abnormalities have been found in humans. Various studies of alcoholic patients have shown reductions in measures of bone formation and an increase in bone resorption (Schnitzler and Solomon 1984), a diminution of bone formation rates in alcoholics with no compensatory decrease in markers of resorption (Diamond et al. 1989), and a 60-percent reduction in the number of osteoblasts and a 50 percent lower mineralization rate in actively drinking alcoholics versus abstinent chronic alcoholics with no differences in resorption (Crilly et al. 1988). The overall impression from these studies seems to be that alcoholic bone disease is characterized by considerable suppression of bone formation, while indices of bone resorption, for the most part, do not differ substantially from those observed in control subjects.

The changes in bone turnover induced by alcohol can apparently be reversed by abstention. Studies have demonstrated a rapid recovery of osteoblast function, as assessed histomorphometrically and by biochemical measures of bone remodeling, within as little as 2 weeks after cessation of drinking (Diamond et al. 1989; Feitelberg et al. 1987; Laitinen et al. 1992). Moreover, a recent report suggests that bone, once lost, can be at least partially restored when alcohol abuse is discontinued (Peris et al. 1994). Hence, the bone loss in alcoholism appears to be a consequence of an imbalance in the normal tight coupling of resorption and formation, with normal resorption activity outstripping a repressed formation process. To date, no histomorphometric analyses have been performed on moderate drinkers. Such studies would be important to confirm and possibly extend the previous reports of increased bone density. The microscopic examination of skeletal tissue has the added benefit of identifying possible cellular mechanisms by which moderate alcohol intake affects bone.

Data from the 1992 National Longitudinal Alcohol Epidemiologic Survey indicate that 8.7 percent of U.S. adults consumed an average of more than two drinks a day (Dawson et al. 1995). Further, an ongoing national survey of high school students recently reported that within the past month, 24 percent of 8th graders, 40 percent of 10th graders, and 51 percent of 12th graders used alcohol (Johnston et al. 1999). The skeletal consequences of alcohol intake during adolescence, when the rapid skeletal growth ultimately responsible for achieving peak bone mass is occurring, may be especially harmful.

In a recent series of experiments, scientists have examined the effect of alcohol on the early phases of skeletal development in a model of a growing animal (Hogan et al. 1997; Sampson et al. 1996, 1997). Rats chronically exposed to alcohol from age 1 month to 3 months—a developmental period comparable to that of human adolescence and young adulthood—were compared with rats fed a diet without alcohol. Calories in the diet without alcohol were also reduced to mimic the reduction in caloric intake associated with alcohol consumption, so that any differences in bone would be due to the presence or absence of alcohol, not overall nutrition. Gross skeletal morphology—the appearance of bones on visual inspection—was not affected by alcohol, but bone density determined by calcium content in the tibial or shin bone was 25 percent lower in the alcohol-exposed animals, and whole bone strength was 40 percent lower.

These studies indicate that the adolescent skeleton is especially sensitive to the adverse effects of alcohol on bone formation. By limiting peak bone mass attainment, the development of osteoporosis later in life may be increased and its onset hastened. Adolescent alcohol consumption is frequently heavy and episodic, in "binges" (Wechsler et al. 1994). No animal studies have, as yet, examined the impact of episodic alcohol intake and compared it with continuous alcohol exposure. Furthermore, studies are needed to determine if alcohol consumption during adolescence has a lasting effect on age-related osteopenia and subsequent fracture risk.

Potential Mechanisms of Alcohol-Induced Bone Disease

Normal bone formation depends on adequate nutrition and the function and interaction of a variety of hormones and intercellular regulating factors. The effect of alcohol on the skeleton could result from a direct toxic effect on bone, or indirectly through an effect on nutritional status or hormonal regulation of bone metabolism. While the exact mechanism has yet to be established, research is providing a variety of potential pathways to alcohol-induced bone disease.

Alcohol and Nutrition

Disturbances in the ongoing balance, or homeostasis, of minerals in the body are an obvious mechanism for bone disease in alcoholics. Mild deficiencies in calcium, phosphate, and magnesium are frequently present in ambulatory alcoholics because of poor diet, malabsorption, and increased renal (kidney) excretion (Bikle et al. 1985; Kalbfleisch et al. 1963; Laitinen et al. 1992; Territo and Tanaka 1974). Yet no histomorphometric study has demonstrated any evidence of nutritional deficiency, except in patients who have previously undergone gastric surgery (Johnell et al. 1982*b*).

Vitamin D is a fat-soluble vitamin that stimulates intestinal absorption of calcium and is necessary for mineralization of new skeletal tissue. Early studies found circulating levels of the vitamin D metabolites to be low in alcoholics (De Vernejoul et al. 1983; Lalor et al. 1986; Mobarhan et al. 1984; Verbanck et al. 1977). However, subsequent investigation has excluded vitamin D deficiency as a major cause of alcohol-induced bone disease by demonstrating normal vitamin D absorption (Scott et al. 1965; Sorenson et al. 1977) and conversion to active metabolites (Posner et al. 1978) in alcoholic individuals and, more directly, by the measurement of normal free concentrations of the biologically active metabolite of vitamin D in patients with alcoholic cirrhosis and alcoholic bone disease (Bikle et al. 1984; Genant et al. 1985). These findings do not exclude the possibility of an alcohol-induced

vitamin D-resistant state, but the lack of histomorphometric evidence of osteomalacia in vitamin D-replete osteopenic alcoholic subjects (Bikle et al. 1985; Diamond et al. 1989) argues strongly against such a possibility.

Alcohol and Calciotropic Hormones

Calcitonin is a peptide produced by the thyroid gland that functions as an inhibitor of bone resorption, in effect protecting bone. In a study in which 0.8 grams per kilogram of alcohol—about 4 drinks for a 150-lb man—were administered to nonalcoholic men, plasma calcitonin levels were 38 percent higher 3 hours later (Williams et al. 1978). Alcohol-induced hypercalcitoninemia might be a mechanism for the observation that moderate intake of alcohol is associated with higher bone density, but no data exist about the duration of this effect in alcoholism.

Parathyroid hormone (PTH) is the principal regulator of blood calcium levels. The production of calcium is stimulated by a decrease in blood calcium; PTH's major actions are to increase the release of calcium from bone and reduce kidney excretion of calcium. An elevated PTH level would be a sensitive indicator of reduced circulating calcium. Most studies have failed to demonstrate a consistent effect of alcohol on PTH levels. They may be normal, reduced, or elevated in alcoholic subjects (Bikle et al. 1993; Bjorneboe et al. 1988; Johnell et al. 1982*a*). A likely explanation for the discrepant reports of PTH values is the molecular heterogeneity not only of the PTH fragments measured in the circulation, but of the radioactively labeled antibodies used in the assays for PTH. In addition, PTH is metabolized in the liver, which is frequently damaged with excessive alcohol ingestion.

Recent studies suggest that alcohol may directly interfere with PTH secretion. Scientists who administered alcohol to normal volunteers over a 3-hour period observed a marked decrease in intact PTH levels (Laitinen et al. 1991*a*). PTH levels then rebounded to above baseline after 8 hours and remained elevated for the remainder of the 16-hour study. The fall in PTH was accompanied by a fall in blood calcium and a dramatic increase in urinary calcium excretion, suggesting that the response of the parathyroid gland is impaired even in the presence of low calcium levels. It is possible that alcohol-induced changes in intracellular calcium, especially within the parathyroid gland, may explain the reduced PTH levels (Brown et al. 1995).

In subsequent studies, scientists examined the effects of more prolonged alcohol consumption and observed an increase in PTH levels accompanied by a rise in serum calcium after 3 weeks (Laitinen et al. 1991*a*). Thus, alcohol appears to have both acute and chronic effects on PTH secretion, with the net result that levels of PTH detected by immune-based assays are slightly increased. There are no reports on PTH bioactivity in the serum of alcoholic subjects to give a definitive account of the effect of long-term exposure to substantial amounts of alcohol. However, the classic signs of hyperparathyroidism are not seen on bone biopsies of affected patients (Bikle et al. 1985; Crilly et al. 1988; Diamond et al. 1989; Lindholm et al. 1991). Thus, no convincing evidence can be marshaled to support a major role for an indirect effect of alcohol on bone via alterations in calciotropic hormone levels.

Sex Hormones

Inadequate gonadal function is a well-described risk factor for osteoporosis. Alcohol abuse has been associated with sexual dysfunction in both men and women (Gavaler 1991; Van Thiel 1983; Wright et al. 1991). Men who have a long-term history of alcohol abuse often suffer from impotence, sterility, and testicular atrophy (Valimaki et al. 1982) and have reduced concentrations of plasma testosterone (Boyden and Pamenter 1983; Van Thiel et al. 1974). In women, the frequency of menstrual disturbances, spontaneous abortions, and miscarriages increases with the level of drinking, and alcohol abuse has adverse effects on fertility and sexual function, often bringing on premature menopause (Gavaler 1985; Hugues et al. 1980; Mello et al. 1993; Valimaki et al. 1984).

There is considerable interest in the question of whether consumption of alcohol at a more moderate level—one drink per day or less for women—might actually increase estrogen. Studies of both pre- and postmenopausal women have yielded mixed results (Dorgan et al. 1994; Purohit 1998; Reichman et al. 1993). In particular, recent studies suggest that alcohol increases estradiol, the most potent form of estrogen, in postmenopausal women on hormone replacement therapy, but results are inconsistent in postmenopausal women not on hormone replacement therapy (Purohit 1998).

Animal studies indicate that moderate alcohol levels increase the production of estradiol through conversion of testosterone (Chung 1990). Relative to the skeleton, studies have shown that osteoblasts possess this conversion capability (Purohit et al. 1992), thus providing a potential source for estradiol in the bone microenvironment. In addition, certain alcoholic beverages contain isoflavanoid compounds known as phytoestrogens (Gavaler 1995). These substances of plant origin are capable of binding to the estrogen receptor (Gavaler et al. 1987) and eliciting estrogen-like responses in both animals and postmenopausal women (Gavaler et al. 1991; Van Thiel et al. 1991).

Additional research is needed to clarify alcohol's effect on estrogen in postmenopausal women. If moderate alcohol consumption does result in elevated estrogen, this could be a plausible mechanism for the observations in certain epidemiologic studies that moderate drinking is associated with increased bone density. However, the level of alcohol consumption is likely to be an important factor relative to bone metabolism and other risks of alcohol consumption.

Alcohol and Bone Cells

Chronic heavy consumption of alcohol is associated with profound alterations in the growth and proliferation of a wide variety of cell types. Biochemical and histomorphometric evaluation of alcoholic subjects reveals a marked impairment in osteoblastic activity with normal osteoclastic activity. These findings argue strongly that a primary target of alcohol's adverse effects on the skeleton is the osteoblast. As bone remodeling and mineralization are dependent on osteoblasts, it follows that a deleterious effect of alcohol on these cells will ultimately lead to reduced bone mass and fractures. A number of researchers have noted that alcohol can reduce proliferation of osteoblasts. In cell culture, alcohol induced a dose-dependent reduction in cell protein and deoxyribonucleic acid (DNA) synthesis in normal human osteoblasts (Friday and Howard 1991). This reduction in proliferation has been confirmed by others studying human cells (Chavassieux et al. 1993).

Alcohol-associated reductions in cell number must stem from either overt toxicity or inhibition of intracellular signaling processes that regulate cell replication. Alcohol has been observed to enhance a process that normally leads to the preprogrammed death, or apoptosis, of particular cells (De et al. 1994; Ewald and Shao 1993).

In many cell types, alcohol-induced reductions in cell division are reversible. These reductions are associated with depletion of naturally occurring compounds called polyamines in the cell (Shibley et al. 1994). Research suggests that polyamines can regulate the synthesis of both DNA (Janne et al. 1978) and protein (Jacob et al. 1981) and may also affect the expression of genes that regulate cell division (Luscher and Eisenman 1988). Chronic exposure to alcohol results in alterations in polyamine metabolism that may contribute to the pathogenesis and progression of liver disease in alcoholic individuals (Diehl et al. 1988, 1990*a*,*b*).

In a series of experiments involving cultures of osteoblast-like bone cancer cells, alcohol impaired the induction of the first, and often rate-limiting, step in polyamine biosynthesis (Klein and Carlos 1995). This effect by alcohol was dose dependent, and it paralleled alcohol's antiproliferative effect on the cells. Addition of polyamines restored the rate of cell proliferation in the alcohol-exposed cell cultures to that observed in cultures untreated with alcohol. Additional studies failed to find any evidence for induction

of apoptosis by alcohol in these osteoblast-like cell cultures (Klein et al. 1996). The half-maximally effective concentration of alcohol to inhibit osteoblast proliferation in culture was well within the physiologic range observed in actively imbibing alcoholic subjects. A concentration of alcohol equivalent to a blood alcohol level of 0.044 percent—about half the blood alcohol level (0.08 percent) that many States define as legally intoxicated—also resulted in a substantial 20-percent decline.

These findings of a direct inhibitory effect of clinically relevant concentrations of alcohol on proliferation of these osteoblast-like cells support the histomorphometric observations of a reduced number of osteoblasts and impaired bone formation activity in humans consuming excessive amounts of alcohol (Bikle 1993; Crilly et al. 1988; De Vernejoul et al. 1983, Diamond et al. 1989; Genant et al. 1985). Furthermore, these studies indicate that impairment of cellular polyamine synthesis plays a critical role in mediating the antiproliferative effects of alcohol because the administration of externally supplied, or exogenous, polyamines overcame the inhibitory effect of alcohol on cell proliferation. Moreover, these studies suggest that alcohol must perturb some intracellular process that normally results in stimulation of the polyamine biosynthetic pathway, a vital step in osteoblast proliferation.

Further evidence implicating a direct effect of alcohol on osteoblast activity comes from studies examining the effects of alcohol on circulating osteocalcin levels. Osteocalcin is a small peptide synthesized by active osteoblasts, a portion of which is released into the circulation. Levels of osteocalcin are positively correlated with histomorphometric parameters of bone formation in healthy individuals (Garcia-Carrasco et al. 1988) and patients with metabolic bone disease (Delmas et al. 1985). Chronic alcoholic patients exhibit significantly lower osteocalcin levels than do age-matched nondrinkers (Labib et al. 1989). Moreover, alcohol exerts a dose-dependent suppressive effect on circulating osteocalcin levels (Laitinen et al. 1991*b*; Nielsen et al. 1990; Rico et al. 1987). The consumption of 50 grams of alcohol (four drinks) over 45 minutes resulted in a 30-percent decrease in serum osteocalcin levels detectable 2 hours later (Nielsen et al. 1990). Beyond these fragmentary attempts at characterization, however, little further is known about the mechanisms whereby alcohol stimulates osteoblast proliferation and growth.

Alcohol and Intracellular Signaling Processes

The subcellular mechanisms for alcohol's ability to damage any part of the body are currently not known. Researchers have suggested that alcohol may disrupt the lipids (fats) in the cell membrane and, in turn, alter the function of proteins residing in the membrane's lipid environment. Alternatively, alcohol may have a direct action on specific proteins in the membrane. There is increasing evidence that alcohol may exert significant effects on transmembrane signal transduction, a major avenue of cellular control (Hoek and Rubin 1990; Hoffman and Tabakoff 1990; Taylor 1997).

For example, a recent study found that, in an osteoblast-like cell line, alcohol can increase levels of the immune-signaling molecule, or cytokine, interleukin-6 (IL-6) (Keller et al. 1997). IL-6 contributes to the development of osteoporosis by stimulating osteoclastic activity. These findings suggest that one avenue of damage to bone from alcohol could be through an effect on IL-6.

Growth factors are signaling molecules that shape the growth and development of cells. Insulin-like growth factors I and II (IGF-I and IGF-II) are considered to be the most important local regulators of bone remodeling. Osteoblastic cells in culture can produce both IGF-I and IGF-II (Canalis et al. 1991). Molecular docking stations, or receptors, exist in the cell for IGF's. The docking of a molecule to the receptor sets off a subsequent signaling cascade within the cell that can then help dictate the nature and rate of specific cell functions. Osteoblasts are dependent on signaling via the IGF-I receptor for survival and proliferation in culture. The IGF's increase the pre-osteoblastic cell population that eventually differentiates into mature osteoblasts. Independent of their effects on cell replication, IGF's

increase collagen synthesis and matrix assembly. Through these actions it is apparent that the IGF's play a fundamental role in the maintenance of bone mass. On the basis of these findings, it is interesting to speculate that the reduced osteoblast number and bone formation that characterize alcoholic bone disease may stem entirely from a single alcohol-induced defect in intracellular signaling by the IGF receptor.

In Closing

Recent studies suggest a dose-dependent relationship between alcohol consumption and risk of fracture in both men and women. This increased risk may be, at least in part, attributable to a reduction in bone density in those with excessive alcohol intake. Alcoholic bone disease is characterized by impaired bone formation in the face of relatively normal bone resorption. The uncoupling of these two physiologic processes results in defective remodeling of skeletal tissue and, in turn, reduced bone mass and increased fracture risk. The growing skeleton may be especially sensitive to the adverse effects of alcohol. Experiments using well-defined osteoblastic model systems indicate that the observed reductions in bone formation result from a direct, antiproliferative effect of alcohol on the osteoblast itself. Further studies are necessary to establish the underlying mechanisms by which alcohol exerts its antiproliferative effects on the osteoblast. At present, sustained reduction in alcohol intake is the only effective therapy for alcohol-induced bone disease. An improved understanding of the pathogenesis of alcohol-induced bone disease may lead to alternative therapeutic avenues.

Because of the potential impact on a large proportion of our society, of considerable interest is the provocative finding of increased bone density in social drinkers with more moderate alcohol consumption. Whether this increase in bone density can be ascribed to direct stimulatory effects of alcohol on estrogen or calcitonin levels, or both, or to concomitant lifestyle and socioeconomic factors has yet to be adequately explored. Specific studies are needed to address the question of whether moderate alcohol consumption is a protective factor against fracture, and if so, at what level the skeletal advantages of alcohol intake are obviated by the increased risks from alcohol excess.

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Alcohol and Breast Cancer

The lifetime risk for breast cancer among U.S. women is estimated to be as high as one in eight (Feuer et al. 1993). Over the past two decades, interest in identifying dietary factors that influence breast cancer has been high, and evidence from a number of epidemiologic studies suggests that alcohol consumption, particularly at high levels, can increase breast cancer risk. Whether a woman consumes wine, beer, or distilled spirits is unimportant; it is the amount she drinks that appears to be critical. Research has begun to shed light on how alcohol could promote breast cancer growth and to identify several factors that influence alcohol's impact on this disease.

The relationship between breast cancer risk and alcohol intake was first noted in the 1970's among women participating in the third National Cancer Survey (Williams and Horm 1977). Approximately 50 epidemiologic studies scrutinizing this association have followed. In addition, combined data from many of these studies have been evaluated using a statistical method called "meta-analysis" (Holman et al. 1996; Longnecker 1994; Longnecker et al. 1988). One such analysis of six case-control studies (comparing women with breast cancer with matched women with no breast cancer) showed that women who drank three or more alcoholic beverages per day (or 40 grams of alcohol, with about 13 grams in a standard drink) had a 69 percent higher risk of getting breast cancer compared with nondrinkers (Howe et al. 1991). A separate analysis of six prospective studies (following healthy women over time, recording their alcohol consumption, and noting which women developed breast cancer) showed that those who had two to four drinks per day (30 to 60 grams of alcohol) had a 41 percent greater risk of getting breast cancer than those who did not drink (Smith-Warner et al. 1998). Over a range of one to six drinks per day, the relationship of alcohol to breast cancer was linear—the more women drank, the higher their risk compared with nondrinkers.

The findings of the meta-analyses and of a majority of these epidemiologic investigations, including two recent large case-control and cohort reports (which study a population rather than selected women with breast cancer), point to an increase in breast cancer risk associated with alcohol consumption (Bowlin et al. 1997; Longnecker 1995; Thun et al. 1997; and World Cancer Research Fund Panel 1997).

Controversy remains over the interpretation of these studies, however (Katsouyanni et al. 1994; Plant 1992; Rosenberg et al. 1993; Roth and Levy 1995; Schatzkin and Longnecker 1994). For epidemiologists, the actual numerical association between alcohol and breast cancer risk is considered relatively modest. In addition, some studies found no link between high alcohol intake and breast cancer risk (Freudenheim et al. 1995; Rohan et al. 1993; Smith et al. 1994).

Nonetheless, substantial evidence, obtained from populations in several countries, suggests that breast cancer risk is elevated for women consuming high levels of alcohol (more than three drinks per day) compared with abstainers. Some studies report a dose-response relationship—drinking larger quantities of alcohol leads to more cases of breast cancer (Longnecker 1994). There is evidence that consuming as few as one to two drinks per day can increase risk, though to a lesser degree than the moderate risk seen with three daily drinks (Longnecker et al. 1988; Smith-Warner et al. 1998). Not all studies have detected this association, however (Zhang et al. 1999).

Scientists have identified plausible biological mechanisms for alcohol's action, an important piece of the puzzle in establishing a connection between alcohol and breast cancer. In many investigations, an effect of alcohol has been

demonstrated after age, family predisposition, and other known dietary and reproductive risk factors have been taken into account. At this time, no other confounding factors have been identified that can reasonably explain the enhancing effect of alcohol consumption on breast cancer risk.

Age, Genetics, and Other Risk Factors

Although no other factors can account for the increased risk associated with alcohol noted in some studies, scientists are investigating other physiologic characteristics of individual women to determine their effect, if any, on alcohol-related risk. For example, although early studies linked alcohol consumed at younger ages with increased breast cancer risk (Harvey et al. 1987; van't Veer et al. 1989), more recent research has found a stronger relationship with risk for recent drinking (Holmberg et al. 1995; Longnecker et al. 1995*a*) or lifetime alcohol intake (Longnecker et al. 1995*b*).

A woman's genetic makeup also may play a role in her susceptibility to alcohol-related breast cancer. For example, a report by Freudenheim et al. (1997) suggests that genetic variations that reduce the effectiveness of the alcohol-metabolizing enzyme alcohol dehydrogenase are linked to an increased risk of breast cancer for premenopausal women who drink heavily. Other physiologic characteristics may influence alcohol-related breast cancer risk. Some, but not all, reports find that thin or lean women have higher risk associated with drinking compared with heavier women (Gapstur et al. 1992). Although there are a number of risk factors for breast cancer other than alcohol, drinking raises breast cancer risk even after age, family history of breast cancer, and other known dietary and reproductive risk factors are adjusted for.

Menopausal Status and Hormones

Research findings suggest a role for alcohol in breast cancer risk in both pre- and postmenopausal women. Several studies report that the risk of premenopausal breast cancer was elevated for women consuming alcohol (Friedenreich et al. 1993; Swanson et al. 1997; Viel et al. 1997). One investigation found this effect to be most apparent for women with advanced breast cancer (Swanson et al. 1997).

In the only study to examine premenopausal bilateral breast cancer (characterized by strong family predisposition), alcohol consumption increased risk (Haile et al. 1996). Other studies showed risk increases for postmenopausal breast cancer (Gapstur et al. 1992; Holmberg et al. 1995; van den Brandt et al. 1995). Still others found that alcohol consumption increases risk for both pre- and postmenopausal breast cancer (Bowlin et al. 1997; Longnecker et al. 1995*a*).

Many postmenopausal women take estrogen as hormone replacement therapy (HRT) to prevent heart disease and osteoporosis and to alleviate the symptoms of menopause. Alcohol use by women receiving HRT may increase risk (Gapstur et al. 1992; Zumoff 1997), although the data are not entirely consistent (Friedenreich et al. 1993).

Breast tumors are evaluated to see whether they contain docking sites, or receptors, on the cell surface for the hormones estrogen and progesterone. This information affects a person's treatment choices and prognosis. The degree to which alcohol raises breast cancer risk—and interacts with other factors such as HRT use to do so—may depend on the estrogen or progesterone receptor status of the breast tumor. One study found that alcohol increased risk for estrogen receptor-negative and progesterone receptor-negative tumors (to a greater extent than the two other types of receptor tumor subtypes) in women who had taken HRT and consumed 4.0 grams or more of alcohol (about a third of a standard drink) per day compared with abstainers who never used HRT (Gapstur et al. 1995). In contrast, a second study showed that the risk for women with estrogen receptor-positive tumors increased as alcohol consumption increased (Nasca et al. 1994). Additional research in this area may both clarify alcohol's interaction with receptors and other health factors and provide information on the mechanisms behind the effect.

Mechanisms of Alcohol-Related Breast Cancer

An important consideration in evaluating the credibility of the alcohol-breast cancer relationship is whether plausible biological mechanisms can be identified. Among the areas scientists have investigated in human studies are alcohol's potential to affect hormone levels, to cause changes in breast tissue, and to influence overall nutrition.

Hormones

Cumulative lifetime exposure to estrogen is considered an important contributor to breast cancer risk (Bernstein and Ross 1993; Toniolo 1997). A number of studies have examined whether alcohol raises estrogen levels in pre- and postmenopausal women. Although some studies report such an effect, the evidence is not conclusive that alcohol raises estrogen levels (Longnecker and Tseng 1998; Purohit 1998).

The question remains important and relevant to breast cancer, however. Some tissues, such as adipose or fat tissue, can produce estrogens from androgens—the "male" sex hormones that include testosterone, androstenedione, and dehydroepiandrosterone sulfate. Blood androgen levels have been shown to increase in premenopausal women who drink (Dorgan et al. 1994; Eriksson et al. 1994; Reichman et al. 1993). For example, blood androstenedione levels in women who consumed moderate amounts of alcohol (0.22 to 0.99 ounces per day, equivalent to less than one drink to up to two drinks) were 27.4 percent higher than in abstainers (Dorgan et al. 1994).

Alcohol intake may also increase exposure to natural or endogenous estrogen through changes in the menstrual cycle. Researchers observed that premenopausal women who drank moderate amounts of alcohol had more regular cycles and fewer long cycles than nondrinkers did (Cooper et al. 1996). This change in cycles would be expected to increase exposure to estrogen during the premenopausal years.

Other studies show that women on HRT who drink alcohol have significantly higher circulating estradiol and prolactin levels than women on HRT who do not drink (Ginsburg et al. 1995*a*,*b*). In a report by Ginsburg et al. (1996), women who drank 0.7 grams of alcohol per kilogram of body weight (two to three drinks for a 120-lb woman) on consecutive days rapidly exhibited a threefold increase in circulating estradiol concentrations compared with abstainers. However, there was no significant increase in the women who drank alcohol but were not on HRT.

Some alcoholic beverages, like bourbon and whiskey, contain compounds called phytoestrogens. These plant products have chemical structures that differ from endogenous estrogens but appear to have similar effects. Postmenopausal women who were given an extract of bourbon that contained no alcohol had a significant decrease in the blood levels of two hormones involved in regulating the menstrual cycle (luteinizing hormone and follicle-stimulating hormone) and a significant increase in prolactin (a hormone capable of supporting tumor growth) (Gavaler 1993).

Also noteworthy is a report that blood levels of the reactive alcohol metabolite acetaldehyde are significantly elevated during the high-estradiol phase of the menstrual cycle of women who drink alcohol and in women who drink and use synthetic estrogens (Eriksson et al. 1996).

Additional research is needed to clarify whether alcohol's effect on estrogens and androgens in women is consistently positive and of sufficient magnitude to contribute to the alcohol's ability to raise breast cancer risk.

Mammary Gland Tissue

Alcohol may alter the normal architecture of the breast. The relationship between the proportion of breast volume occupied by densities (found on mammography) and breast cancer risk is well established (Warner et al. 1992). Some, but not all, observational studies have reported that

women who drank alcohol had more areas within the breast occupied by these mammographic densities (Boyd et al. 1989; Funkhouser et al. 1993; Herrington et al. 1993). Additional studies are needed to establish the consistency and magnitude of any increase in mammographic parenchymal densities associated with alcohol intake, as well as to determine why and how these changes occur.

Nutrition

Alcohol consumption may influence food choices and disturb the body's use of essential nutrients. Several dietary factors have been linked to breast cancer risk (Hunter and Willett 1996). In particular, it has been reported that women who consume the lowest quantities of fruits and vegetables are at increased risk for breast cancer (Freudenheim et al. 1996). Women who consume alcohol, especially in higher quantities, have been reported to eat fewer fruits and vegetables (Millen et al. 1996; Serdula et al. 1996) and less beta-carotene (D'Avanzo et al. 1997). Alcohol consumption also has been associated with decreased blood concentrations of beta-carotene, lutein/zeaxanthin, and vitamin C, food components thought to help prevent cancer (Drewnowski et al. 1997; Forman et al. 1995). Therefore, part of alcohol's effect on breast cancer risk may be through decreased intake or impaired use of nutrients that may be capable of reducing cancer risk.

Animal Models of Alcohol and Breast Cancer

Investigators have used animal models to explore the relationship between alcohol intake and breast cancer (reviewed in Singletary 1997). Generally, three types of models have been used: spontaneous tumor development, chemically induced tumor development, and implantation of cancer cells. The results to date have been inconsistent, partly due to the small number of studies and the wide variety of experimental conditions, including the timing, manner, and dose in which the alcohol was administered; the use and dosage of cancer-causing agents or carcinogens; and dietary composition (Singletary 1997).

For example, in the rodent spontaneous mammary tumor model, only two of six published experiments showed enhancement of mammary tumor development for animals fed alcohol-containing diets compared with controls (Hackney et al. 1992; Holmberg and Ekström 1995; Schrauzer et al. 1979, 1982).

The chemically induced rodent mammary tumor model can be used to examine the effect of alcohol on specific stages in the cancer process. Alcohol provided to animals prior to or during administration of a carcinogen would be expected to influence the early or initiation stage of cancer development, whereas alcohol provided after carcinogen dosing would influence later steps in carcinogenesis, the promotion stage. In studies in which alcohol was fed to animals during both the initiation and promotion stages, development of chemically induced mammary tumors was not enhanced (McDermott et al. 1992; Rogers and Conner 1990). However, there was evidence of an enhancing effect when alcohol was provided during either the initiation or promotion stage (Grubbs et al. 1988; Singletary et al. 1991, 1995), although intermediate levels of alcohol were more effective than high levels in promoting tumors. In five experiments, alcohol fed to female rats during the initiation stage increased mammary tumor development (Grubbs et al. 1988; Singletary et al. 1991, 1995), and in two experiments, alcohol stimulated the promotion stage of mammary tumorigenesis compared with controls (Singletary et al. 1991, 1995). However, a typical dose-response relationship was not observed. In other words, mammary tumor development was significantly increased for animals fed intermediate (15 to 20 percent of calories) but not high (30 percent of calories) levels of alcohol (Singletary et al. 1991, 1995).

Alcohol may be capable of enhancing the progression of cancer as well. Increased metastasis (proliferation beyond the site of origin) of implanted breast cancer cells was observed for rats given alcohol in a liquid diet (Yirmiya et al. 1992).

Tumor Initiation. Several mechanisms have been proposed to explain the ability of alcohol to

initiate cancers in laboratory animals in different organs, including the breast (Garro and Lieber 1990; Rogers and Conner 1991; Seitz and Simanowski 1988). Although alcohol is not a genotoxic or directly deoxyribonucleic acid (DNA)-altering carcinogen, it can act as a cocarcinogen by influencing processes in the body associated with the initiation and promotion stages of carcinogenesis.

For example, alcohol induces the expression of select cytochrome P450's, a class of alcohol-metabolizing enzymes that can activate various carcinogens. Alcohol may also impair the liver's ability to clear certain carcinogens from the body, leaving the cancer-causing compounds to circulate among tissues such as the breast (Anderson et al. 1995).

Alcohol and its highly reactive metabolite, acetaldehyde, also have been linked to the body's inability to repair carcinogen-induced DNA damage (Espina et al. 1988). If left unrepaired, damage to critical regions of DNA in breast cells could lead to mutations and the subsequent initiation of cancer. Thus, in addition to stimulating carcinogens to do their damage, alcohol may inhibit the ability of some cells to detoxify and eliminate carcinogens. Finally, in studies of female rats, alcohol consumption was associated with the growth of more mammary gland terminal end buds, structures that have greater susceptibility to carcinogen-induced DNA damage than do other mammary gland structures, providing another possible contributing mechanism for cancer vulnerability (Singletary and McNary 1992).

Alcohol influences factors in the cell nucleus that regulate the expression of genes in the DNA. This feature of alcohol's action can have diverse effects, depending on the genes involved. For example, alcohol has demonstrated effects on nuclear factor kappa B, a factor that modulates the transcription of DNA to ribonucleic acid in the cell nucleus, a key step in protein synthesis and, thus, the expression of genes (Zakhari 1996). How alcohol alters gene expression—with effects that may include the promotion of cancer—is an important area for continued research.

Tumor Promotion. Alcohol intake may stimulate the second, or promotion, stage of tumor development by several possible mechanisms. Alcohol consumption has been associated with increased mammary gland cell multiplication in female rats treated with a breast carcinogen (Singletary and McNary 1994). The rate of cell proliferation is believed to be one of several important factors determining risk for cancer (Preston-Martin et al. 1990). When rodents are fed alcohol, their levels of circulating prolactin—a hormone that can stimulate the growth of breast tissue—increase (Dees and Kozlowski 1984).

Reactive oxygen species, highly reactive molecular fragments that are a by-product of alcohol metabolism, can harm cells and contribute to tumor promotion (Nordmann et al. 1990). Alcohol intake also decreases the immune system's ability to detect and destroy cancer cells (Yirmiya and Taylor 1993). This may be an important factor in explaining why breast cancer metastasis is enhanced in alcohol-consuming rats.

In Closing

Epidemiologic studies provide substantial support that breast cancer risk is increased for women consuming alcoholic beverages compared with abstainers. This effect is modest in magnitude and is not restricted to one type of alcoholic beverage. The risk is most pronounced at high intakes of alcohol. Increased exposure to estrogens and androgens with alcohol consumption is one plausible—but as yet unconfirmed—biological mechanism to explain alcohol's effect on breast cancer risk. To clarify alcohol's role in enhancing susceptibility to breast cancer, further research is needed in a number of areas, including specific drinking patterns, body mass index, dietary factors, family history of breast cancer, use of HRT, tumor hormone receptor status, and immune function status. Information gathered from animal studies is less compelling but nonetheless provides evidence that alcohol

may act as a weak cocarcinogen and weak breast tumor promoter. These actions in animals may be explained in part by alcohol's effect on induction of cancer-promoting biochemical pathways, circulating hormone levels, structural development of the mammary gland, mammary gland cell proliferation, and immune system function.

The relationship between alcohol consumption and breast cancer risk will be better understood as more information about the interactions between alcohol and other risk factors becomes available and as additional insight into biological mechanisms is gained. The need to clarify this issue is a priority, since alcohol intake appears to be one of the few modifiable breast cancer risk factors yet identified (Hankinson and Willett 1995; Rosenberg et al. 1993).

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Prenatal Exposure to Alcohol

Fetal Alcohol Syndrome (FAS) is a set of birth defects caused by maternal consumption of alcohol during pregnancy. At birth, children with FAS can be recognized by growth deficiency and a characteristic set of minor facial traits that tend to become more normal as the child matures. Less evident at birth—but far more devastating to FAS children and their families—are the lifelong effects of alcohol-induced damage to the developing brain.

FAS is considered the most common nonhereditary cause of mental retardation. In addition to deficits in general intellectual functioning, individuals with FAS often demonstrate difficulties with learning, memory, attention, and problem solving as well as problems with mental health and social interactions. Thus these individuals and their families face persistent hardships in virtually every aspect of life.

Estimates of FAS prevalence vary from 0.5 to 3 per 1,000 live births in most populations, with much higher rates in some communities (Stratton et al. 1996). However, the diagnosis of FAS identifies only a relatively small proportion of children affected by alcohol exposure before birth. Children with significant prenatal alcohol exposure can lack the characteristic facial defects and growth deficiency of FAS but still have alcohol-induced mental impairments that are just as serious, if not more so, than in children with FAS. The term "alcohol-related neurodevelopmental disorder" (ARND) has been developed to describe this condition. In addition, prenatally exposed children without FAS facial features can have other alcohol-related physical abnormalities of the skeleton and certain organ systems; these are known as alcohol-related birth defects (ARBD).

Because the effects of prenatal alcohol exposure on the developing brain appear to be especially long lasting and debilitating, a significant proportion of research has concentrated on brain malformations as well as cognitive and behavioral abnormalities. In this chapter, the section on "Prenatal Alcohol Exposure: Effects on Brain Structure and Function" describes research using neuroimaging techniques to provide precise pictures of brain abnormalities found in persons exposed to alcohol before birth. The studies strongly support the notion that alcohol has specific, rather than global, effects on the developing brain. The section also describes current research on the many behavioral manifestations of this structural brain damage, including problems with cognitive and motor functions as well as mental health and psychosocial behavior.

It is unlikely that a single mechanism can explain all of the deleterious effects that result from alcohol exposure during pregnancy. As described in the section "Underlying

Mechanisms of Alcohol-Induced Damage to the Fetus," alcohol exerts its effects on the developing fetus through multiple actions at different sites. In the developing brain, for example, alcohol has been shown to interfere with the development, function, migration, and survival of nerve cells. Also, in the embryonic cell layer that develops into the bones and cartilage of the head and face, alcohol exposure at critical stages of development induces premature cell death that is thought to be linked to the FAS facial defects. These actions of alcohol have provided scientists with numerous paths for pursuing possible biochemical mechanisms for these actions. Better understanding of the mechanisms may point to pharmacologic approaches for intervening or for preventing alcohol-related fetal injury.

Although research in animals and humans is continuing to provide details about alcohol-induced deficits, efforts to prevent these problems are not nearly so advanced. The section "Issues in Fetal Alcohol Syndrome Prevention" notes that numerous strategies to prevent FAS have been implemented in recent years, but that rigorous analysis of the effectiveness of these approaches is in its infancy. The section summarizes major reviews of FAS prevention efforts, presents issues related to research methods and evaluations, and describes research on prevention approaches targeted to women at different levels of risk.

Recent research underscores an intensifying need for effective prevention strategies. One study found that although alcohol use among pregnant women decreased between 1988 and 1992 (from 22.5 to 9.5 percent), by 1995 it had increased to 15.3 percent (Ebrahim et al. 1998). Moreover, binge drinking (defined in the study as five or more drinks per occasion) among pregnant women, a particularly hazardous drinking pattern in terms of FAS risk, increased significantly between 1991 and 1995 (from 0.7 to 2.9 percent of pregnant women) (Ebrahim et al. 1999). In light of these unsettling findings, and because FAS and other adverse effects of drinking during pregnancy are completely preventable, the need for a solid research base to guide prevention program developers is critical.

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Prenatal Alcohol Exposure: Effects on Brain Structure and Function

Fetal Alcohol Syndrome (FAS), a devastating developmental disorder resulting from heavy maternal alcohol consumption during pregnancy, was first identified in France in 1968 (Lemoine et al. 1968) and in the United States in 1973 (Jones et al. 1973). FAS can be readily diagnosed shortly after birth when characteristic facial features and growth retardation are present, coupled with known prenatal alcohol exposure. Not as obvious at birth—but with more serious, pervasive, and lifelong consequences—are the effects of alcohol-induced damage to the developing brain and spinal cord, or central nervous system (CNS). Problems that become apparent later include reductions in general intellectual functioning and academic skills as well as deficits in verbal learning, spatial memory and reasoning, reaction time, balance, and other cognitive and motor skills. Some deficits, like problems with social functioning, appear to worsen as these individuals reach adolescence and adulthood, possibly leading to an increased rate of mental health disorders.

A greater understanding of both the structural damage to the CNS from alcohol exposure (the "neuroanatomical" effects) and the resulting behavioral manifestations (the "neurobehavioral" effects) will be critical to future research on effective therapies for FAS. In recent years, the principal advances have occurred in three areas: (1) the introduction of a new diagnostic system for categorizing fetal alcohol effects, (2) neuroimaging studies that have provided insights into the structural damage to the brain from prenatal alcohol exposure, and (3) the delineation of specific patterns of behavioral impairment in children with FAS. Each of these is described in this section.

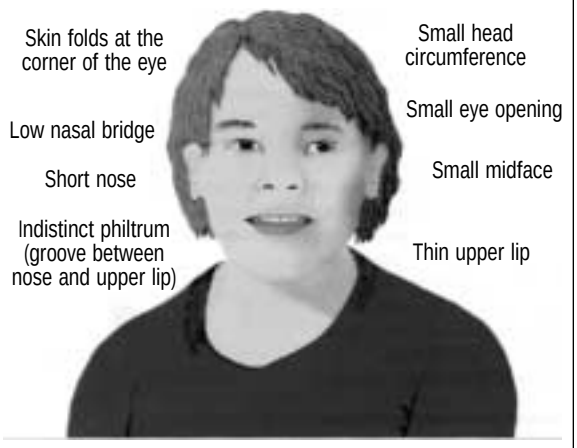
Diagnosing the Effects of Prenatal Alcohol Exposure

Researchers first outlined the diagnostic criteria for FAS in 1973 (Jones and Smith 1973; Jones et al. 1973). Although the terms used to describe the condition have changed over the years, the criteria for its diagnosis—growth deficiency, CNS dysfunction, and characteristic facial defects—have remained essentially the same.

Perhaps the most immediately obvious of alcohol's effects on the fetus is a pattern of abnormal facial features (figure 1) (Jones et al. 1973; Stratton et al. 1996). Although these facial abnormalities are a hallmark of FAS, they are not present in all children who have been exposed to alcohol before birth. More subtle neuroanatomical and neurobehavioral problems often occur in alcohol-exposed children without these facial abnormalities.

At one time, FAS was not diagnosed without confirming the mother's alcohol use during pregnancy. Unfortunately, this requirement resulted in many cases of prenatal alcohol exposure being overlooked or ruled out, especially when the child did not have the facial abnormalities of FAS. Another term, "fetal alcohol effects" (FAE), has been used for many years to describe individuals known to be exposed to alcohol before birth who

Figure 1: Facial features of FAS



Source: Gordis 1991.

Table 1: Criteria for diagnosing the effects of prenatal alcohol exposure

Diagnosis	Diagnostic criteria: FAS facial features	Diagnostic criteria: Confirmed prenatal alcohol exposure	Diagnostic criteria: Additional criteria
Fetal Alcohol Syndrome (FAS) with confirmed maternal alcohol exposure	Yes	Yes	
FAS without confirmed maternal alcohol exposure	Yes	No	Growth retardation; central nervous system (CNS) abnormality; or evidence of a behavioral or cognitive disorder inconsistent with the expected developmental level, with hereditary factors, or with the environment
Partial FAS with confirmed maternal alcohol exposure	Some	Yes	
Alcohol-related birth defects (ARBD)	No	Yes	Any of a number of anomalies (such as heart or kidney defects) present at birth that are associated with maternal alcohol consumption during pregnancy
Alcohol-related neurodevelopmental disorder (ARND)	No	Yes	Evidence of CNS abnormality (such as an abnormally small head, abnormal brain structures, and neurological signs); evidence of a behavioral or cognitive disorder inconsistent with the expected developmental level, with hereditary factors, or with the environment; or both

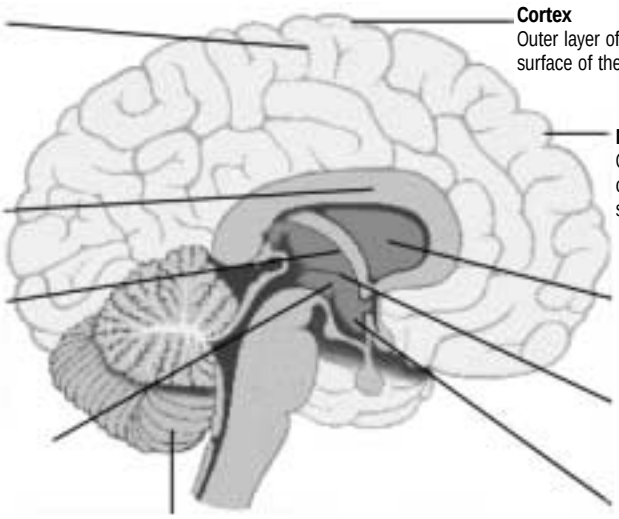
Source: Stratton et al. 1996. Reprinted with permission from *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. Copyright 1996, National Academy of Sciences, Washington, DC.

do not have the FAS facial features but who do have other critical hallmarks of FAS (Clarren and Smith 1978). Of late, however, new diagnostic criteria and terminology have come into use.

A 1996 report sponsored by the Institute of Medicine (IOM) of the National Academy of Sciences classifies the effects of prenatal alcohol exposure into five categories (table 1) (Stratton et al. 1996). The IOM scheme includes three categories for individuals with all or some of the FAS facial features and two categories for alcohol-affected children without FAS facial features: "alcohol-related birth defects" (ARBD) and "alcohol-related neurodevelopmental disorder" (ARND).

The diagnoses of ARBD and ARND require confirmation of the mother's alcohol use during pregnancy in addition to a psychological or neurological assessment of the child. Without the facial features of FAS, however, these two classifications are the most difficult to characterize. Researchers will need to conduct large studies of children with these diagnoses in order to link specific physical and functional differences to prenatal alcohol exposure, and thus better define these two categories. In addition, the use of labels such as ARND indicates that psychological or neurological assessments are part of the diagnostic process, which is only now becoming more of the norm rather than the exception.

Figure 2: Anatomy of the brain



Source: Mattson et al. 1994a.

Neuroimaging: Precise Pictures of Structural Damage to the Brain

For many years, information on the neuroanatomical effects of prenatal alcohol exposure came from autopsies of children with FAS (Clarren 1986; Mattson and Riley 1996). Autopsied brains showed widespread and severe damage that included the following (figure 2):

- Malformations of the brain tissue (both in the "gray matter" regions, which contain mostly nerve cell bodies and extensions called dendrites, and in the "white matter" regions composed primarily of nerve fibers, or axons, that transmit impulses).

- Failure of certain brain regions to develop at all (such as the corpus callosum, the central tract inside the brain that unites the left and right hemispheres).

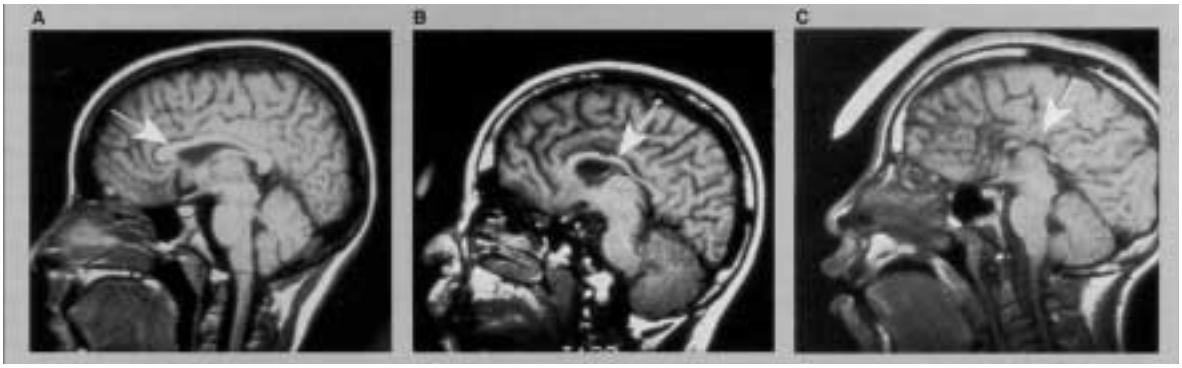
- Failure of certain cells to migrate to their appropriate locations during embryonic brain development.

- A tendency for the tissue to die off in other brain regions (such as the cerebellum, a region at the base of the brain that coordinates body movements).

The extent of these abnormalities initially led researchers to conclude that there was neither a specific pattern of brain changes nor a consistent behavioral profile among children exposed to alcohol prenatally (Clarren 1986).

In the decade since that conclusion, however, the use of neuroimaging techniques to visualize the living brain has provided a more precise picture of the brain structure of children with FAS. Using magnetic resonance imaging (MRI) and computed tomography, which measure the area or volume of a body structure, researchers have documented reduced overall brain size in children with FAS (Mattson et al. 1994*b*, 1996*c*). Several brain structures appear to be especially sensitive to prenatal alcohol exposure (Mattson and Riley 1996), whereas others do not seem to be affected at all. These findings suggest that alcohol exposure may be specific, rather than global,

Figure 3: Effects on the corpus callosum



(A) Magnetic resonance imaging showing the side view of a 14-year-old control subject with a normal corpus callosum; (B) a 12-year-old with Fetal Alcohol Syndrome and a thin corpus callosum; and (C) a 14-year-old with Fetal Alcohol Syndrome and agenesis (absence due to abnormal development) of the corpus callosum.

Source: Mattson et al. 1994a.

in its teratogenicity, or ability to cause developmental abnormalities.

Several MRI studies of children with FAS confirmed a link between prenatal alcohol exposure and anatomical defects at the midline of the brain and face (Johnson et al. 1996; Mattson et al. 1992; Riley et al. 1995; Swayze et al. 1997). The areas affected included those surrounding the fissure between the two sides of the brain, particularly the corpus callosum, which is sometimes missing (figure 3) (Johnson et al. 1996; Mattson et al. 1992; Riley et al. 1995; Swayze et al. 1997). The high incidence of anomalies in the middle of the brain suggests that this area is particularly sensitive to alcohol exposure before birth. Because specific regions of the brain are associated with certain physical and mental behaviors, data showing such region-specific effects may lead to a greater understanding of the behavioral manifestations of FAS.

Cerebellum

The cerebellum appears to be especially affected by prenatal alcohol exposure. This structure is located at the back of the brain and is thought to be involved primarily in movement, but also in cognitive processes such as attention. Case studies (Riikonen 1994; Robin and Zackai 1994) and autopsy reports (Clarren 1986; Mattson and Riley 1996) have identified smaller size and other abnormalities of the cerebellum in alcohol-exposed children with and without FAS. A recent imaging study has also revealed volume reductions in the cerebellum and has suggested that this structure is affected more than other brain regions by prenatal alcohol exposure (Harris-Collazo et al. 1998).

Another recent study examined changes in an area of the cerebellum called the vermis, which connects the two halves of the cerebellum (Sowell et al. 1996). The researchers found that 5 of 10 mapped regions in the vermis were significantly smaller in children who were exposed to alcohol prenatally than in those who were not. It is not entirely clear what behaviors are correlated with the cerebellar vermis, but there may be some relationship to gross motor functioning (such as balance) and attention.

Research suggests that the death of certain types of cells in the cerebellum may be responsible for its reduced size. These specialized cells, called Purkinje cells, send out nerve signals in response to sensory and motor impulses from the rest of the nervous system. A study in rats demonstrated that those animals exposed to alcohol shortly before or after birth (correlating with the third trimester of pregnancy in humans) had fewer Purkinje cells in some regions of the cerebellum than did nonexposed animals (Goodlett et al. 1990).

Basal Ganglia

The basal ganglia are paired masses of gray matter located deep within the white matter of the cerebrum. They include a structure called the caudate nucleus, which governs voluntary movement and some cognitive functions related to perception, thinking, and memory.

Two recent studies of children with FAS found significant reductions in the volume of the basal ganglia (Harris-Collazo et al. 1998; Mattson et al. 1996*c*). The results confirmed earlier findings that, even when reductions in overall brain size are accounted for, the basal ganglia (and especially the caudate nucleus) are significantly smaller in children exposed to alcohol before birth (Mattson et al. 1992, 1994*b*).

Other Brain Regions

In some areas of the brain, the effects of prenatal alcohol exposure may be minimal or nonexistent. This possibility has been strengthened by results from a recent neuroanatomical study in which researchers analyzed the "mean proportional volume"—the average volume of any given region in relation to overall brain size—of the four regions of the cerebral cortex (the thin outer layer of gray matter covering the surface of the cerebrum) (Harris-Collazo et al. 1998). The researchers found no significant differences between individuals with and without FAS, matched for age, in the mean proportional volume of the cerebral cortex and certain underlying regions (including the thalamus, basomesial diencephalon, substantia nigra, insula, and nucleus accumbens). Also unaffected were the brain areas that make up the limbic system (the hippocampus, parahippocampus, amygdala, and cingulate), which is associated with emotions and certain aspects of memory. These preliminary data need confirmation, however, especially since the number of subjects was small in this study. Size differences between segments of the brain may become evident as larger numbers of people are studied.

In addition to using imaging technologies, researchers have used population-based epidemiologic methods to add to the knowledge of how prenatal alcohol exposure affects the development of CNS structures. In a study of premature infants, researchers found that alcohol exposure was related to bleeding within the brain as well as damage to the brain's white matter (Holzman et al. 1995). Specifically, this risk was higher in premature infants of women who had had at least seven alcoholic drinks per week or at least three alcoholic drinks per occasion during their pregnancies. Another study investigated alcohol use by parents and defects of the neural tube, the embryonic structure that becomes the brain and spinal cord (Shaw et al. 1996). The results indicated that parental alcohol use was not associated with an increased risk for neural tube defects in their infants.

Physical Measures of Altered Brain Function: Cry Patterns and EEG's

Although pinpointing the structural changes in the brain provides important, dramatic evidence of alcohol-induced damage, it is equally important to quantify the resulting changes in function. If the alcohol-induced changes in brain function could be identified very early in a child's life, it might be possible to mitigate some of the adverse consequences as the child grows. Such identification efforts are hampered, however, by the difficulty in making diagnoses in the absence of FAS facial features and in measuring neurobehavioral effects at very young ages. Two lines of research have used tools that physically measure changes in brain function and may help in diagnosing and determining the prognosis for alcohol-exposed children who do not have the FAS facial features: acoustic analyses of babies' cry patterns, and electroencephalography (EEG) evaluations of brain electrical activity.

Acoustic Cry Analyses

By performing acoustic analyses of babies' cry patterns, researchers have detected subtle alcohol-related changes in neurobehavior in infants (Nugent et al. 1996; Zeskind et al. 1996). The characteristics of an infant's cry, which are at least partly determined by the CNS, can be affected by prenatal exposure to alcohol and other drugs. In one study of 3-day-old infants, researchers examined three characteristics of the crying of

babies with and without prenatal alcohol exposure: (1) threshold, or the intensity at which a stimulus provokes crying; (2) latency, or the time between the stimulus and the infant's cry; and (3) pitch, or the highness or lowness of the cry (Zeskind et al. 1996). The researchers discovered that all three of these characteristics differed significantly between the two groups of infants. Moreover, the differences were related to the amount of alcohol consumed by the mother during her pregnancy.

In another study, the same three cry characteristics were compared at 2, 14, and 28 days of age in alcohol-exposed infants and in control group infants (Nugent et al. 1996). The researchers found a number of significant differences between the two groups. The crying threshold was greater in the alcohol-exposed infants than in the nonexposed infants at 2 days of age, the cry latency of the alcohol-exposed infants was longer at 14 days, and the average pitch of the cries was higher among the control infants at day 2 but was higher among the alcohol-exposed infants at days 14 and 28.

Although these studies indicate that prenatal alcohol exposure interferes with subtle aspects of neurobehavior, researchers have yet to determine how differences in cry characteristics may relate to later neurobehavioral outcomes, such as learning or attention. Studies of other babies with health problems, such as those born prematurely, suggest that there is such a relationship (see Nugent et al. 1996). If this can be confirmed, it may be possible to use analysis of cry patterns to predict the later neurobehavioral effects of prenatal alcohol exposure.

EEG's

Investigations using EEG, which records the brain's electrical activity, suggest that EEG and neurological testing could help to identify less severe effects of alcohol exposure, such as ARND. Researchers used EEG measurements to compare children with FAS, children with Down syndrome, and normally developing control subjects (Kaneko et al. 1996*a,b*). Children with Down syndrome were included to rule out electrical patterns related to mental retardation. In the first of these studies, EEG was used to measure alpha waves, which are emitted by the brain when the body is in a state of deep relaxation (but not sleep) (Kaneko et al. 1996*b*). The EEG recordings found lower alpha wave activity in both the FAS and the Down syndrome children than in the control subjects. The characteristics of the alpha wave patterns differed, however, in that those of the Down syndrome children were slower, whereas those of the FAS children were weaker, than those of the control group children. Also, the reduced activity in the FAS children was found mainly in the left hemisphere of the cerebral cortex, whereas in the Down syndrome children it was mainly in the posterior cerebral cortex. These data suggest that the effects of prenatal alcohol exposure may specifically target the brain's left hemisphere and that they differ from the effects of other congenital disorders.

In a second study, neurological responses were recorded in the same group of children as they listened to sounds of various qualities and frequencies (Kaneko et al. 1996*a*). Researchers observed a delayed response in the brains of children with FAS and in the brains of those with Down syndrome. As in the previous study (Kaneko et al. 1996*b*), the region of the brain that was affected in the FAS children differed from the brain region affected in the Down syndrome group. These studies on brain activity indicate that children with prenatal alcohol exposure and children with Down syndrome have distinct profiles of brain electrical and neurological activity.

Effects on Cognitive and Motor Functions

Much of the research on the effects of prenatal alcohol exposure has focused on overall intellectual functioning, as measured by intelligence quotient (IQ) scores. In recent years, studies have turned to more specific aspects of brain functioning and behavior. Two broad assessments of neuropsychological functioning in preschool (Janzen et al. 1995) and school-age (Mattson et al. 1998) children found that children with FAS, as well as alcohol-exposed children who did not meet all the FAS criteria, had deficits in numerous areas. The most prominent of these

deficits were in integrating visual information with coordinated movements, controlling precise movements (for example, speed and coordination of finger movements), language, and general intellectual functioning. As described below, researchers have pursued the details of these deficits in recent years, focusing on learning and memory, visual-spatial functioning, executive functioning, attention, and motor control.

Although it is well established that heavy prenatal alcohol exposure leads to neurobehavioral impairment, the effects of lower levels of alcohol exposure are not as clear (National Institute on Alcohol Abuse and Alcoholism 1997). It appears that many of the problems linked to FAS also are found in children whose mothers drank moderate amounts of alcohol when pregnant, including deficits in general intellectual functioning (Larroque et al. 1995), visual-spatial reasoning (Hunt et al. 1995), attention (Jacobson et al. 1994; Streissguth et al. 1994*b*, 1995), and academic achievement (Goldschmidt et al. 1996; Streissguth et al. 1994*a*). In contrast, studies have found no effects of low alcohol exposure on gross motor functioning in young children (Chandler et al. 1996; Fried and Watkinson 1990; Richardson et al. 1995).

Learning and Memory

To assess learning and memory in children with and without FAS, researchers gave the children a standardized test (the California Verbal Learning Test–Children's version [CVLT–C]), which showed differences in immediate recall, delayed recall, and recognition of words that had been read aloud (Mattson et al. 1996*b*).

The children in this study were read a list of words and then asked to recall them immediately afterward and again after 20 minutes had passed. The children with FAS had difficulty recalling the words immediately after hearing them. After the 20-minute delay, they recalled fewer words than did the control group subjects. The FAS children also tended to offer words not on the list and to repeat words when trying to remember those on the list. When they were given a choice of words, the children with FAS had difficulty identifying which were on the original list and which were not. They also more often incorrectly identified words as being on the list. There were, however, no differences between the FAS and the control group in the percentage of the learned words they were able to recall after 20 minutes. In other words, the FAS children did not learn as many words as the control group children did, but the rate at which words were forgotten was the same in both groups.

The findings suggest that children with FAS have profound deficits in learning when material is presented verbally but are capable of retaining the information they learn. Similar results were obtained among children with prenatal alcohol exposure but without a diagnosis of FAS (Mattson et al. 1998).

In a study of implicit memory—the unconscious recall of a previously performed task—comparisons were made among children with heavy prenatal alcohol exposure (including FAS), children with Down syndrome, and normally developing children (Mattson and Riley 1999). The children, aged 8 through 17 years, studied a list of words that were both written and read aloud by an examiner. When asked what words they remembered from the list, the alcohol-exposed children could not name as many as the control group. But when asked which of two words they remembered (one on the list and one not), the two groups of children performed similarly.

In that same study, the children were also asked to fill in the missing letters of words from the list they had just studied (for example, "sm___ = small, mo____ = mother"). The alcohol-exposed group and the control group correctly completed the same number of these words. These findings suggest that the two groups of children were equally able to use previously learned information without being told to do so. In contrast, the children with Down syndrome were impaired on all three memory tasks. Overall, these findings suggest that prenatal alcohol exposure does not impair some types of memory, and that despite some learning deficits, children with FAS are able to retain learned information.

Visual-Spatial Functioning

The ability of persons with FAS to see objects and understand their spatial relationships, or "visual-spatial functioning," has received little research attention to date. The studies conducted thus far suggest that alcohol-exposed children have deficits in specific aspects of visual-spatial processing. In one of these studies, children with FAS were presented with a group of objects and later asked to recall them (Uecker and Nadel 1996). The children could remember what the objects were, but they had more trouble than the control group children in remembering the objects' locations in relation to each other. In addition, after 24 hours, the children with FAS had greater difficulty than the other children in remembering both the objects and their relative locations.

In another study, children with prenatal alcohol exposure were asked to remember certain figures composed of both large, simple shapes and small details (Mattson et al. 1996*a*). When the children tried to recreate the figures, their drawings lacked detail. The results of both of these studies suggest that alcohol-exposed children have problems in perceiving and remembering spatial relationships and in recalling visual details (Mattson et al. 1996*a*; Uecker and Nadel 1996). More research is needed to further define the nature of these deficits.

Executive Functioning

Higher order cognitive processes called "executive functions" are activities that require complex thought processes and behaviors, such as planning, organizing, sequencing, and other forms of abstract thinking. These are abilities that allow successful "independent, purposeful, self-serving behavior" (Lezak 1995). Persons with deficits in these areas may have difficulty with self-care and independence. For example, routine activities that require a sequence of steps, such as getting dressed or writing a check, may be problematic.

In two studies, children with FAS or FAE were evaluated on their abilities in planning, verbal fluency, using information held in short-term memory, using feedback to modify behavior, and set shifting (such as switching from naming animals to naming furniture and back to animals) (Goodman et al. 1998; Kodituwakku et al. 1995). The alcohol-exposed children had much more trouble performing these tasks than did the children in the control group. In one of the studies, however, the alcohol-exposed children had difficulty only with certain tasks involving memory skills; in other areas, they tested similarly to the control group children (Kodituwakku et al. 1995). Again, these findings support the conclusion that prenatal alcohol exposure targets specific areas of the brain.

In another study assessing executive functioning, teenagers and adults with FAS or FAE were able to read and write numbers as well as control subjects (Kopera-Frye et al. 1996). The individuals with FAS or FAE, however, had more difficulty in calculating and estimating magnitude. Nearly all the alcohol-exposed subjects could identify the larger of a pair of numbers (which suggests an understanding of magnitude), but they could not apply this knowledge to estimate magnitude. For example, one task consisted of questions for which most people do not know the exact answer (for example, "What is the height of the White House?"). Nearly half of the subjects with FAS or FAE could not make a reasonable estimate; for 20 percent of the subjects, this was the only task they had trouble performing. Although it is unclear to what extent these difficulties are related to lower overall intellectual ability, the results of this study support those of others documenting specific mathematical and problem-solving difficulties in persons with prenatal alcohol exposure (Goldschmidt et al. 1996; Kodituwakku et al. 1995; Mattson et al. 1996*d*; Streissguth et al. 1994*a*).

Attention

Problems in maintaining attention have long been associated with FAS and are quite common, affecting 6 in 10 children and adolescents with FAS (Nanson and Hiscock 1990; Streissguth et al. 1995, 1996). Deficits in attention have also been reported for children exposed to relatively low levels of alcohol before birth (Streissguth et al. 1995).

In one recent study, children with FAS were compared with children with attention deficit-hyperactivity disorder (ADHD) and children with neither condition (Coles et al. 1997). The first two groups performed more poorly than the control group, but they also performed differently from each other. The FAS children performed most poorly on tasks that required shifting attention from one feature of an attention stimulus to another—a function that is related to set shifting. The ADHD group had more difficulty sustaining attention over time and focusing attention in order to exclude extraneous information.

This and similar studies indicate that the attention disruption associated with prenatal alcohol exposure is different from that arising from other disorders, like ADHD. If this is indeed the case, it has important implications for diagnosing and treating attention disorders that are specifically due to prenatal alcohol exposure.

Motor Control

Studies of humans (Kyllerman et al. 1985; Streissguth et al. 1980) and animals (Goodlett et al. 1991; Hannigan and Riley 1989; Meyer et al. 1990) exposed to alcohol prenatally have consistently found impairments in the development of motor control, which directs voluntary movement. Motor control is a complex function influenced by the CNS; by the peripheral nervous system, which provides feedback to the CNS from the body's sensory organs, such as the eyes, ears, and skin; and by the vestibular system, located in the inner ear, which is involved in the sense of balance and the motor reactions used to maintain it. Because defects in any of these systems can affect motor control, researchers have attempted to separate out alcohol's effects on the different systems experimentally.

In one such effort, school-age children with a history of prenatal alcohol exposure, with or without a diagnosis of FAS, were compared with children without alcohol exposure (Roebuck et al. 1998*a*). The children were tested for their ability to maintain their balance under varying conditions, such as with open or closed eyes or while standing on a stable or a moving surface. Those with heavy prenatal alcohol exposure were able to maintain their balance under normal conditions and when the visual information was altered. But when both the visual system and the somatosensory system (which uses feedback from the skin, muscles, and joints) were challenged, the alcohol-exposed children had more difficulty than the control group children. The researchers concluded that the alcohol-exposed children were overly reliant on somatosensory information to maintain motor control over balance and were not able to use other sensory systems, such as their visual or vestibular systems, to compensate. They stated that the deficits may be related to abnormalities in the cerebellum (which is involved in movement as well as cognitive functions), as previously reported in FAS children.

In a follow-up study, researchers also examined the children's motor reactions to correct balance disruptions, an ability that relies on the vestibular system (Roebuck et al. 1998*b*). To assess this ability, the researchers disrupted the children's balance and then measured the reactions of their muscles with electromyography (EMG), a technique that uses electrical stimulation to provide feedback about the functioning of the skeletal muscles. The results revealed significant differences between the alcohol-exposed and the nonexposed children. But the differences were seen only in certain types of motor responses—specifically, those thought to involve a pathway through the brain's cerebral cortex. The EMG data thereby support the notion that balance deficits may be due to problems of the CNS rather than the peripheral nervous system. This hypothesis is also supported by related work suggesting that abnormal balance and gait in children with prenatal alcohol exposure are due to inadequate motor coordination by the CNS rather than to an impaired vestibular system (Church et al. 1997).

Effects on Mental Health and Psychosocial Behavior

Although not as extensively studied as cognitive and motor skills, the psychosocial and psychiatric effects of prenatal alcohol exposure also have profound implications for the lives of alcohol-exposed children and their families. Impaired social functioning, disturbed behaviors, and psychiatric disorders are common in people with FAS. These problems, which can occur with or without mental retardation and persist into adulthood, often disrupt daily life and magnify other FAS-related problems.

Mental Health

In a large study of secondary disabilities in persons of various ages with FAS or FAE, the great majority of the 415 participants—94 percent—were found to have a history of mental health problems (Streissguth et al. 1996). Attention deficits, as mentioned previously, were the most frequent problems in children and adolescents, reported in 61 percent of both groups. Among adults, depression was the most frequently reported problem (52 percent).

Another, smaller study also found that the proportion of subjects who had ever had a psychiatric disorder was far greater than what would be expected in the general population (Famy et al. 1998). Psychiatric interviews with 25 adults with FAS or FAE showed that 74 percent previously had psychiatric treatment; among the diagnoses were current or past alcohol or drug abuse (60 percent), major depressive disorder (44 percent), and avoidant personality disorder (29 percent).

Similar disturbances were reported in a study of 44 children with FAS whose mental health histories were tracked over 10 to 14 years (Spohr et al. 1994). The most commonly reported disorders were emotional disorders (50 percent), persistent repetition of meaningless gestures (50 percent), speech disorders (35 percent), and hyperactivity (32 percent).

Two other psychiatric disorders have received attention in FAS research: Tourette syndrome and autism. Tourette syndrome is a neurological condition characterized by tics—involuntary, sudden, repetitious movements. Researchers conducted a large survey of individuals with Tourette syndrome, some of whom also had obsessive-compulsive disorder (OCD), a psychiatric disorder in which a person engages in repetitive actions in order to relieve anxiety (Santangelo et al. 1994). The authors reported that OCD in persons with Tourette syndrome was associated with prenatal exposure to "relatively high levels" of alcohol (defined as more than two drinks per day), coffee (more than two cups per day), or cigarettes (more than 10 per day). They suggested that, for some individuals with Tourette syndrome, early brain damage, such as that caused by alcohol exposure, may play a role in the development or worsening of coexisting OCD. Although there are no other published reports of Tourette syndrome in individuals with prenatal alcohol exposure, the presence of tics was reported in over 10 percent of one study population with FAS (Spohr et al. 1994).

Autism is a developmental disorder characterized by severe social, communication, and behavioral problems, such as social withdrawal, aggression, and/or absence of or limited language. Autistic behaviors have been noted in school-age children who were exposed to alcohol prenatally (Nanson 1992) and, more recently, in younger children (Harris et al. 1995). Among the behaviors noted in these children were impairments in social interaction and communication, which are typical of autism. Autistic behaviors have also been noted in alcohol-exposed children both with and without the diagnosis of FAS.

Psychosocial Behavior

Other studies that use questionnaires and rating scales to assess social abilities and psychological functioning have indicated impairments in alcohol-exposed children. In one of these studies, the Personality Inventory for Children (PIC) was used to study children with heavy prenatal alcohol exposure, with or without FAS (Roebuck et al. 1999). The PIC measured a wide range of psychological and social measures and accomplishments of the children, as noted by their

parents. The alcohol-exposed children had significantly higher scores, indicating greater problems, than did the control group children in a number of areas, including anxiety, social skills, and academic achievement. In another study, the Child Behavior Checklist was used to score alcohol-exposed and control group children, matched for verbal IQ and other demographic variables, on a number of behavioral problem scales, such as anxiety, depression, and attention problems (Mattson and Riley 2000). Again, the alcohol-exposed children scored significantly higher than the control group children on all of the problem scales. Both studies indicate that prenatal alcohol exposure, regardless of whether it has resulted in a diagnosis of FAS, can lead to significant psychosocial impairment.

Studies have found that alcohol-exposed children have a variety of impairments in social abilities that could affect them throughout their lives. In one study, FAS children were compared with normally developing control group children and also with a separate group of control children who were matched for overall intellectual ability (Thomas et al. 1998). The children with FAS had more deficits in social skills, such as manners and interactions with others, than did the non-exposed children (Thomas et al. 1998). This difference was greater at older ages, indicating that social skills developed more slowly in the FAS children. Other studies have also found deficits in social skills among adolescents and adults with FAS or FAE (Mattson and Riley 1998; Streissguth et al. 1991).

In a recent effort to help evaluate behavioral disorders in alcohol-exposed individuals, researchers have designed a behavior scale based on data from 472 patients (Streissguth et al. 1998). The scale has been used to identify individuals with presumed or known alcohol exposure and to predict whether alcohol-exposed individuals would be able to live independently. Further testing will be required to evaluate whether the scale is sensitive enough to distinguish individuals with alcohol-related impairments from those with other developmental disorders.

In Closing

Imaging studies have demonstrated abnormalities of certain brain regions in persons exposed to alcohol prenatally, whereas other regions seem to be spared structural damage. Similarly, research shows that many neurobehavioral deficits are notably linked to prenatal alcohol exposure, while other functions appear to remain intact. These studies strongly support the notion that alcohol has specific, rather than global, effects on the developing brain.

By understanding the areas of the brain that are affected by alcohol, and how these brain changes affect behavior, researchers can work more effectively to design means of intervention and perhaps prevention. Relatively little research has been conducted in this area; there is a need for more well-designed studies that focus on brain-behavior correlations. Future research can draw from an extraordinary body of literature based on nearly three decades of research using animal models.

Although research in animals and humans is continuing to provide details about alcohol-induced deficits, efforts to prevent or ameliorate the effects of alcohol exposure are not nearly as advanced. Research on effective prevention strategies is critical to reducing the impact of prenatal alcohol exposure (see the section "Issues in Fetal Alcohol Syndrome Prevention" later in this chapter).

What we do know, however, is that prenatal alcohol exposure can cause specific, irreversible brain damage that can have a devastating impact on affected individuals, their caretakers, and society. These brain and behavior changes are seen in children with heavy prenatal alcohol exposure both with and without the facial features necessary for a diagnosis of FAS. Future research focusing on the diagnostic categories of ARBD and ARND will greatly expand our knowledge of alcohol's effects on the developing CNS and allow better, more appropriate intervention strategies for the full spectrum of alcohol-related effects.

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Underlying Mechanisms of Alcohol-Induced Damage to the Fetus

Research has firmly established that maternal alcohol consumption can lead to fetal alcohol syndrome (FAS), a disorder defined in the early 1970's that is characterized by brain damage, physical defects of the face (called craniofacial defects), and growth deficiency. Current research on FAS seeks to delineate the specific mechanisms of damage to the fetus as well as the conditions that influence the extent of this damage.

Numerous factors complicate this research. First, the process of development itself is enormously complex and not yet fully understood (see the box, below, and figure 1). Second, because no single mechanism can account for the variety of structural, functional, and behavioral problems found in FAS, scientists believe that a number of distinct mechanisms work simultaneously along different biochemical pathways and at different

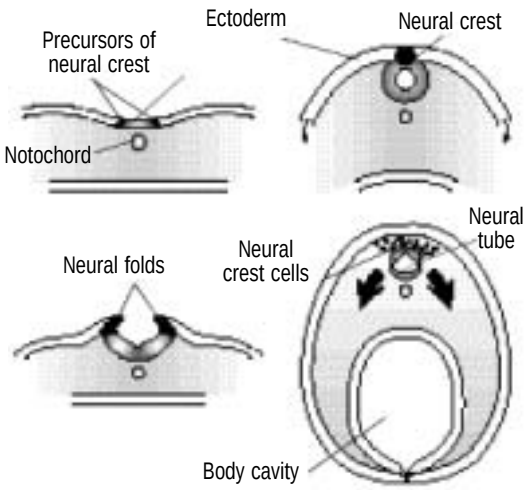
Embryonic Development of the Nervous System

Embryonic development is basically the same in all vertebrates, although the timing of developmental stages varies among species. In the human embryo, about 2 weeks after fertilization, in a process called gastrulation, the embryo develops three distinct layers: the ectoderm, the endoderm, and the mesoderm. These undifferentiated cell layers are eventually transformed into different body structures. The ectoderm produces the skin and nervous system; the endoderm forms the lining of the digestive tract, respiratory tubes, and associated organs; and the mesoderm produces the cardiovascular system, bones, muscles, and connective tissue.

In the early development of the nervous system, at about 3 weeks after fertilization in the human embryo, a strip of cells in the mesoderm (the notochord, which will eventually form the spinal column) induces the ectoderm above it to fold upward, where it forms two ridges at the embryo's midline. The tops of these ridges, known as the neural fold, then curve inward, and by the fourth week the ridge tops meet and fuse to form a tube. This is the neural tube, which will eventually form the brain and spinal cord. Cells originating from the fused tips of the neural fold are called neural crest cells. These cells migrate to specific locations in the embryo, where they differentiate into specific types of cells and begin to form a variety of body structures. By the end of the eighth week, the elements of all major body systems are in place.

Cells of the neural crest are particularly sensitive to alcohol-induced injury and death. Therefore, FAS research has focused on these cells, particularly on a subset of cells known as cranial neural crest cells, which give rise to facial cartilage and bone as well as many other body structures. The eventual fate of the cranial neural crest cells—the specific body structure and type of tissue that they will develop into—is predetermined before the cells begin migration. Another subset of cells, the trunk neural crest cells, gives rise to elements of the peripheral nervous system. These cells differ from the cranial neural crest cells in that their eventual fate is not predetermined before migration, but depends upon the environment into which they migrate. The trunk neural crest cells seem to be less affected by alcohol than the cranial neural crest cells, which may reflect their greater adaptability.

Figure 1: Origin of the nervous system



Early in embryonic development, the ectoderm directly above the notochord begins to form the primitive nervous system (the neurepithelium) (A). The neurepithelium then curves upward to form two ridges, called the neural folds (B). The tips of the neural folds fuse to form the neural tube, and cells from the fused tips of the neural folds form the neural crest (C). The neural crest cells migrate to various locations within the embryo, where they will initiate the development of various body structures (D).

Source: Smith 1997.

physical sites in the developing embryo. And third, the ways in which these alcohol-induced mechanisms produce damage to the fetus depend on several variables, including the timing, frequency, and amount of maternal drinking during pregnancy; the mother's health status and habits; and the genetic makeup of the mother and fetus.

Despite the complexity of FAS, scientists have made significant progress in defining its underlying mechanisms in recent years. This section first describes the multifaceted aspects of FAS that challenge research in this area, then presents findings from current studies, focusing on mechanisms of damage to the brain and craniofacial region.

Challenges to FAS Research: Multiple Mechanisms, Sites of Action, and Risk Factors

Research on FAS has shown that alcohol exerts its effects on the developing fetus through multiple actions at different sites (Abel 1990, 1995; Diamond and Gordon 1997; National Institute on Alcohol Abuse and Alcoholism [NIAAA] 1997*a,b*; Peoples et al. 1996; West et al. 1994). In the developing brain, for example, alcohol has been shown to interfere with nerve cell development and function in a variety of ways (see the box, below). Thus, the brains of individuals with FAS show that certain regions have not developed normally, certain cells are not in their proper locations, and tissue has died off in some regions (for information about the functional consequences of these abnormalities, see the previous section, "Prenatal Alcohol Exposure: Effects on Brain Structure and Function"). These known actions of alcohol on the developing brain have provided scientists with numerous paths for identifying the biochemical mechanisms behind the actions, as described later in this section.

At a different site in the developing embryo—the cell layer that develops into the bones and cartilage of the head and face—alcohol exposure at critical stages of development induces the premature death of cells. This cell death, most

Actions of Alcohol on the Developing Nervous System

Alcohol interacts with the developing and adult central nervous system through multiple actions at different cellular sites. The list below outlines the major known actions of alcohol that provide candidate mechanisms of damage to the developing brain. Alcohol can:

- Interfere with the normal proliferation of nerve cells (Cook et al. 1990; Miller 1988, 1989, 1995, 1996; Pantazis et al. 1993).
- Increase the formation of free radicals—cell-damaging molecular fragments (Cedarbaum 1989; Chen and Sulik 1996; Davis et al. 1990; Henderson et al. 1995; Montoliu et al. 1995; Nordmann et al. 1992).
- Alter the cell's ability to produce or respond to factors that regulate cell growth, division, and survival (Bhave and Hoffman 1997; Crews et al. 1996; Cui et al. 1997; Deltour et al. 1996; Dohrman et al. 1997; Heaton et al. 1995*b*; NIAAA 1997*b*; Singh et al. 1996*b*; Valles et al. 1994).
- Impair the development and function of astrocytes—cells that guide the migration of nerve cells to their proper places (Guizetti et al. 1997; Miller 1993; Miller and Robertson 1993; Phillips and Krueger 1990; Valles et al. 1994, 1996; Zoeller et al. 1994).
- Interfere with the normal adhesion of cells to one another (Charness et al. 1994; Ramanathan et al. 1996).
- Alter the formation of axons—nerve cell extensions that conduct impulses away from the cell body (Dow and Riopelle 1985; Messing et al. 1991; Roivanen et al. 1995; Rosenberg and Noble 1994; Saunders et al. 1995; Zou et al. 1993).
- Alter the integrity and function of cell membranes (Chen et al. 1996; Devi et al. 1993).
- Alter the pathways of biochemical or electrical signals within cells (Davis-Cox et al. 1996; De et al. 1994; Diamond and Gordon 1997; Dohrman et al. 1996; Roivanen et al. 1995; Yang et al. 1996).
- Alter the regulation of calcium levels in the cell (Dildy and Leslie 1989; Gruol and Curry 1995; Webb et al. 1996*a,b*).
- Alter the expression of certain genes—in which the gene's encoded information is converted into a product such as a protein (Fletcher and Shain 1993; Miles et al. 1991)—including genes that regulate cell development and survival (Hogan and Barnes 1992; Rifas et al. 1997).

likely the product of several interacting biochemical mechanisms also described later, is thought to be linked to the facial abnormalities found in FAS.

A number of risk factors influence the degree to which alcohol exposure causes the different forms of fetal damage expressed in FAS. Through basic studies in animals and cell cultures, for example, researchers have shown that susceptibility to specific FAS defects appears to be directly related to the timing of maternal drinking, that is, whether drinking occurs during critical periods of vulnerability for different organ systems, regions, or cell types (Coles 1994; Goodlett and Johnson 1999; Maier et al. 1996). Animal studies have also shown that the type and extent of fetal damage are related to the pattern of maternal drinking, with binge drinking being particularly damaging (Goodlett et al. 1997, 1998); the particular profiles of blood alcohol concentrations produced (West et al. 1990); the duration of exposure during development (Maier et al. 1996); and differing levels of susceptibility related to the genetic makeup of the mother and fetus (Thomas et al. 1998). Moreover, the effects of alcohol may be enhanced by other conditions that adversely affect the fetus, such as the use of tobacco and other drugs by the mother (Abel and Hannigan 1995; Maier et al. 1996; Phillips et al. 1989) and abnormalities in the mother's physiology, including those caused by malnutrition (Polache et al. 1996).

In addition to directly affecting fetal tissues, alcohol can act indirectly through its effects on placental function and maternal-fetal blood flow (Altura et al. 1982; Falconer 1990; Karl and Fisher 1994; Phillips et al. 1989; Randall and Saulnier 1995; Randall et al. 1989; Savoy-Moore et al. 1989; Schenker et al. 1989, 1990; Siler-Khodr et al. 1996; Taylor et al. 1994). Moreover, although alcohol itself is generally considered to be the primary cause of FAS (Michaelis 1990; Michaelis and Michaelis 1994), a contributing factor may be the action of acetaldehyde, a by-product of the metabolism of alcohol (Hamby-Mason et al. 1997; Webster et al. 1983; Zimmerman et al. 1995).

To unravel the complex underlying mechanisms of FAS, scientists have needed to isolate specific aspects of FAS and investigate them in well-controlled studies. Progress in this field would not have been possible without research techniques involving animal models and tools of cellular and molecular biology (see the box "In Vivo and In Vitro Model Systems"). Results of these investigations have led researchers to propose a number of probable or "candidate" FAS mechanisms, which are described below.

Candidate Mechanisms for Central Nervous System Damage

Because the most disabling and permanent effects of FAS arise from alcohol's effects on the developing central nervous system (CNS)—the brain and spinal cord—a significant proportion of FAS studies have pursued mechanisms of CNS damage (see the chapter on neuroscience and neurobehavior for descriptions of the structural and functional components of the CNS). As noted, CNS damage can occur when alcohol interferes with the normal development and migration of nerve cells (neurons), disrupts cell functions, and causes cell death, either indirectly or by direct action on critical cellular components. Although some of the mechanisms underlying CNS damage are specific to nervous system tissue, others also affect development of the craniofacial region or other body areas. Regardless of the site of action, the timing, amount, and duration of alcohol exposure play a crucial role in determining the type and extent of damage.

Timing of Exposure

In the developing brain, alcohol exposure during various stages of development can harm different populations of neurons through different processes. Animal research has shown, for example, that if alcohol exposure occurs during the cell proliferation stage in early development, when brain cells undergo rapid division and growth, it can cause fewer cells to be generated (Miller 1995). If alcohol exposure occurs later, when the cells are differentiating and becoming specialized, some of the cells die after cell division (Miller 1995).

In Vivo and In Vitro Model Systems

Studies of the effects of alcohol on the developing embryo and fetus depend upon a variety of model systems using either living animals (in vivo studies) or cell cultures and embryo cultures (in vitro studies). With these systems, investigators are able to control and manipulate doses, timing and pattern of exposure, blood levels of alcohol, and routes of administration, as well as nutrition and the environment.

Research using animal models has shown that each of the major characteristics of human Fetal Alcohol Syndrome (FAS), including craniofacial abnormalities, growth deficiency, and abnormalities of the central nervous system, occurs in one or more of these animals, including mice, rats, chicks, and primates. Because different species, and even strains within species, show different degrees of vulnerability to alcohol, experimental results must be interpreted with a measure of caution (Becker et al. 1994, 1996; Melcer et al. 1995; Thomas et al. 1998). However, the most common animal models for FAS research—mice and rats—are very similar genetically to humans, and their biochemical processes are virtually the same.

Selective breeding techniques have produced strains of mice and rats in which individuals are virtually identical genetically. Thus, variations in responses between individuals of the same strain can be attributed to environmental causes, while variations between animals of different strains can be attributed to genetic causes. Selective breeding has also been used to produce paired strains in which animals that are otherwise identical will vary significantly in one particular trait. For example, several pairs of rat lines have been produced in which animals of one strain will voluntarily consume high quantities of alcohol, while animals in the otherwise identical paired strain will drink very little. (The section "Animal Genetic Studies on Alcoholism" in the chapter on genetic and psychosocial influences describes the development of these and other strains.)

Two recently developed animal models are "knockout" strains of mice and rats, where one specific gene has been inactivated, or knocked out, and transgenic strains, where a foreign gene is integrated into the animal's DNA. Because of the high degree of similarity between locations of specific genes on mouse and human chromosomes, a trait that has been genetically mapped in the mouse can be located fairly accurately in human chromosomes.

Cell cultures allow detailed manipulation and analysis of cellular and molecular processes in closely defined cell populations, such as cells from one specific area of the brain. Whole embryos of mice and rats can be grown in culture, and chick embryos can be studied through holes cut into the egg. These models allow researchers to analyze the molecular mechanisms involved in alcohol's effects on living cells. Although in vitro studies are providing important information on molecular mechanisms of action, caution must be used in extrapolating these findings to actual pathways in the whole organism.

Some types of neurons are extremely vulnerable during the early stages of differentiation and when synapses are being formed (Bonthius and West 1991; Goodlett and Johnson 1999; Goodlett et al. 1998; Marcussen et al. 1994). In other instances, neurons die when alcohol exposure either prevents them from migrating properly (Liesi 1997) or induces a delayed cell death that occurs after migration, even though exposure occurred before migration started (Cartwright et al. 1998).

It is likely that, at least in some cases, distinctly different mechanisms will be found to be responsible for different effects of alcohol at different stages of CNS development. In addition, it is possible that different forms of cell death (described next in this section) may be induced at different times of exposure or at different alcohol concentrations. Moreover, multiple mechanisms may operate simultaneously to produce abnormal cell development or cell death.

Cell Death Modes

Cell death is the endpoint of many of the FAS mechanisms described in this section. Although any number of events may lead to cell death, it ultimately occurs by one of two recognized pathways: necrosis, a reaction to injury or disrupted cell metabolism, or apoptosis, a "programmed" self-destruction that is necessary for normal development but can be triggered to

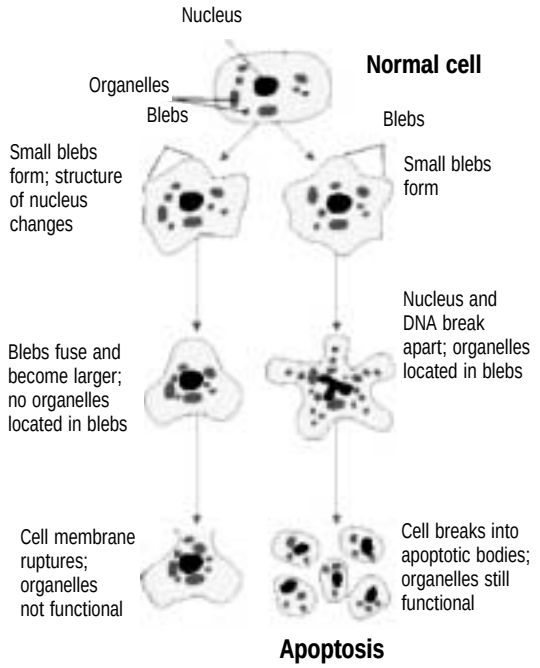
Cell Death Modes: Necrosis and Apoptosis

There are two modes of cell death: necrosis, which is a response to injury, and apoptosis, a form of "programmed" self-destruction where cells are induced to destroy themselves, apparently in response to instructions from their own genes. In the adult organism, apoptosis normally serves the purpose of maintaining a balance between the proliferation of new cells and the death of senescent or damaged cells. However, in the embryo this mode of cell death is necessary for proper development and shaping of tissues and organs, such as the removal of webbing between fingers and toes. Most cell death during normal development occurs by apoptosis, and apoptotic cell death is particularly important for normal development of the central nervous system. Whether prenatal alcohol exposure results in cell death by necrosis or by apoptosis depends on the severity, timing, and duration of the exposure.

Necrosis and apoptosis differ significantly in the biochemical and physical changes involved. During necrosis, the cell swells, metabolic functions cease both in the cell and in the intracellular organelles, and the cell membrane ruptures, releasing its contents into the surrounding tissue and causing inflammation. In contrast, apoptosis is an orderly process where the cell shrinks and the nucleus and the cell's DNA become fragmented, but the cell's metabolic processes continue. The cell develops small, bubble-like blebs on its surface and breaks up into small fragments called apoptotic bodies, each enclosed within a membrane and each containing still-functioning organelles. The process does not cause inflammation, and the apoptotic bodies are eventually absorbed by neighboring cells.

The signaling pathways that lead to apoptosis involve *bcl-2* genes, a family of genes that can either promote or inhibit apoptosis. The balance in expression of these genes regulates the "decision" between survival and cell death. The pathways to apoptosis involve the activation of death-promoting substances called caspases, which are enzymes that act as "executioners" by literally cutting apart the cell's proteins. It is likely that the apoptosis-inhibiting *bcl-2* genes act by inhibiting caspase activation. However, once the apoptosis-promoting cascade of reactions has begun, the inhibitory *bcl-2* genes usually cannot prevent cell death.

Figure 2: Modes of cell death



In necrosis (left), the cell forms bubble-like projections, or blebs, and the cell and its organelles become nonfunctional. The blebs fuse and become larger, but do not contain organelles. The cell membrane ruptures, releasing the cell's contents into the surrounding tissue, causing inflammation. In apoptosis (right), the cell similarly forms blebs, but the blebs contain still-functioning organelles. The nucleus becomes fragmented, and the cell breaks up to form apoptotic bodies, which remain metabolically functional. The apoptotic bodies are eventually engulfed by neighboring cells.

Source: Nanji and Hiller-Sturmhöfel 1997.

The mitochondria—intracellular organelles that play an important role in energy metabolism—may also play a role in the initiation of apoptosis. In response to certain signals that affect the mitochondrial membrane, the mitochondria may release cytochrome c and other substances into the cytoplasm. The cytochrome c, in turn, can activate genes that initiate the caspase cascade.

an excessive degree by toxins such as alcohol (Bredensen 1995, 1996*a,b*; Cartwright, et al. 1998; Ewald and Shao 1993; Wyllie et al. 1984) (see the box, above, and figure 2). While cell death by apoptosis is critical to healthy CNS development (Oppenheim 1991), this type of cell death also is involved in a broad range of human CNS disorders, including amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) and Alzheimer's disease (Beal 1997).

Both modes of cell death, which can occur in response to the same toxin, appear to involve dysfunction of the cell's mitochondria (Keller et al. 1998; Kroemer et al. 1997; Schinder et al. 1996). The proportion of cells that follow each mode of death depends upon the intensity or duration of the toxic insult and upon the extent of mitochondrial damage (Ankarcrona et al. 1995; Bonfoco et al. 1995; Choi 1995; Keller et al. 1998; Kroemer et al. 1997; Pang and Geddes 1997). In addition, changes in the expression of certain genes (*bcl-2* genes) can determine whether or not cells die by apoptosis (Davies 1995; Li et al. 1997; Merry and Korsmeyer 1997; Reed 1997; Vaux and Strasses 1996; Yang et al. 1997). These and other recent advances in knowledge about cell death modes provide the basis for FAS studies on the role of alcohol in inducing cell death in developing tissues.

Free-Radical Damage

Free radicals are highly reactive molecular fragments that may be formed as a by-product of alcohol metabolism. It is very likely that formation of these fragments plays an important role in producing cell damage in FAS, both in the CNS and in the craniofacial region (Beal 1997; Cedarbaum 1989; Chen and Sulik 1996; Chen et al. 1997; Davis et al. 1990; Dykens 1994; Henderson et al. 1995; Montoliu et al. 1995; Nordmann et al. 1992). Free radicals can disrupt a cell's outer membrane or the membranes surrounding its organelles, such as mitochondria. In so doing, they upset the delicate balance of water, calcium, proteins, and other components within cells. Numerous studies have indicated that alcohol may damage or kill fetal cells by causing the breakdown of mitochondria (Devi et al. 1993, 1994), a process that can be initiated by excessive amounts of free radicals (Chen and Sulik 1996; Guerri et al. 1994; Henderson et al. 1995; Montoliu et al. 1994, 1995).

Antioxidants—such as vitamin C, vitamin E, and glutathione—are molecules that neutralize free radicals. Research has demonstrated that the addition of antioxidants to cell cultures can prevent cell death, suggesting the potential for therapies with antioxidant treatment (Chen and Sulik 1996; Chen et al. 1997; Davis et al. 1990; Reyes and Ott 1996; Reyes et al. 1993).

Interference With Growth Factor Functions

A number of chemicals, called growth factors, control cell proliferation and promote cell survival in the developing fetus (Henderson 1996). Current research indicates that alcohol exposure may disrupt the developing CNS by interfering with the production or function of some of these growth factors (Luo and Miller 1996, 1997; Resnicoff et al. 1993*a*,*b*, 1996). Described here are studies focusing on insulin-like growth factors, nerve growth factor, basic fibroblast growth factor, and a neurotrophic growth factor.

For cells to enter the stage of cell division in which the chromosomes are duplicated, the action of insulin-like growth factors (IGF-I and IGF-II) on the cells' IGF receptors is generally required (Rubin and Baserga 1995; Singh et al. 1996*b*). However, research has indicated that in the presence of alcohol, IGF-I binds with its receptors on the surface of neurons but is no longer able to stimulate cell proliferation (Resnicoff et al. 1993*a*,*b*, 1996). Studies on strains of mice that have been genetically engineered to inactivate the IGF-I receptors showed that intrauterine growth was severely stunted (Baker et al. 1993). IGF-I also supports the survival of nondividing cells and can prevent apoptosis in several types of cells, including specialized neurons in the cerebellum called granule cells (Galli et al. 1995). Recent studies have found that alcohol blocks this protective effect of IGF-I against apoptosis in granule cells (Zhang et al. 1998) and also in connective tissue cells called fibroblasts (Cui et al. 1997).

Evidence from studies using cultured cells of neural tumors (neuroblastoma) has supported these findings. Neuroblastoma cells that had been stimulated by growth factors showed that alcohol inhibited cell proliferation (Luo and Miller 1996, 1997). In contrast, neuroblastoma cell lines that did not normally respond to growth factors remained unaffected by alcohol (Resnicoff et al. 1996).

Two other growth factors—nerve growth factor and basic fibroblast growth factor—have also been shown to protect cultures of several types of brain cells from alcohol-induced death (Heaton et al. 1993, 1994, 1995*a,b*; Luo et al. 1997). Recent work has also shown that a growth factor called glial-derived neurotrophic factor protects against alcohol-induced cell death in cultures of specialized neurons of the cerebellum, called Purkinje cells (McAlhany et al. 1997). This protective effect appears to be an important clue into alcohol-induced loss of Purkinje cells, an effect that has been studied extensively in animals and for which issues of alcohol concentrations and stages of vulnerability are now relatively well understood (Goodlett and Johnson 1999).

Adverse Effects on Astrocyte Formation

Astrocytes are star-shaped cells of the nervous system that, unlike neurons, do not actively transmit information to other cells by communication across a synapse. Nevertheless, astrocytes interact intimately with neurons and other astrocytes and play critical roles in the developing CNS (Kettenman and Ransom 1995; Rakic 1991). One possible mechanism for alcohol-induced abnormalities in the fetus involves errors in the process of astrocyte formation.

Early in the fetal development of the brain, elongated cells that are precursors to astrocytes, called radial glia, act as tracks to guide migrating neurons to their appropriate destinations in the brain. Just as the period of neuronal migration ends, the radial glia normally transform into astrocytes and cease to provide tracks. In a study of rats, prenatal alcohol exposure caused radial glia to change into astrocytes prematurely, before the stage of neuronal migration was complete (Miller and Robertson 1993). This may explain why, in rats exposed to alcohol prenatally, neurons that develop late in the migration period were not found in appropriate places in the brain (Miller 1993).

More recently, researchers have found that alcohol interferes with the normal growth and function of astrocytes. For example, alcohol has been found to inhibit the normal proliferation of astrocytes in vitro (Guizetti et al. 1997; Holownia et al. 1997; Luo and Miller 1996) and in rats exposed to alcohol prenatally (Miller and Potempa 1990). Other in vitro studies found abnormalities in various aspects of astrocyte development (Guerri et al. 1993; Kim and Druse 1996*a*; Lokhorst and Druse 1993; Saez et al. 1991; Valles et al. 1996).

Depending on the stage of development, alcohol exposure causes different problems in astrocyte formation. As noted, when the exposure occurs during gestation, studies in rats have found diminished or delayed astrocyte development. However, when exposure occurs later, as modeled in a study of binge exposure in which alcohol was administered directly into the stomach of newborn rats (a developmental stage equivalent to the third trimester in humans), researchers found that the astrocytes became abnormally large and numerous and that protein levels increased (Fletcher and Shain 1993; Goodlett et al. 1993, 1997). These changes were dramatic but transient. In contrast, this reaction did not occur when newborn rats inhaled alcohol (Ryabinin et al. 1995). The reasons for these different reactions are not known, but the findings imply that alcohol exposure even late in human pregnancy may affect fetal astrocytes.

Abnormal Development of Neurotransmitter Systems

Neurons communicate via chemicals called neurotransmitters, which are released from an extension of the nerve cell body called the axon terminal. The neurotransmitter then travels across a narrow synaptic gap and binds to specific receptors on the target neuron. Research shows that alcohol has significant effects on two neurotransmitter systems that play important roles in fetal brain development: the serotonin system and the glutamate system.

Serotonin. An important step in the development of the cerebral cortex (the thin layer of tissue covering the cerebrum) appears to be the early embryonic growth of serotonin-releasing (serotonergic) neurons into the region that eventually develops into the cortex (Whitaker-Azmitia et al. 1996).

In studies of rats, very early prenatal exposure to alcohol significantly delayed the development of the serotonergic system, reducing serotonin levels and altering the binding of serotonin to receptors in many target sites during periods that are likely to be critical for normal brain development (Druse et al. 1991; Druse Manteuffel 1996). This effect may involve alcohol's interference with a process in which the developing nerve cells release serotonin, which stimulates specific receptors (called 5-HT_{1A} receptors) on neighboring astrocytes. These astrocytes, in turn, release growth factors that promote the growth, development, and survival of the nerve cells (Azmitia et al. 1990; Kim and Druse 1996*a*; Whitaker-Azmitia et al. 1990, 1996). Remarkably, one study found that treatment of pregnant rats with a medication that stimulates the same serotonin receptors—the antidepressant buspirone—protected against the alcohol-induced deficits in serotonin development (Kim and Druse 1996*b*).

The findings to date in this area suggest two important directions for future research: (1) characterizing the specific effects of alcohol-induced deficits in the serotonin system on the development of the cortex and other brain regions, and (2) identifying the serotonin-related mechanisms of nerve cell growth that involve the stimulation of astrocytes to release growth factors and the effects of alcohol on these mechanisms.

Glutamate. The neurotransmitter glutamate, considered the most important of the excitatory neurotransmitters (which increase neuronal activity), plays a major role in controlling brain function. During development, the activation of one type of receptor for glutamate—called the NMDA (*N*-methyl-D-aspartate) receptor—appears to be critical for establishing and stabilizing newly formed synapses, especially in the developing visual system and other CNS systems (Bear et al. 1990; Constantine-Paton 1994; Kirkwood and Bear 1994). Because alcohol is known to interfere with the function of NMDA receptors (Crews et al. 1996; Hoffman et al. 1989; Lovinger et al. 1990), exposure to alcohol during critical periods of synapse generation has been suggested as a likely mechanism for long-term effects on the organization of the CNS. (Glutamate and the NMDA receptor are extensively discussed in the chapter on neuroscience and neurobehavior.)

In contrast to the increase in number and sensitivity of NMDA receptors that occurs with chronic alcohol exposure in adult animals and in cell cultures (called up-regulation) (Follesa and Ticku 1996; Snell et al. 1996; Trevisan et al. 1994), prenatal alcohol exposure even in moderate concentrations results in a decrease in the number and function of NMDA receptors (called down-regulation) throughout development (Abdollah and Brien 1995; Diaz-Granados et al. 1997; Hughes et al. 1998; Lee et al. 1994; Morrisett et al. 1989; Savage et al. 1991; Spuhler-Phillips et al. 1997). Several studies in rats have shown that NMDA receptor down-regulation is most likely to occur when alcohol exposure occurs shortly after birth, a stage that correlates with third-trimester exposure in humans, and to last well past the period of alcohol exposure (Diaz-Granados et al. 1997; Gruol et al. 1998). Alcohol's effects on NMDA receptors during critical periods of brain development may play a major role in the mental and behavioral deficiencies found in FAS.

An important current avenue of study is the possible role of damage to the developing CNS from increased NMDA receptor activity that occurs during acute withdrawal periods associated with binge drinking (Thomas et al. 1998). One study in rats, using a model of binge exposure during CNS development, found that a medication that blocked NMDA receptor function (dizocilpine) lessened some of the long-term behavioral consequences of the alcohol exposure, such as hyperactivity (Thomas et al. 1997). Further studies are needed to identify the specific contribution of acute withdrawal effects to alcohol-induced brain damage.

Altered Glucose Transport and Uptake

Most cells of mammals contain specialized proteins that transport glucose from the blood

into the cells. Cells need glucose not only for energy metabolism, but also for metabolizing free radicals (Baquer et al. 1988) and for synthesizing vital chemicals, including neurotransmitters and nucleic acids. A number of studies have demonstrated that alcohol can impair glucose transport and uptake during development. For example, cell culture studies show that alcohol exposure can reduce glucose transporter protein levels and glucose uptake by certain brain neurons from fetal rats (Hu et al. 1995) and astrocytes from newborn rats (Singh et al. 1996*a*). These reductions also occurred in cells from the cerebral cortex during prolonged alcohol exposure in fetal rats (Singh et al. 1992). Studies on cultured rat embryos suggested that alcohol inhibited glucose transport in these embryos as well (Snyder et al. 1992). Other researchers, using chick embryos, found that alcohol reduced glucose uptake but increased insulin-stimulated uptake (Pennington et al. 1995) and altered some transporter proteins (Eckstein et al. 1997). Further research on the mechanisms of glucose transport and uptake could contribute significantly to knowledge about alcohol's effects on developing cells.

Abnormal Cell Adhesion Molecules

Cell adhesion molecules influence the ability of CNS cells to migrate properly, to develop branching extensions such as axons and dendrites, and to survive. Defects in one particular cell adhesion molecule, called L1, can lead to abnormalities in brain development and mental deficiencies (Wong et al. 1995) that are similar to those seen in children with FAS (Mattson and Riley 1996).

Some cell culture studies have shown that low levels of alcohol interfere with the ability of L1 to regulate the clustering or clumping together of cells that is needed for brain structures to develop (Charness et al. 1994; Ramanathan et al. 1996). The disruption of cell adhesion seems to depend on the type of cell culture used, however, as another study using a different type of cell culture found that alcohol did not interfere with L1-regulated cell clumping (Vallejo et al. 1997). Although the reasons for this discrepancy are not understood, additional research on the L1 defect mechanism may provide more insights into errors in cell migration, cell contact, and other aspects of FAS defects.

Altered Regulation of Gene Expression

The process of converting a gene's encoded information into a gene product (such as a protein) is called gene expression. In alcohol research, scientists are particularly interested in the expression of homeobox genes, which regulate the activation and timing of steps in the formation of specialized tissues and organs in the body (Hogan and Barnes 1992; Jonk et al. 1994; Marshall et al. 1996). Although it is known that alcohol can affect the expression of some genes, it is not yet certain whether these include homeobox genes.

In one study, a heavy dose of alcohol in pregnant mice at 7 days of gestation nearly eliminated the expression of a certain homeobox gene (called *msx2*) in the fetuses 3 days later and produced severely abnormal fetal growth (Rifas et al. 1997). However, it was not clear whether the lack of gene expression caused abnormal fetal growth or whether the abnormal growth prevented expression of the homeobox gene. Additional research will help elucidate this process.

The lack of information on how alcohol affects the regulation of genes that control the formation of the CNS and other body parts creates a major gap in our understanding of the mechanisms underlying FAS. (One exception is research on a mechanism involving retinoic acid production and craniofacial defects described next in this section.) In addition to homeobox genes, more knowledge is needed about alcohol's effects on genes that control cell survival and cell death, such as the *bcl-2* genes. Cell death can be blocked by *bcl-2* genes that inhibit apoptosis, presumably through inhibition of enzymes called caspases, the "executioners" that cut apart the cell's proteins (Cohen 1997; Du et al. 1997; Hara et al. 1997; Jung et al. 1996; Kane et al. 1993; Kermer et al. 1998; Nicholson et al. 1995; Parsadanian et al. 1998). Studies on alcohol-induced changes in gene expression during critical periods of development constitute one of the most promising areas for new FAS research.

Candidate Mechanisms for Craniofacial Defects

Animal studies have linked the characteristic facial abnormalities in FAS to cell death by apoptosis of certain embryonic cells, called neural crest cells, during a very defined and narrow period of vulnerability (the embryonic stages of gastrulation or neurulation) (Cartwright et al. 1998; Sulik et al. 1981). One mechanism by which this occurs is thought to be the formation of free radicals (Kotch et al. 1995). In studies of mouse neural crest cells, alcohol was associated with cell death due to the formation of free radicals, a process that could be prevented with antioxidants (Chen and Sulik 1996; Chen et al. 1997; Davis et al. 1990).

Two other possible mechanisms, described in more detail below, are a deficiency in retinoic acid and altered expression of homeobox genes. All three of these mechanisms are likely interrelated, since retinoic acid is a key regulator of gene expression, and both free-radical toxicity and altered gene expression can produce apoptosis. The effects of these mechanisms, as with those that damage the CNS, depend in part on the timing of alcohol exposure.

Timing of Exposure

In mouse and chicken embryos, exposure to alcohol during certain periods of development can give rise to the craniofacial abnormalities associated with FAS (Cartwright and Smith 1995*a,b*; Cartwright et al. 1998; Kotch and Sulik 1992*a,b*; Sulik and Johnston 1983; Sulik et al. 1981, 1988; Webster et al. 1983). In mice, a narrow period of vulnerability to craniofacial abnormalities was observed about 7 days after fertilization (Duester et al. 1996). Extensive research with chicken embryos also revealed that exposure to alcohol during narrow windows of vulnerability caused the death of neural crest cells by apoptosis (Cartwright and Smith 1995*a,b*; Cartwright et al. 1998). These researchers demonstrated that, to induce apoptosis, alcohol exposure must occur before the neural crest cells begin to migrate and that cells do not actually die until after migration.

Retinoic Acid Deficiency and Altered Gene Expression

Extensive evidence indicates that retinoic acid, a derivative of retinol (vitamin A), is essential for controlling the normal pattern of development of tissues and organs in vertebrate animals (Boncinelli et al. 1991; Durston et al. 1989; Hofmann and Eichele 1994; Hogan and Barnes 1992; Jonk et al. 1994; Mangelsdorf et al. 1994). Research shows that retinoic acid is necessary for the development of neural crest cells into craniofacial features (Morriss-Kay 1993; Morriss-Kay and Sokolova 1996) and strongly suggests that it acts in this capacity by binding with receptors that regulate the expression of homeobox genes (Hogan and Barnes 1992; Jonk et al. 1994; Marshall et al. 1996).

Ultimately, deficiencies or abnormalities in retinoic acid or its receptors cause neural crest cells to die by apoptosis, leading to craniofacial defects (Dickman et al. 1997; Grummer and Zachman 1995; Grummer et al. 1993; Henion and Weston 1994; Hofmann and Eichele 1994; Mangelsdorf et al. 1994; Morriss-Kay 1993; Morriss-Kay and Sokolova 1996).

In 1991, it was proposed that the craniofacial features of FAS are caused by low concentrations of retinoic acid in the embryo (Duester 1991; Pullarkat 1991). Research since then has shown that alcohol exposure at specific periods of embryonic development can reduce the production of retinoic acid (Deltour et al. 1996). Some studies also suggest that decreased levels of retinoic acid may contribute to alcohol-related heart defects (De Jonge and Zachman 1995; Twal and Zile 1997).

For cells to convert retinol to retinoic acid, the action of certain forms of the alcohol-metabolizing enzyme alcohol dehydrogenase (ADH) is required (Ang et al. 1996*a,b*; Duester et al. 1996; Kim et al. 1992; Zgombic-Knight et al. 1995). In a study of mice, one form of ADH (Class IV) first appeared 7 days after fertilization (Duester et al. 1996), which is also when retinoic acid is first produced (Ang et al. 1996*a,b*). Another study showed that the addition of a high concentration of alcohol

to cultures of mouse embryos during this same time frame—7 to 8 days after fertilization—caused a decrease in the amount of retinoic acid in neural crest cells (Deltour et al. 1996). These results suggest that, in neural crest cells, alcohol successfully competes with retinol to bind with Class IV ADH. In this way, alcohol limits the formation of retinoic acid during a critical period of embryonic development.

Several studies have found that certain retinoic acid receptors control the specific homeobox genes that regulate the timing and coordination of craniofacial development (Hogan and Barnes 1992; Jonk et al. 1994; Marshall et al. 1996; Rifas et al. 1997). Although alcohol has been shown to reduce retinoic acid levels, a recent study using chick embryos found that alcohol had no effect on the expression of the homeobox gene *msx2*, which is known to be involved in normal development of neural crest cells, nor did it affect a related growth factor (BMP4) (Cartwright et al. 1998). The BMP4-msx2 pathway is a signaling pathway that induces apoptotic cell death in neural crest cells (Davidson 1995; Graham et al. 1994). This finding contrasts with another recent study in which expression of the same homeobox gene in mouse embryos was dramatically altered by a binge pattern of alcohol exposure, leading to severe growth deficiencies (Rifas et al. 1997). Although species differences may explain the discrepancies, it is also possible that the lack of homeobox gene expression in the mouse cells was a result of massive apoptotic cell death following administration of alcohol. As mentioned earlier, future research on FAS mechanisms will need to fill the gaps in our understanding of alcohol-induced changes in gene expression.

In Closing

Advancements in our understanding of mechanisms of FAS damage will guide the development of new ways to protect against or limit alcohol-induced damage to the fetus. Opportunities exist, for example, to identify windows of time in which treatments may block specific types of damage or rescue otherwise vulnerable cell populations. Identification of specific mechanisms and biochemical markers of damage should accelerate early detection or allow better prediction of specific types of damage in at-risk pregnancies. Such advances could help to identify cases at greatest risk for developmental disorders and to improve outcomes through targeted interventions.

Clarifying the mechanisms of brain damage in FAS should yield insights into the long-term adaptations of CNS cells and the potential for neuronal plasticity, in which neurons surrounding an injury change their synaptic connections to compensate for cell death or injury. Advances in knowledge about these long-term CNS adaptations could provide a basis for therapeutic approaches to the problems of long-lasting deficits in behavior and learning that are typical of FAS. From a public health perspective, knowledge of specific mechanisms of damage should be a powerful tool for effective public education and counseling of alcohol-dependent women in their childbearing years and could help guide clinical decisions about the most effective allocation of medical and psychological support services.

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Issues in Fetal Alcohol Syndrome Prevention

Unlike most other birth defects, Fetal Alcohol Syndrome (FAS) has the potential to be entirely preventable because its direct cause—maternal drinking—is presumed to be a controllable behavior. Although many strategies to prevent FAS have been developed and implemented in recent years, rigorous scientific research on the effectiveness of these approaches is, relatively speaking, in its infancy.

In the decades since FAS was discovered, more than 1,000 research articles have been published on the topic (see reviews in Stratton et al. 1996; Streissguth et al. 1985; Waterson and Murray-Lyon 1990). Most of this literature has emphasized the biochemical mechanisms of damage to the fetus, the physical characteristics of the syndrome in humans and animals, and biologic descriptions of the birth defects associated with the syndrome. Substantially less information has been published about the patterns of drinking by pregnant women, the social and psychological risk factors associated with drinking during pregnancy and the birth of FAS children, or the processes by which drinking, particularly heavy drinking, by pregnant women can be prevented. Because FAS is theoretically completely preventable through behavioral change, it is of vital importance to increase our understanding of the essential ingredients of behavioral change and of effective ways to encourage pregnant women to adopt them.

This section summarizes several major reviews of FAS prevention efforts, describes issues related to research methods and evaluations, and presents research findings on prevention approaches targeted to women at different risk levels. The prevention approaches are grouped into three categories set forth in an Institute of Medicine (IOM) report (Stratton et al. 1996): "universal" approaches, which are broad, populationwide strategies such as media campaigns aimed at all women of childbearing age regardless of risk; "selective" prevention strategies aimed at women known to be at some increased risk because they are drinking while pregnant or belong to a vulnerable subgroup; and "indicated" prevention strategies aimed at women who are at the highest risk because of their heavy drinking levels or history of having had a child with FAS. Brief mention of international implications is included as well.

Reviews of Prevention Programs and Research

One of the earliest comprehensive literature reviews on FAS prevention summarized more than 200 relevant articles and books and described the state of knowledge about FAS prevention in both the United States and the United Kingdom (Waterson and Murray-Lyon 1990). The authors identified two major shortcomings in the literature on FAS prevention: (1) most of the prevention projects and studies did not take full advantage of the existing theory and knowledge base in the fields of health promotion and health education, and (2) inadequate attention was paid to the risk factors that affected the targeted populations' heavy drinking and other relevant behaviors.

A second review of more than 160 articles described treatment programs designed to reduce fetal alcohol exposure and damage in alcohol- and drug-dependent women (Finkelstein 1993). According to the author, "research suggests that programs that provide comprehensive and coordinated treatment are better able to draw pregnant women into care as well as provide more effective treatment" (Finkelstein 1993, p. 1275). A number of sources reviewed in this article recommended comprehensive social, cognitive-behavioral, medical, and referral services for women who are abusing alcohol as the most effective treatment approach. The article also notes that coordination of services through an active case manager is considered by many to be essential (Finkelstein 1993; see also Brindis and

Theidon 1997; Godley et al. 1994; Siegal et al. 1995). In addition, other reports (Hughes et al. 1995; Kaufman 1996; Namyniuk et al. 1997) have indicated that comprehensive programs should include active outreach strategies to attract high-risk drinkers, and may need to offer family support and counseling services as well as medical and psychiatric care.

A third review (May 1995) differed from earlier summaries in emphasizing a public health approach to the prevention of FAS. The author contended that prevention programs should be based on the epidemiology of both FAS and adult drinking patterns in the target population and should focus on specific maternal risk factors, which he identifies (table 1). Drawing on more than 170 sources, the author classified strategies from the perspective of the three levels of prevention commonly used in the field of public health: primary prevention approaches, which attempt to stop maternal drinking before it starts; secondary approaches, which facilitate early detection and treatment of maternal drinking problems before they lead to FAS; and tertiary approaches, which attempt to change the behaviors of women who are at very high risk because they have already delivered a child with diagnosable FAS or other alcohol-related disorders, such as alcohol-related birth defects (ARBD) and alcohol-related neurodevelopmental disorder (ARND). On the basis of national survey data on alcohol and other

Table 1: Major maternal risk factors associated with Fetal Alcohol Syndrome and alcohol-related birth defects

Factor	Reference(s)
Age: >25 years	Abel and Sokol 1987; May et al. 1983
Number of children: >3	Abel 1988; Abel and Sokol 1987; Davis and Lipson 1984; Hankin and Sokol 1995
Separated, divorced, or never married	Gehshan 1995; Hilton 1991; Wilsnack et al. 1991
High blood alcohol concentration	Chang et al. 1997; Day et al. 1993; Godel et al. 1992
Binge drinking	Chang et al. 1997; Day et al. 1993; Godel et al. 1992
Long history of drinking	May et al. 1983; Sokol et al. 1980
Heavy drinking by male partner	Wilsnack and Beckman 1984; Wilsnack et al. 1991
Heavy drinking by any family member	Abel 1988
Culture tolerant of heavy drinking	May et al. 1983; Robinson et al. 1987
Low socioeconomic status	Abel 1995; Abma and Mott 1991; Bingol et al. 1987; Sokol et al. 1986
Work in male-dominated occupation	Gehshan 1995; Wilsnack and Wilsnack 1992; Wilsnack et al. 1991
Unemployment	Gehshan 1995; Wilsnack and Wilsnack 1992; Wilsnack et al. 1991
Social transience	May et al. 1983; Streissguth et al. 1985
Low self-esteem	Kaskutas 1996
Loss of children to foster or adoptive care due to neglect, abuse, or abandonment	Habbick et al. 1996; May et al. 1983; Streissguth et al. 1985
Sexual dysfunction	Wilsnack et al. 1991
Use of multiple substances	Day et al. 1993; Godel et al. 1992; Serdula et al. 1991
Cigarette smoking	Day et al. 1993; Godel et al. 1992; Serdula et al. 1991

Source: Adapted and updated from May 1995.

drug use patterns, the author estimated that primary prevention is all that is needed for most (78 percent) of the female population who are of childbearing age (defined in the article as aged 18 through 49), secondary prevention may be necessary for approximately 14 to 25 percent, and tertiary prevention is appropriate for only 2 to 6 percent (May 1995).

More recently, the IOM's Committee to Study Fetal Alcohol Syndrome reviewed a vast body of FAS literature and proposed its own comprehensive recommendations, which included a variety of prevention measures (Stratton et al. 1996). The review prompted the committee to adopt a prevention system that was somewhat different in theory and terminology from the standard public health categories of primary, secondary, and tertiary prevention. The three levels of prevention in the IOM scheme, as mentioned previously, are called universal, selective, and indicated:

- Universal approaches attempt to promote the health and well-being of all individuals in society or in a particular community, without regard to individual risk, through use of the media to educate the public and through policy and environmental change.

- Selective preventive interventions target individuals and subgroups who are at excess risk of developing the problem, such as women of childbearing age who drink alcohol. The IOM report (Stratton et al. 1996) notes that selective interventions should be given by health care providers who are trained to question women about their drinking and contraceptive histories and to deliver interventions that are proportional to the woman's level of risk.

- Indicated interventions are targeted to women who are at high risk of giving birth to an alcohol-impaired child, not simply because they belong to a vulnerable population but because, for instance, they are drinking at a level that is likely to produce FAS-affected offspring or they have already delivered one child with FAS.

For this last category of indicated interventions, the IOM report recommends that providers offer treatment in the form of brief interventions or more formal approaches as needed. Although prevention strategies generally stop short of treatment, the logic underlying this recommendation is that "treatment of alcohol problems in women (and their partners) is an appropriate indicated preventive intervention for the fetus being carried by the woman, as well as for children who might subsequently be conceived and borne by her" (Stratton et al. 1996, p. 36). The report also states that referral to birth control information and services may be appropriate and that case management should extend to "aftercare," a program component that maintains contact with FAS mothers and children to address social issues over time (Stratton et al. 1996).

Methodological and Evaluation Issues

Researchers who have reviewed and summarized the FAS prevention literature have emphasized the need for scientifically rigorous evaluations of prevention strategies that have been implemented in clinic and community settings. In a critical analysis of primarily clinical intervention research (Schorling 1993), three basic criteria were used to select studies for review: (1) prospective determination of alcohol use among a cohort of pregnant women, (2) implementation of a specific intervention among women at risk, and (3) postintervention assessment of alcohol use among the target population. At the time of that review, only five studies met these criteria for inclusion. Eight standards were then imposed on the studies for methodological efficacy, including the use of a control group, sufficient sample size, and consistent follow-up of study participants. None of the studies involved randomization; only two used a control group, and neither of those found any postintervention difference in alcohol use between the treatment and control groups.

In a later review, the IOM's Committee to Study Fetal Alcohol Syndrome evaluated methodologies reported in the literature on FAS prevention, including both published reports and unpublished materials from projects supported by Federal Health and Human Services agencies (Stratton

et al. 1996). The committee concluded that controlled research on the prevention of FAS is scarce and that the "utility and value of many of these programs as prevention efforts is unknown because of the limited evaluative component of the programs" (Stratton et al. 1996, p. 113).

A third review that focused on design and methodological issues identified five key elements for future FAS prevention research (May 1996):

- Prevalence: Baseline determination of the exact birth prevalence of FAS (and, if possible, ARBD and ARND) in the target population through active surveillance.

- Social and Medical Risk Factors: Detailed analysis of the social and medical risk factors of mothers of alcohol-impaired children so that appropriate high-risk groups and situations can be targeted.

- Role of the Male Partner: Delineation of the explicit behavioral, social, and psychological role of the male partner in enabling FAS (see, for example, Ihlen et al. 1990; Rubin et al. 1988).

- Emphasis on High-Risk Women: Focusing evaluations on indicated and selective prevention modalities because of the concentrated risk for FAS among a relatively small number of heavily drinking women.

- Community Trials: Institution of well-evaluated, comprehensive, communitywide prevention trials that use public health approaches and include matched control communities and the collection of baseline and postintervention data.

A major methodological impediment to evaluating community-based FAS prevention programs is the difficulty in determining a baseline prevalence figure for the target population. To date, the prevalence of FAS has been determined almost exclusively in certain American Indian and Alaskan Native communities (May 1996), where integrated public health care systems and well defined, homogeneous populations make such ascertainments possible. In larger communities, it will be necessary to develop representative sampling protocols and appropriate statistical corrections.

To gain estimates of FAS prevalence, it may be possible to use proxy measures that indicate likely alcohol-related effects. A number of studies have established or examined potential proxy measures, including facial defects and other physical abnormalities, growth and development indicators, and neurobehavioral indicators (see, for example, Day et al. 1989, 1990, 1991; Godel et al. 1992; Jacobson and Jacobson 1994; Jacobson et al. 1993; Rostand et al. 1990; Streissguth et al. 1990, 1994; Walpole et al. 1990). Although studies of the prevalence of characteristics consistent with prenatal alcohol exposure are currently ongoing, caution is warranted in using such proxy measures to evaluate the effectiveness of interventions. Not all problems found in alcohol-exposed children are necessarily caused by alcohol exposure; the actual fraction attributable to alcohol consumption needs to be determined (Khoury et al. 1996).

Reaching to All, Regardless of Risk: Universal Prevention Approaches

Surveys have found that most women reduce or cease their drinking during pregnancy (Kaskutas and Graves 1994). Research indicates that this reduction may be linked to universal prevention messages in reading material and in radio and television advertisements (Waterson and Murray-Lyon 1989) or to increased exposure to messages from a variety of sources during pregnancy, including having personal conversations about drinking during pregnancy (Kaskutas and Graves 1994). However, another study found that decreases in alcohol consumption during pregnancy are not necessarily associated with exposure to messages of any kind, including conversations (Kaskutas et al. 1998). The authors suggest that this may be occurring because in recent years, pregnant women have been less frequently exposed to advertisements advising them not

to drink and may have had fewer conversations about drinking during pregnancy.

One universal prevention strategy is the use of alcoholic beverage labels that warn about the risks of birth defects if women drink alcohol during pregnancy. Some research (Hankin et al. 1993*a*, 1994, 1996) has found that the labels have a preventive effect on lighter drinkers but not on women who are the heaviest drinkers and who are thereby at greatest risk of bearing a child with FAS. Similar problems in affecting heavily drinking pregnant women also seem to characterize other public education approaches, such as warning signs on buses or billboards (Fitzgerald 1988; Little et al. 1981, 1984, 1985; Weiner et al. 1989). Other studies also suggest that women who are the heaviest and most long-term drinkers show the least amount of change in their drinking behavior once they become pregnant (Serdula et al. 1991; Smith et al. 1987).

Some recent comprehensive community-based approaches to preventing FAS contain strong, universally focused strategies in addition to their emphasis on targeting high-risk women with selected and indicated interventions (May 1996; see also May et al. 1993; Oetting et al. 1995; Soman 1992). Although some limited communitywide approaches were instituted early in the history of FAS prevention efforts in the northwestern United States (Little et al. 1981, 1984, 1985; Streissguth et al. 1985), this early literature primarily stressed the need for smaller scale, treatment-based interventions.

A prototype for community-based research on interventions to prevent FAS is offered by the quasi-experimental trials to prevent cardiovascular disease through changes in knowledge, attitudes, beliefs, and lifestyles (Farquhar et al. 1990; Luepker et al. 1993). These evaluative research designs used control (or comparison) communities as well as pre- and posttest measures to assess effects of the prevention strategies. A new National Institute on Alcohol Abuse and Alcoholism-supported FAS prevention trial in relatively high-prevalence American Indian communities has adopted a similar model (CRISP 2000).

Since the early 1990's, community-based trials of interventions to prevent alcohol abuse and related problems have become relatively frequent. However, with few exceptions, they have not focused on the reduction of alcohol-induced birth defects or drinking by pregnant women. Generally speaking, these studies have used quasi-experimental and experimental (randomized) designs to test the effectiveness of strategies to reduce underage drinking and alcohol-related trauma, which is largely induced by drinking and driving (Hingson et al. 1996; Holder 1997; Perry et al. 1996; Wagenaar et al. 1994, 1999, 2000, in press). Current methodologies now permit the analysis of neighborhoods (subcommunities) within larger urban areas (Gruenewald 1997), which has implications for FAS prevention research because higher risk populations may be concentrated in definable neighborhoods.

Targeting Those at Increased Risk: Selective Prevention Approaches

Much information regarding risk factors for FAS (such as age, socioeconomic status, and spousal characteristics) is available and can help provide appropriate population targets for selected and indicated prevention strategies (see Abma and Mott 1991; Coles et al. 1997; Gehshan 1995; Testa and Leonard 1995). Although an abundance of prevention programs dealing with prenatal alcohol abuse exist throughout the country, few have been evaluated (Stratton et al. 1996). In some cases in which data have at least been collected before and after the intervention, it may be possible to conduct retrospective data analyses as a means of pilot-testing hypotheses and drawing insights about the effectiveness of particular approaches to prevention and treatment. For example, a retrospective study of pregnant women and mothers who participated for at least 5 months in a California substance abuse treatment program indicated that high-risk women who received more basic therapeutic and case management services, especially family therapy services, were more likely to remain abstinent from alcohol and other drugs than were those who did not receive these services (Zlotnick et al. 1996).

In selective prevention approaches, the major research and evaluation issues are threefold. First, it is necessary to determine the effect of alcohol-focused interventions (including health information, screening, and advice or counseling) aimed at high-risk groups. Second, it is important to determine the extent to which strategies to promote birth control can have an impact. Finally, it is appropriate to assess the possible benefits of combining these approaches, especially for women who may be resistant to abstinence or who are at excess risk of having unplanned pregnancies.

Women at increased risk of having FAS children need to be accurately and efficiently identified through screening in settings such as clinics that provide primary and prenatal care to low-income women (Chang et al. 1997; Hankin and Sokol 1995; Harwell et al. 1996; Kaskutas 1996; Loneck et al. 1997). Some investigators have provided guidelines for detecting higher risk drinkers in primary care settings (Chang et al. 1997; Hankin and Sokol 1995). Once such women are identified, a number of other questions become paramount, such as their readiness for change, the factors that affect readiness, and actual turning points toward abstinence (Kaskutas 1996). These issues need to be addressed and evaluated, as they now are in other alcohol research that does not involve pregnant women.

Many of the screening questionnaires most commonly used to identify problem drinking are less accurate for women than for men (Bradley et al. 1998). The same may be true for more open-ended screening interviews. Reasons for this difference probably include the increased stigma experienced by women who drink (Gomberg 1988), which may lead them to underreport alcohol problems. Women are also less likely to have experienced some of the more adverse consequences of drinking, such as employment, economic, or social problems (Robbins 1989; Weisner 1990); thus, standard screening instruments may fail to identify women whose drinking problems are expressed in other ways. In addition, screening questionnaires may not detect drinking problems as readily in women (Bradley et al. 1998; Dawson 1994), because women experience greater physical effects of alcohol at lower levels of consumption than men do.

Attempts to improve identification of women who drink during pregnancy have focused on comparing the accuracy of various screening instruments with each other and with informal questioning by health care workers. In one study (Chang et al. 1998), the T-ACE questionnaire (table 2) was more effective than assessments by health care staff in identifying pregnant women at risk for problem drinking. Other efforts to develop accurate screening instruments for use among women have taken place among American Indian populations (Bull et al. 1999). However, because alcohol use during pregnancy is not confined to cultural and racial/ethnic minorities or to low-socioeconomic groups (Chang et al. 1998), more such work is needed to develop instruments for use among general populations of women of childbearing age.

Women who give birth to FAS children are somewhat unstable in occupational, marital, and familial relationships and tend to be geographically mobile (May et al. 1983; Streissguth et al. 1985). No specific prevention studies (other than a few analyses of case management) have effectively addressed these problems. Problems related to transience (when patients leave a prevention or treatment program) are not only an issue for FAS prevention but also for research, because they can distort the results of evaluation studies. Research is therefore necessary on how best to attract highly mobile, high-risk individuals to prevention and treatment programs and to identify incentives that will encourage long-term participation for both therapy and longitudinal research (Siegal et al. 1995). Existing methods of longitudinal tracking used in other areas of research might be adapted to studies of FAS prevention.

Helping Those at Highest Risk: Indicated Prevention Approaches

Effective approaches to FAS prevention among the highest risk women (particularly mothers who have previously given birth to an alcohol-impaired child) would eliminate most of the existing FAS problem, because these women account for the majority of FAS cases. Epidemiologic studies of various populations have shown that women who have one child with FAS are likely to have other children with alcohol-related impairments in subsequent pregnancies (May et al. 1983).

Reaching these high-risk women is problematic. Many of the programs described in the FAS clinical intervention literature deal with women who have been referred from prenatal clinics because they exhibit signs of early-onset, high-risk drinking. However, a large number of heavily drinking pregnant women never present themselves to prenatal clinics and are otherwise elusive. If they receive therapy for their alcohol dependence, such treatment rarely includes an emphasis on FAS prevention. Although a few programs in small communities throughout the United States are designed to target women at

Table 2: Commonly used screening questionnaires for identifying problem drinking

CAGE:

- Have you ever felt you should **C**ut down on your drinking?
- Have people **A**nnoyed you by criticizing your drinking?
- Have you ever felt bad or **G**uilty about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**E**ye opener)?

Each item receives a score of 1 for a positive response (Ewing 1984).

T-ACE:

- **T**olerance—How many drinks can you hold?
- Have people **A**nnoyed you by complaining about your drinking?
- Have you ever felt you ought to **C**ut down on your drinking?
- **E**ye opener—Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?

A score of 2 is given for a positive response to the tolerance question; 1 point each is scored for the other three questions (Sokol 1989).

TWEAK:

- How many drinks can you hold? (**T**olerance)
- Does your spouse [or do your parents] ever **W**orry or complain about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (**E**ye opener)
- Have you ever awakened the morning after some drinking the night before and found that you could not remember a part of the evening before? (**A**mnesia)
- Have you ever felt you ought to cut [**K**ut] down on your drinking?

Positive answers to the tolerance and worry questions score 2 points each; the other three questions score 1 point each (Chan et al. 1993).

MAST (Michigan Alcoholism Screening Test):

Consists of 25 questions, each weighted 0, 1, 2, or 5, and when summed yielding scores of 0 to 53 (Selzer 1971).

highest risk for having FAS children, little is known about the effectiveness of these programs. They are generally funded by community services and agencies that tend not to require outcome evaluations.

Because barriers to treatment for these highest risk women clearly exist (Breitbart et al. 1994; Klein and Zahnd 1997; Messer et al. 1996), there is a critical need for research that develops and tests aggressive targeting strategies, referral patterns, and intervention components (Loneck et al. 1997).

For those women identified as having the greatest risk of an FAS birth, a wide range of indicated prevention strategies exists. The research task at hand is to determine which types of therapy are most effective for which subtypes of women (see Loneck et al. 1997; Peterson and Lowe 1992). Specifically, studies need to assess the comparative effectiveness of brief versus extended interventions; coercive versus voluntary therapies, such as motivational enhancement (Miller and Rollnick 1991); and group versus individual approaches (see Stratton et al. 1996, pp. 138–145). This goal can be achieved through systematic assessments that adapt state-of-the-art evaluation methodologies to these particular groups of women, and perhaps through the development of unique evaluation techniques that take into account the fact that FAS, ARBD, and ARND are relatively rare conditions. Also needing evaluation are various prototypes of case management, social network therapy, support groups for FAS mothers, environmental change, and "social model" approaches to recovery, such as the community reinforcement approach (Meyers and Smith 1995; Meyers et al. 1996).

One effective strategy noted in the literature is intensive case management for alcohol-abusing women who have had FAS children (Bacon 1988; Davis and Frost 1984; Masis and May 1991; Rosett et al. 1981; Stratton et al. 1996; Weiner et al. 1989). Another approach used in some indicated prevention programs combines alcohol interventions with the promotion of contraceptive use (Masis and May 1991; May 1995), although the relative benefits and costs of this approach have not yet been determined.

The effectiveness of another indicated prevention strategy, the use of "aftercare" programs for women who have had FAS births, also needs more study. By maintaining contact with these women, aftercare programs may help in eliminating alcohol in breast milk, protecting against further FAS births, encouraging better health status, and coordinating alcohol and other drug abuse care across relevant health agencies. Aftercare studies could additionally evaluate such variables as job placement, education, housing, and legal matters (Klein and Zahnd 1997), as well as marital relations and emotional state. In addition, aftercare might be an effective FAS prevention strategy for new mothers identified as early-onset heavy drinkers, even when their babies do not show evidence of alcohol impairment. Self-help groups, such as Alcoholics Anonymous and Women for Sobriety, might effectively be involved in aftercare support for these women (Kaskutas 1996).

According to the IOM report (Stratton et al. 1996), indicated prevention can be promoted through intensive professional education (Bowen and Sammons 1988; Davis and Frost 1984; Little et al. 1981). Because pregnant women frequently delay obstetric care until the third trimester or delivery, the report recommends that any health care provider who encounters women who are abusing alcohol should consider brief intervention therapy, counseling regarding the risks of prenatal alcohol exposure, and (if appropriate) referral to more formal alcohol abuse treatment (Stratton et al. 1996). This type of approach has been termed "inreach" (Howard 1982, 1987), because health care providers are piggybacking preventive interventions on patient visits that have presumably been scheduled for other purposes.

For women who continue to abuse alcohol during pregnancy, comprehensive clinical treatment programs may be necessary (Finkelstein 1993; Jessup and Green 1987; Rosett and Weiner 1981). These programs generally include medical and obstetric care in addition to alcohol and other

drug abuse services, which in turn involve individual or group counseling, family therapy, referral to self-help groups, parenting skills training, and case management (Stratton et al. 1996), as well as information on the effects and risks of alcohol consumption. Changes in the environment of pregnant women may also be involved through the use of voluntary halfway houses or sheltered living and through changes in social networks (Namyniuk et al. 1997).

A number of communities have mandated court-ordered or involuntary participation in alcohol abuse treatment for heavily drinking pregnant women as a means of preventing FAS. These types of coercive programs have stimulated legal and ethical debates in the literature concerning the comparative rights of the pregnant woman, the fetus, and society at large (Chavkin and Breitbart 1997; Garcia 1993; May 1995; Peak and Del Papa 1993; Vanderveen 1989). However, there have been few descriptions, let alone studies, of this approach as a prevention strategy (Berkowitz et al. 1996*a*; Hughes et al. 1995; Loneck et al. 1997). Although important questions about the effectiveness of such programs remain unanswered, certain findings are encouraging. One study reported that women mandated for drug treatment by courts in California were more likely to comply with and complete alcohol and other drug abuse treatment (Berkowitz et al. 1996*b*). Similarly, another report found that coerced referrals for alcohol and other drug abuse, including Johnson-style, high-intensity family confrontations (a therapeutic technique in which members of the person's family confront him or her about the damage the drinking or other drug use has caused and the action they will take if treatment is refused), significantly increased the likelihood of completed treatment (Loneck et al. 1997). The authors therefore concluded that "to continue to routinely use low-intensity referrals for women is tantamount to withholding a more potent form of treatment" (Loneck et al. 1997, p. 43).

Conversely, critics of this point of view are concerned about the possible deterrent effect of court sanctions and coercive treatment referrals on pregnant women's participation in prenatal care settings where their alcohol abuse may be detected (Chavkin and Breitbart 1997; Peak and Del Papa 1993). To resolve the controversy, future evaluations would need to include not only women for whom treatment had been mandated but also heavily drinking pregnant women without mandated treatment, and to investigate changes in actual drinking behavior, not simply the completion of treatment.

International Considerations

With the exception of certain selected communities and particular racial/ethnic groups such as American Indians in the United States, most groups have been slow to promote aggressive prevention of FAS and to evaluate it carefully. This may be due, in part, to the fact that full-blown FAS occurs rarely and in specific subsets of the general population. The highest rates for FAS in the United States have been found in inner-city, low-socioeconomic areas (Abel 1995) and in certain high-risk American Indian communities (Duimstra et al. 1993; May 1991; Quaid et al. 1993; Robinson et al. 1987). In those American Indian communities where FAS has been found to be highly prevalent, prevention has been a strong community concern. In the past two decades, many American Indian communities have openly lent themselves to epidemiologic studies in their populations and have consequently provided valuable information that may be relevant to prevention in other populations (Masis and May 1991).

Recent National Institute on Alcohol Abuse and Alcoholism-supported pilot studies in the Republic of South Africa have shown patterns of FAS occurrence, maternal risk, and FAS characteristics that are similar to those documented in North American communities, except that the prevalence of FAS in certain South African communities is quite high (May et al. 1999*a*). For these studies, the researchers measured FAS prevalence by surveying the entire first-grade population in a South African community, which bypassed the difficulties of diagnosing FAS in newborns and infants. In South African populations, patterns of binge

drinking and heavy drinking that produce FAS tend to be associated with rapid community change, detribalization, rural-to-urban transitions, and progressions from traditional to modern (secular) culture (May et al. 1999*a*). These associations are similar to those seen in the United States (May 1991, 1995). In these changing social and cultural contexts, alcohol and other drug use begin to replace other activities as major forms of adaptation, coping, and recreation (May et al. 1999*b*). Moreover, the high rate of FAS found in selected areas of South Africa may well foreshadow increases in FAS in other parts of that country and in other developing societies throughout the world, where similar social changes are superimposed on groups with existing vulnerabilities and risk factors for FAS.

In Closing

Progress in the prevention of FAS will need to begin with research that establishes baseline information about the prevalence of FAS and identifies more precisely those women who are at highest risk of bearing an alcohol-affected child. Equally important, the effectiveness of different FAS prevention approaches must be determined through carefully controlled evaluation studies. Each of the levels of prevention (universal, selected, and indicated), as well as the specific modalities used within each, will need to be examined both in isolation and as part of comprehensive programs. Because FAS and other adverse effects of drinking during pregnancy are theoretically 100-percent preventable, it is vital to make every effort to achieve this goal.

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Economic and Health Services Perspectives

Economic research contributes to our understanding of alcohol consumption behavior and the prevention and treatment of alcohol-related problems in several ways. This chapter reviews three areas in which the tools of economic analysis have produced significant insights in recent years. First, economic researchers have analyzed the effects of beverage prices and taxation on alcohol consumption and on adverse consequences associated with alcohol use. Second, analyses of the costs and cost-effectiveness of treatment for alcohol use disorders have provided insight into the long-term costs and benefits of alternative approaches to alcoholism treatment. Finally, studies have incorporated economic techniques in estimating the overall magnitude of the burden placed on society by the misuse of alcoholic beverages.

Among the most traditional areas of economic research is demand analysis, which emphasizes the role of prices in determining how much of a particular good consumers will choose to purchase. Because changes in levels of alcohol consumption may have significant health effects, and because prices can be influenced by changes in tax policies, there is keen interest among researchers and policy makers to understand how changes in alcoholic beverage prices may affect alcohol consumption and alcohol-related problems.

The first section of this chapter reviews recent studies of the effects of alcoholic beverage prices and taxes on the consumption of alcohol and on adverse consequences of alcohol consumption, particularly traffic crash fatalities. There is a well-established consensus in the research literature that alcohol consumption responds to price or tax changes in the same way that most other goods do, which is that consumption declines in response to increases in price. However, estimates of the magnitude of the response—that is, of just how sensitive consumption may be to price or tax changes—exhibit a fairly wide range. Recent research has analyzed a variety of issues related to the effects of changes in alcoholic beverage prices or taxes, including possible interactions with demands for other goods and considerations that bear on the choice of appropriate tax rates. Recent studies that show particular promise have looked at how price or tax effects may vary across different groups of drinkers or different categories of drinking behavior.

Economic reasoning also has a central role in health services research. Health services research has been defined as studies of "the impact of the organization, financing, and management of health services on the quality, cost, access to and outcomes of care" (P.L. 101-321, Section 409). This research has assumed growing significance in the full range of issues pertaining to health care, including issues relating specifically to treatment of alcohol use disorders. Studies of the costs and cost-effectiveness of alcoholism

treatment are firmly within the mainstream tradition of health services research, and research developments in this area may find further application in other areas of health services research as well. Similarly, estimates of the economic costs of alcohol abuse—which incorporate the total costs of treating alcohol use disorders and the various medical consequences of alcohol consumption—have been at the forefront of research on the economic costs associated with particular diseases and conditions. Continued progress in these areas may contribute to health services research more broadly as well as to our understanding of issues pertaining specifically to alcohol.

The second section of the chapter reviews research on the costs and cost-effectiveness of alcohol treatment services. Some of the topics that fall under this heading, such as studies of the extent to which treatment for alcoholism leads to subsequent reductions in overall health care costs, are well established in the literature. Other topics have garnered the attention of researchers more recently, such as analyses of the relative cost-effectiveness of different lengths of stay for inpatient alcoholism treatment. These developments have been complemented by significant advances in the methodological tools available for measuring costs and conducting cost-effectiveness studies.

The final section of this chapter reviews the latest estimates of the economic costs of alcohol abuse. The most recent study of this issue reports that the overall estimated cost of alcohol abuse was $184.6 billion for 1998, and documents the portions of the overall cost attributed to various components, such as health care services, premature deaths, reductions in workers' productivity, and costs associated with alcohol-related crime and motor vehicle crashes. The latest study also examines how the burden of these costs was distributed across different segments of society. The study found that less than half of the costs were borne by alcohol abusers and members of their households; the majority of costs were borne by other parts of society. The nature and measurement of these costs, as well as limitations associated with these and similar estimates, are discussed in the third section of this chapter.

Effects of Changes in Alcohol Prices and Taxes

Alcohol research is carried out from a variety of disciplinary backgrounds and perspectives. From an economic perspective, alcoholic beverages are consumer goods, and therefore what is known about consumer behavior in general is likely to provide insights into alcohol consumption in particular. Perhaps the most basic prediction from the economic model of consumer behavior is that, other things being equal, consumer demand for a given good falls when the price of that good rises. A large body of research shows that this "law of demand" holds for alcoholic beverages. This means that excise taxes and other public policies that affect the price of alcohol can influence the demand for alcohol.

Because excessive consumption of alcohol has adverse consequences for health and safety, the consumer response to changes in alcoholic beverage prices is an especially important topic for investigation. One research approach, pioneered in the early 1980's (Cook 1981; Cook and Tauchen 1982), is to examine the direct relationships between alcohol tax rates and such public health outcomes as traffic fatalities and cirrhosis of the liver. An alternative approach is to examine the linkages through which an alcohol tax increase might reduce alcohol-related problems. Taking this approach leads to questions such as: How much does the consumption of alcoholic beverages fall when prices increase? Do persons who drink heavily respond as much to price changes as lighter drinkers do? Do college students and young adults respond as much to price changes as other adults do? The two approaches complement each other and provide a richer and more complete understanding of the nature of price and tax effects.

This section reviews recent economic research on the relationship between alcohol prices or taxes and alcohol consumption and related problems. Because the focus is on recent research findings, this section does not contain a comprehensive review of earlier research on these topics (such reviews can be found in Chaloupka 1993; Chaloupka et al. 1998; Cook and Moore 1993*a*; Kenkel and Manning 1996; Leung and Phelps 1993). In addition, although this section is limited to studies of alcohol prices and taxes, economic research has made other important contributions to the field of alcohol research. These include studies of the effect of advertising on alcohol demand (Saffer 1996); the geographic relationships between outlet density, alcohol availability, and alcohol-related problem rates (Gruenewald et al. 1996); the effect of raising legal drinking ages on traffic fatalities (Wagenaar 1993); the effects of macroeconomic conditions on alcohol consumption and drinking and driving (Ruhm 1995, 1996); and the relationship between alcohol consumption and earnings (French and Zarkin 1995; Kenkel and Ribar 1994; Mullahy and Sindelar 1993).

Public Policies and Alcohol Prices

Public policies can affect alcoholic beverage prices in several ways. One is that national, State, and local governments impose excise taxes on alcoholic beverages. An excise tax is based on the quantity of alcoholic beverage purchased, in contrast to a sales tax, which is based on the price of a purchased good. Current Federal excise tax rates are $0.58 per gallon for beer, between $1.07 and $3.40 per gallon for wine (depending on the type), and $13.50 per proof gallon of distilled spirits (a "proof gallon" is the amount of liquid that contains one-half gallon of pure alcohol). These rates translate into taxes of about 10 cents for each ounce of pure alcohol in beer, 7 cents in wine, and 21 cents in spirits.

The excise tax rate is an important factor, but not the only factor, in determining the price of alcoholic beverages. An important variable is the

extent to which increases in excise taxes are passed along to consumers as opposed to being absorbed by firms. For competitive industries with constant average costs of production, economists expect taxes to be fully passed through to consumers—a 1-cent tax increase would result in a 1-cent price increase. This may not apply to business sectors in which competition is limited, which some authors have suggested is the case for alcoholic beverages (Cook and Moore 1993*b*). In such industries, a 1-cent increase in taxes may increase prices, but by less than or more than 1 cent. In addition, an excise tax may be passed to customers at different rates depending upon where the purchase is made, as the price of the same beverage can differ widely within a given geographic area even though the tax rates are the same (Treno et al. 1993). It is difficult to quantify the relationship between taxes and prices for alcoholic beverages because, to date, little research has been conducted on the topic.

Some States exercise more direct influence over alcoholic beverage prices by maintaining monopoly control over the retail and wholesale sale of alcoholic beverages, usually covering distilled beverages and sometimes wine as well. Retail monopolies generally control sales for off-premise consumption, while wholesale monopoly operations often serve as the exclusive source of supply for outlets with on-premise consumption. Where State retailing monopolies exist, the prices of alcoholic beverages are under direct government control. Limited evidence suggests that alcoholic beverage prices have, on average, been about the same or only slightly higher in States with monopoly control (Nelson 1990) and that privatization has sometimes, but not always, resulted in lower prices (MacDonald 1986).

Public policies can also indirectly affect alcohol prices by making alcoholic beverage markets more or less competitive in other ways. For example, in the beer industry, 24 States have exclusive-territory mandates that require brewers to have only one distributor marketing their products within a given area (Sass and Saurman 1993). Researchers have estimated that these mandates raise retail beer prices, but they have found no resulting significant change in beer consumption. It may be that the existence of exclusive territories encourages dealer-level promotional activities (which tend to increase consumption) but also limits competition, which raises prices (and tends to decrease consumption). This example illustrates a more general point that a given policy can have multiple effects on alcoholic beverage markets.

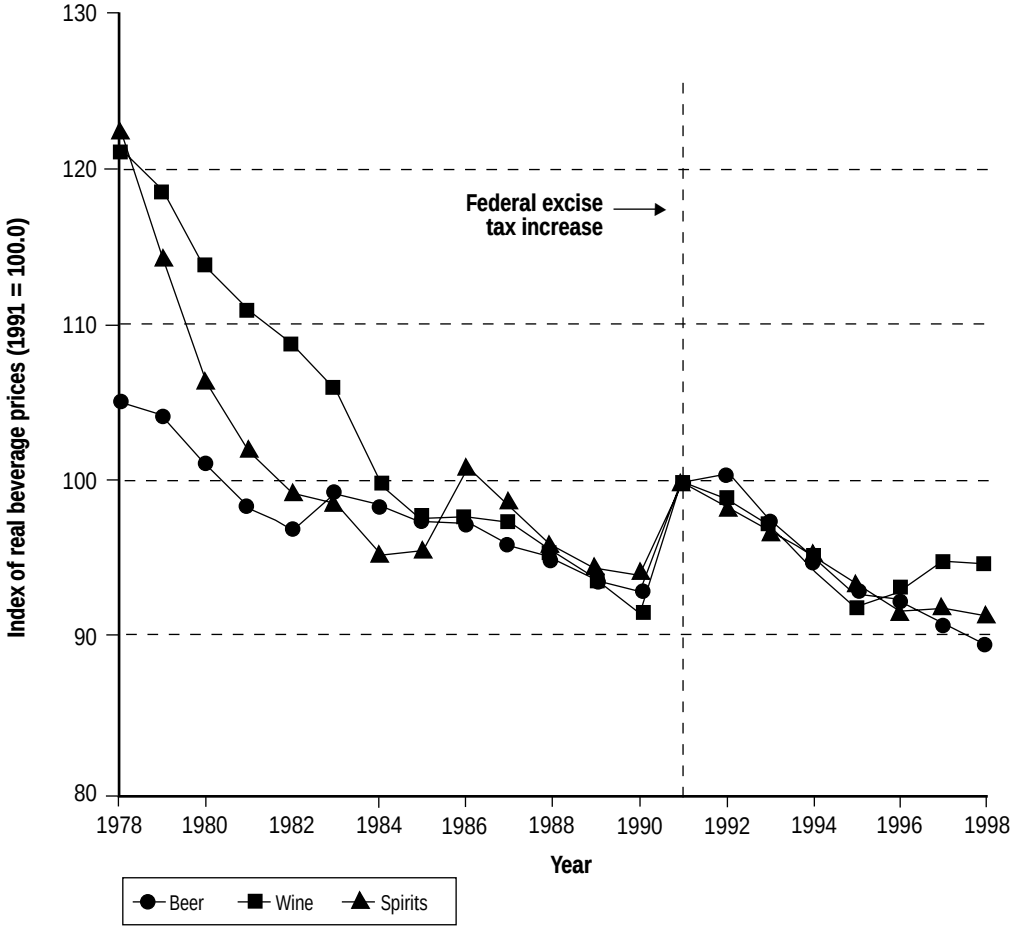
When evaluating alcohol price and tax policies, it is important to consider the context provided by private market forces, other public policies, and general economic conditions. For example, alcohol excise tax rates are not routinely increased to compensate for the effects of inflation. As a result, the "real" (that is, inflation-adjusted) tax rates have declined over most of the postwar period, except for the significant tax increase that took effect in 1991. This erosion of real tax rates has contributed to overall declines in real beverage prices over time (figure 1).

Alcohol Prices, Taxes, and Consumption

Although there is a consensus among researchers that higher alcoholic beverage prices and taxes result in less drinking and fewer drinking-related problems, the precise magnitude of consumer response to price or tax changes has been somewhat harder to determine. Economists measure consumer response to price changes by computing the "price elasticity," defined as the percentage change in the quantity demanded that results from a 1-percent change in price (see the box on page 344).

Price changes seem to affect the demand for beer less than they do the demands for wine and spirits. A 1993 review of 15 studies that used State and national consumption data found that every 1-percent increase in price translated to a 0.3-percent decrease in demand for beer, a 1.0-percent decrease in demand for wine, and a 1.5-percent decrease in demand for spirits (Leung and Phelps 1993). Thus, this study supported benchmark price elasticities of –0.3 for beer, –1.0 for wine, and –1.5 for spirits.

Figure 1: Inflation-adjusted alcoholic beverage prices, 1978–1998



Source: Calculated from Consumer Price Index data, not seasonally adjusted, for all items: beer, ale, and other malt beverages at home; distilled wine at home; and spirits at home. Data obtained from the Bureau of Labor Statistics web site (http://stats.bls.gov/sahome.html) December 1999.

A more recent study provided evidence that alcohol demand may not respond as much to price changes as previously thought (Nelson 1997). The researcher analyzed data from a number of sources, including quarterly data from 1974 through 1990 on per capita consumption, real income, real alcohol prices, and the age composition of the U.S. population. The study found relatively unresponsive price elasticities of –0.16 for beer, –0.58 for wine, and –0.39 for spirits, with an overall price elasticity of –0.52.

The analysis also provided an explanation of what might appear to be a puzzling feature of general trends in U.S. alcohol consumption and prices. The real prices of alcoholic beverages have been declining in the United States since 1978 (see figure 1), and per capita consumption of alcohol also has been declining over most of the same period (figure 2). These trends seem to contradict the law of demand, which predicts that falling prices will lead to higher consumption, other things being equal.

As Nelson's analysis revealed, however, other things were not equal; important determinants of alcohol consumption changed over the time period studied. Specifically, the study showed that the demographic shift to an older population—which consumes less alcohol—outweighed the impact of falling real prices. Other factors, such as a shift to healthier lifestyles, also may help explain the decrease in consumption, but the study was not designed to evaluate those factors.

Measuring Consumer Response to Price Changes

When the prices of goods rise or fall, the quantity of goods that consumers choose to purchase tends to change in response. Economists estimate the "price elasticity of demand" to measure consumers' responsiveness to changes in prices. Estimates are computed with the following formula:

$$\text{Price elasticity} = \frac{\%\text{ change in quantity demanded (+ or –)}}{\text{change in price (+ or –)}}$$

Example: A 5% price drop leads to a 10% increase in quantity demanded: $\frac{+10\%}{-5\%} = -2$

Some features of elasticity measures include the following:

- Price elasticities are negative for almost all goods, as consumers tend to choose to purchase greater quantities of goods at lower prices and fewer at higher prices.
- Elasticities of less than –1.0 indicate that demand is relatively responsive to changes in price (also called "elastic"). This is illustrated in the example to the left.
- Elasticities in the range between –1.0 and zero indicate that demand is relatively unresponsive (also called "inelastic"). For example, if a price drops 5 percent and the quantity demanded increases only 2 percent, the price elasticity is –0.4.

Demand for Alcohol by Youths and Young Adults

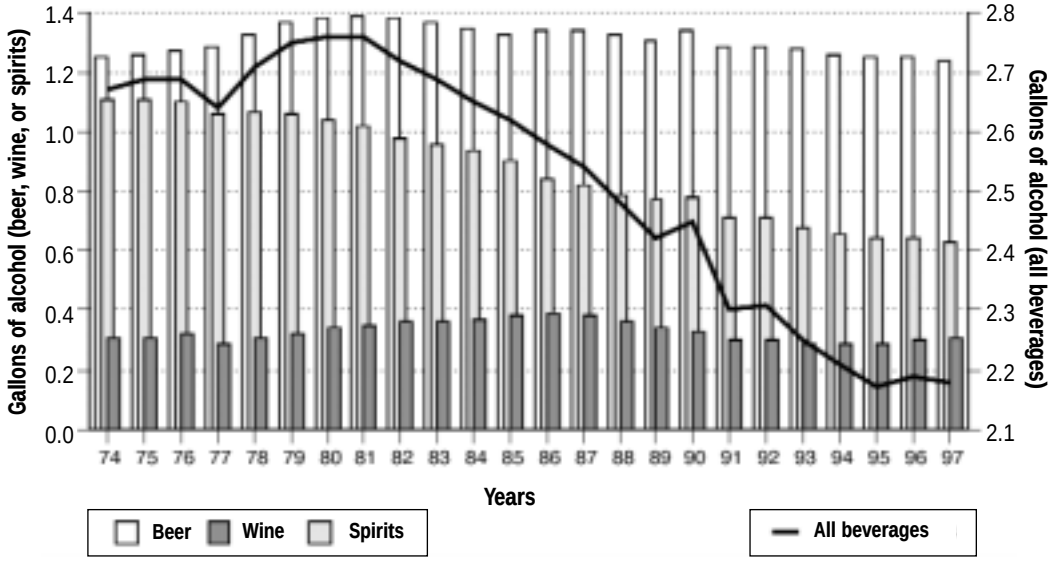
Some important questions, such as how subgroups in a population differ in terms of their responses to price changes, cannot easily be addressed using State- or national-level data that reflect the drinking behavior of the population as a whole. A number of recent studies have used individual-level data to focus on alcohol demand by youths and young adults, who are considered a group at particularly high risk for alcohol problems.

A recent study used survey data to explore the determinants of alcoholic beverage demand among young adults (Grossman et al. 1998). This study featured several innovations. First, it followed the same individuals over time using a "panel" data set formed from the national Monitoring the Future (MTF) Study of high school seniors (MTF surveys are widely used to track trends in adolescent substance use and abuse). Starting with the class of 1976, a subset of respondents was selected for follow-up, thus creating the MTF panels. For this study, the researchers used the MTF panels from 1976 through 1985 to create a sample of more than 7,000 individual respondents with an average of three observations per respondent.

Second, this study made a conceptual refinement by testing an innovative theory of the demand for addictive goods (Becker and Murphy 1988). Previous research had applied economic demand models that account for habit formation by exploring past consumption of alcohol as a possible determinant—through acquired taste or addiction—of current consumption (see, for example, Andrikopoulos et al. 1997). The Becker and Murphy theory of addiction takes this line of reasoning one step further by positing that consumers may anticipate that their current use of alcohol will influence their future demand for it. If so, expected future consumption is also a possible determinant of current alcohol demand, and factors that can be anticipated to affect future consumption also have an impact on current consumption choices. The relevant policy implication of this theory is that long-run demand for addictive goods is actually more responsive to price than is short-run demand. (For applications of this theory to the study of demand for cigarettes, see Becker et al. 1994; Chaloupka 1991; Keeler et al. 1993.)

The study results did support the implication that alcohol demand responds more to price in the long run than it does in the short run (Grossman et al. 1998). The analysis yielded long-run elasticities ranging from –0.26 to –1.25, which were a little more than 1.5 times larger (in absolute magnitude) than the short-run elasticities (which ranged from –0.18 to –0.86). In addition

Figure 2: Per capita alcohol consumption by beverage type, United States, 1974–1997



Source: Nelson 1997. Reprinted with permission from *Empirical Economics*, Vol. 22, pp. 83–102, 1997. Copyright 1997, Springer-Verlag GmbH & Co., Heidelberg, Germany.

to supporting the addiction theory, these results suggested that raising alcohol prices would be an effective policy to reduce alcohol consumption among youths.

In contrast, a recent study reported that beer taxes have a relatively small and statistically insignificant effect on teen drinking (Dee 1999). Using a limited set of variables from the MTF Study for 1977 through 1992, the researcher examined the effects of beer taxes and minimum legal drinking age laws on the prevalence of teen drinking in three categories (1 or more drinks in the past month, 10 or more drinks in the past month, 5 or more drinks in a row in the past 2 weeks). Dee hypothesized that there might be unobserved, State-specific factors that affect teenagers' alcohol consumption (such as shared cultural attitudes toward drinking). To explore this hypothesis, the study estimated the effects of within-State variation in beer tax rates on consumption. This approach contrasts with most other studies, which have relied mainly on cross-State variation in taxes or prices to identify the effects of these variables on consumption. The results suggested that raising the legal drinking age above 18 significantly reduced the number of high school seniors in each drinking category. However, the within-State comparisons found beer tax rates to have no significant effect in reducing these drinking prevalence rates. The contrast between these findings and the accumulated weight of previous research indicate a clear need for additional studies to clarify how taxes and other factors affect various patterns of drinking among different groups.

College students as a group are at particularly high risk for alcohol-related problems. An analysis using data from the 1993 College Alcohol Study, a nationally representative survey of more than 17,000 college students at 140 4-year U.S. colleges and universities, reported that almost 40 percent of female college students and about 50 percent of male college students reported binge drinking (defined in that study as drinking four or more drinks on a single occasion for females and five or more drinks for males) (Chaloupka and Wechsler 1996). To estimate alcohol demand functions for this high-risk subpopulation, the researchers merged the college drinking data with measures of beer prices and an index of drunk driving laws prevailing in the locations of the colleges.

The results suggested that alcohol prices were a less salient determinant of the drinking behavior of college students than they were in other population groups. Male college students' drinking was virtually unresponsive to price. Higher prices were estimated to have a negative and statistically significant impact on the drinking of underage female college students, but the effect was still relatively small.

The researchers did find, however, that more severe drunk driving penalties tended to reduce both drinking and binge drinking. These effects were found among underage and older students, both male and female. In addition, they found that more alcohol outlets near campus, higher fraternity and sorority membership levels, and a higher percentage of students living on campus were associated with higher levels of drinking and binge drinking. It should be noted, however, that the researchers were unable to determine whether these environmental variables played a causal role in drinking decisions, or whether college students who were predisposed to heavy drinking sorted themselves into these types of college environments. Clarifying the direction of causality in this relationship is an important goal for future research.

International Research on Alcohol Price and Consumption

Several studies, using data from other countries, shed additional light on the effect of prices on alcohol consumption. Using an approach similar to the 1997 study by Nelson, another research group analyzed annual data from Australia, Canada, Finland, New Zealand, Norway, Sweden, and the United Kingdom (Clements et al. 1997). Most data were from the mid-1950's to the mid-1980's, though the periods of analysis varied from country to country. Averaging the results for all seven countries, the researchers found price elasticities of –0.35 for beer, –0.68 for wine, and –0.98 for spirits. In every country, beer demand was the least responsive to price changes. In a reversal of the U.S. findings just mentioned, this study found that wine demand in these countries was less responsive to price changes than was spirits demand.

Another 1997 study employed a similar approach with data from Ontario, Canada, from 1958 through 1987, but incorporated into the analysis the hypothesis that consumption is influenced not only by such economic factors as price and income, but also by habit formation (Andrikopoulos et al. 1997). Thus, the study examined past consumption levels of alcoholic beverages as determinants of current consumption. The analysis, which separated domestic and imported alcoholic beverages, estimated price elasticities ranging from –0.34 for imported spirits to –1.02 for imported beer.

Broadly speaking, the results from the international literature on price elasticities are consistent with the results from the domestic literature. Price elasticities for alcoholic beverages are generally negative, meaning that increases in price lead to decreases in the amount consumed. Recent studies have found these elasticities to be mostly in the "relatively unresponsive" range of –1.0 to zero. Consumption of distilled spirits appears to be more responsive to price changes than is wine consumption, which in turn is more responsive than is beer consumption.

Alcohol Taxes and Traffic Fatalities

Research indicates that higher beverage taxes affect not only alcohol consumption but also various alcohol-related problems, the most studied of which is the effect of beer taxes on traffic fatalities. For higher taxes to affect traffic fatalities, it is assumed that the taxes lead to reduced consumption, which in turn leads to fewer traffic fatalities. However, most studies have examined the direct relationship between taxes and traffic fatalities without examining the role of consumption as an intervening variable. Although the previous discussion suggests that overall demand for alcohol is only moderately responsive to price changes, a number of studies have found that higher alcohol taxes are linked to lower traffic fatality rates.

Using U.S. data from 1982 through 1988, one study confirmed earlier findings that higher beer taxes are associated with lower rates of traffic fatalities (Ruhm 1996). In estimating the

determinants of total vehicle fatalities per capita, the researcher found that for every 1-percent increase in the price of beer, the traffic fatality rate declined by nearly the same proportion, or 0.9 percent (this translates into a "fatality price elasticity" of –0.9). When the researcher performed a second analysis using fatalities per total vehicle miles driven, he found nearly identical results.

Moreover, the study showed that rates for nighttime fatalities and for people aged 18 through 20 were even more responsive to an increase in beer prices in that a 1-percent increase in price translated into a 1.4-percent decrease in each of these categories of fatalities (a fatality price elasticity of –1.4). On the basis of these results, the researcher calculated that increasing the Federal excise tax on beer in 1988 to the inflation-adjusted equivalent of its value in 1975 would have saved between 3,300 and 3,700 lives annually (Ruhm 1996).

Similar results have been found in previous studies. In an early research review that focused on drinking drivers under age 22 who were killed in vehicle crashes, the researcher reported fatality price elasticities ranging from –0.7 to –1.3 (Phelps 1988). More recently, a 1993 review of the literature reported overall fatality price elasticities in the range of –0.5 to –1.0, with a higher range among young adults of between –0.7 to –1.6 (Kenkel 1993). These studies suggest that a tax increase may be a useful tool to reduce traffic fatalities, particularly among youths and young adults.

A recent study (Dee 1999) contended that the reported effects of beer taxes on traffic fatality rates (for example, Ruhm 1996) were implausibly large and suggested that changes in fatality rates that have been attributed to beer taxes might be linked more strongly with other factors that were omitted from the analyses. Dee found no statistically significant effects of beer taxes on youth fatality rates when the analysis included State-specific time-trend variables to account for the effects of unobserved, State-specific factors. The researcher regarded these results as somewhat inconclusive because the trend variables were highly correlated with changes in real beer tax rates over time. However, using an approach similar to that used in previous studies, Dee estimated that the effect of beer taxes on daytime fatalities was somewhat smaller than the effect on nighttime fatalities, but still statistically significant and of substantial magnitude. The researcher found this result implausible, because alcohol is far more likely to be involved in nighttime fatalities than daytime fatalities, and concluded that taxes may be less effective at reducing traffic fatalities than has been suggested by a number of published studies. Further research clearly is needed to reconcile the apparent discrepancies between the recent findings of Dee (1999) and the substantial body of prior research that has found significant effects of prices or taxes on youth fatality rates.

In addition to investigating price effects among youths, researchers have studied price effects in other subgroups with a high risk of traffic crashes: those who engage in binge drinking and those who engage in regular, heavy drinking. One such study investigated the potential effects of price on binge drinking (defined in the study as consuming five or more drinks on one occasion in the past month) (Sloan et al. 1995). The study also investigated several other factors that might influence decisions regarding drinking and driving, including insurance rules, tort liability (rules governing civil suits for injuries or damages), and criminal sanctions. Findings from the study, based on a random sample of 49,199 individuals surveyed between 1984 and 1990, suggested that a 10-percent increase in the price of alcoholic beverages would decrease the number of binge-drinking episodes per month by approximately 8 percent. The research also indicated that liability and insurance rules were more effective in reducing binge drinking than were criminal sanctions. With any of the factors under study, most of the deterrent effects appeared to influence the decision to binge; the results suggested that once individuals decide to binge, policies probably have little influence on the decision to drive after drinking.

Another 1995 study found, however, that persons who drank extremely heavily were unresponsive to price increases (Manning et al. 1995). While this study was concerned only with the effects of price on consumption and did not go on to analyze the effects on subsequent problems, such as traffic crashes, the findings implied that among the very heaviest drinkers, the effects of tax increases on alcohol consumption would be limited. Presumably this would translate into a limited effect on traffic crashes among this group, although tax increases could still reduce drunk driving incidents occurring among those who are not extremely heavy drinkers.

Research on the effects of price or tax changes shows considerable variation in the magnitude of estimated effects. Overall, the weight of evidence indicates that prices have modest effects on overall consumption and somewhat more substantial effects on traffic crash fatality rates. It is plausible, although by no means established, that small effects on consumption could have substantial effects on outcomes like traffic fatalities. One way this could be true is if higher prices tend to reduce the riskiest drinking behaviors more than they reduce overall alcohol consumption. If, for example, higher prices reduce the number of drinks consumed on a given occasion of heavy drinking, the effect on the of traffic crashes could be significant, as shown by Phelps (1988), who found that the relative risk of traffic crashes increased sharply with the sixth drink on a given occasion. Clarifying the nature of price effects on different aspects of consumption—such as frequency of drinking and quantity per occasion—and on important health-related outcomes remains a critical task for future research.

Alcohol Demand and Marijuana Demand

The idea that tax increases might be used to reduce alcohol use by raising beverage prices raises an important, related concern. One possible, but unintended, consequence of such a policy may be that consumers might decide to use less alcohol but more marijuana in response to increased beverage prices. Two recent studies have examined this issue, with contrasting results.

In economic parlance, this debate centers on whether alcohol and marijuana are "substitutes" for each other or "complements." When two goods are substitutes, an increase in the price of one good causes a shift in consumption and increase in demand for the other good. When two goods are complements, an increase in the price of one good causes a drop in consumer demand for both goods. The goods are complements in the sense that they tend to be used together, as with gin and tonic water. If gin suddenly becomes more expensive, consumers will choose to drink fewer gin and tonics, resulting in a lower demand for both gin and tonic water. To determine whether a particular pair of goods are substitutes, complements, or unrelated, economists estimate a "cross-price elasticity," which is an estimate of how the demand for one good is affected by a change in the price of another good. A positive cross-price elasticity indicates substitution; a negative cross-price elasticity indicates complementarity.

One study used data from the 1984 National Longitudinal Survey of Youth and found that alcohol and marijuana were economic complements (Pacula 1998). An increase in the beer tax was estimated to reduce the demand for marijuana. This research employed a sample of about 8,000 individual respondents, with an average age of about 22.5 years at the time of the interview in 1984. Consumption had been measured for the 30 days preceding the interview, in terms of the number of drinks of any alcoholic beverages and the number of times marijuana was smoked. The investigator merged the individual-level survey data with a set of variables indicating the prices of alcoholic beverages and marijuana as well as the legal environment the young adults faced in their geographic areas of residence. The study's estimates suggested that doubling the beer tax would reduce the quantity of alcohol consumed by 8.1 percent and reduce the quantity of marijuana consumed by 13.2 percent. This finding should be viewed with caution, however, because an analysis of this sort can arrive at a false relationship between beer taxes and marijuana use if States with lower beer taxes also have more tolerant social attitudes toward substance abuse.

Another qualification was the finding that higher marijuana prices reduced marijuana consumption but did not significantly affect alcohol demand. The evidence on whether alcohol and marijuana are economic complements was thus somewhat mixed in this study, because complementarity implies that the demand for both goods should fall when the price of either good is increased.

In contrast, another study found evidence that alcohol and marijuana were substitutes (Chaloupka and Laixuthai 1997). This study examined the effects of beer prices and marijuana prices on the demand for alcohol among young adults. The first part of the analysis used measures of drinking and heavy drinking among high school seniors who participated in the 1982 and 1989 waves of the MTF Study. Consistent with previous studies, the results showed that raising both the price of beer and the minimum legal drinking age (to 21) reduced youth demand for alcohol. Moreover, when the 1982 and 1989 samples were pooled, the results suggested that marijuana decriminalization reduced youth drinking. Under decriminalization, youths face lower potential costs of marijuana use, so the pattern found in this study suggested that youths substitute marijuana and use less alcohol in States where marijuana is decriminalized. In addition, in analyzing the 1989 data, the researchers were able to include an estimate of the price of marijuana, and found that higher marijuana prices increased alcohol demand. This finding is also consistent with the conclusion that the two substances are substitutes.

Given the conflicting findings between these two studies, one of which found alcohol and marijuana to be complements (Pacula 1998) and one of which found alcohol and marijuana to be substitutes (Chaloupka and Laixuthai 1997), further research is needed to clarify the nature of the relationship between the demands for alcoholic beverages and marijuana.

Benefits and Costs of Taxation

The bulk of research evidence shows that higher alcohol taxes or prices lead to reductions in alcohol consumption and in some of the adverse consequences of alcohol abuse. But how heavily should alcoholic beverages be taxed? Studies of "optimal taxation" provide a framework for answering this question by balancing the benefits of alcohol taxation with the costs that alcohol taxes impose on moderate drinkers and on alcoholic beverage producers.

Several studies have concluded that substantial increases in alcohol taxes would yield social benefits that exceed their costs (Manning et al. 1989, 1991; Pogue and Sgontz 1989). The social benefits of alcohol taxation flow from reductions in alcohol-related health problems and other adverse consequences of drinking. Economists distinguish alcohol-related consequences that individual drinkers create for themselves, termed the "private costs" of alcohol abuse, from consequences that their drinking imposes on others, termed the "external costs" of alcohol abuse. Important components of the external costs are the thousands of nondrinkers killed by drunk drivers each year and the extra health care costs attributable to drinking that heavily drinking persons do not pay.

Some studies have estimated that alcohol tax rates in the mid- to late 1980's were about one-half the amount necessary to cover the external costs of excessive drinking (Manning et al. 1989, 1991). Other researchers have concluded that during the same period, the benefits of higher taxes would have substantially exceeded the costs and that optimal taxes on alcoholic beverages were probably much higher than the rates that were then in force (Kenkel 1996; Pogue and Sgontz 1989). By "optimal tax," these researchers mean tax rates that would balance the reduced social costs of heavy drinking with the losses in enjoyment experienced by more moderate drinkers.

In contrast, another study concluded that alcohol tax levels were too high (Heien 1995–96). The researcher identified several factors that helped to explain why the conclusion differed from those of previous studies. One was that the study used data from 1993, which already showed the effects of higher tax rates because of the 1991 increase in

Federal excise tax rates. In addition, the sharp decline in alcohol-related traffic fatalities in the late 1980's and early 1990's reduced the potential effects of higher taxes and other policy changes.

This study also differed from other studies of the optimal taxation of alcoholic beverages in an important way. Based on an unpublished report, the analysis incorporated the assumption that drinkers have lower health care costs than do nondrinkers. As a result, the study reported that drinkers imposed, at most, zero net health care costs on others, and that drinkers may actually have generated an "external benefit" for nondrinkers by subsidizing their health insurance premiums by as much as $21.6 billion. Under this framework, increased alcohol tax rates would reduce moderate drinking and thereby reduce these external benefits. This factor, which was not considered in previous studies, could be of considerable significance if moderate drinkers are particularly responsive to price changes, as Manning and colleagues (1995) found.

However, assessing the net effects of alcohol consumption on health is difficult, and assessments may vary over the life span (Dufour 1996)—complexities that were not considered in the Heien study. For example, low-level alcohol consumption may generate net health benefits for some people, such as postmenopausal women with risk factors for heart disease. However, even low levels of consumption may pose risks to others, such as teenagers, for whom alcohol-related traffic crashes are a leading cause of death (Dufour 1996). Predicting the health impact of an increase in alcohol taxes requires assessing the health effects of all the changes in drinking behaviors that result from the tax change.

Further research is needed to explore the differences between existing studies (see the analyses of findings presented by Grossman et al. 1995; Heien 1995) and to incorporate new findings into the calculations. For example, none of the studies mentioned in this section measured the potential benefits alcohol taxation may create by reducing violent behavior (Cook and Moore 1993*a*).

Another important issue is how the benefits and costs of alcohol taxation are distributed across the population. Distributional issues of this sort are inextricably related to subjective notions of fairness. One often used means of assessing the fairness of a particular tax is to consider the extent to which the burden of the tax falls disproportionately on lower income members of society. A tax that consumes a larger share of the income of poorer households is termed "regressive," while a tax that consumes an increasing fraction of income as income rises is considered "progressive." Determining the degree of regressivity or progressivity of a given tax is technically quite complex, depending on the consumption patterns of households at different income levels and on the "incidence" of the tax, that is, on who actually bears the burden of the tax. The incidence may fall on individuals other than those from whom the tax is actually collected. Often the burden of an excise tax is shared among consumers, sellers, and those whose incomes derive from businesses related to the taxed good.

A study by the Congressional Budget Office (Sammartino 1990) examined the distributional effects of changes in Federal excise taxes on alcoholic beverages. The study found that, across households, expenditures on alcoholic beverages increased as income increased, but at a slower rate. As a result, lower income households paid less in alcohol excise taxes than did higher income households on average, but the taxes nevertheless consumed a larger proportion of income in lower income households. Adjusting for some of the broader effects of excise tax changes, the study concluded that the regressivity of alcohol excise tax increases would be reduced by the changes in income tax liability and Social Security benefits that were assumed to result from the excise tax changes. Because a family's income in a particular year may not reflect its economic circumstances very accurately, the study also considered the effects of excise taxes as a share of total household expenditures instead of income. With this approach, the apparent regressivity of alcoholic beverage excise taxes was reduced but not completely eliminated. This finding was reinforced by a more recent study (Lyon and

Schwab 1995), which found that alcohol taxes were still regressive, but slightly less so, when measured with respect to lifetime income instead of current income.

Another issue related to tax fairness concerns employment. The argument is sometimes raised that alcohol tax increases will hurt workers whose livelihoods depend on the production and sale of alcoholic beverages. However, the overall level of employment in the United States is determined by macroeconomic conditions, not adjustments in the tax rates on specific industries. When the national economy is not in a recession or depression, workers laid off or not hired by industries affected by an alcohol tax increase would find employment in other sectors of the economy. The distinction between job losses and worker displacement is crucial: a tax increase could cause a permanent job loss in the alcohol industry, but research on labor economics suggests that the displaced worker almost certainly would find employment elsewhere eventually. Worker displacement remains costly during the spell of unemployment as well as in the long run because displaced workers appear to earn less on their new jobs (Jacobson et al. 1993; Ruhm 1991). Following the standard methodology of cost-benefit analysis, these transitional costs should be included as an extra cost of increasing alcohol taxes, but most or all of the employment losses in the alcohol industry will eventually be offset by employment gains in other sectors of the economy (Kenkel and Manning 1996).

In Closing

Ongoing research is increasing knowledge of the effects of changes in alcohol prices or taxes on the consumption of alcohol and on alcohol-related health outcomes. Recent studies have examined economic and other determinants of the level of alcohol consumption and have confirmed earlier findings that beer, wine, and spirits consumption do respond to changes in price. There is disagreement about how large such effects may be, however. The weight of evidence suggests that the effects are relatively modest, with a 1-percent increase in price expected to lead to less than a 1-percent decrease in consumption.

Other studies have addressed whether higher alcohol prices or taxes reduce drunk driving and alcohol-related traffic fatalities. Recent research confirms that higher taxes can contribute to these public health goals. New studies have introduced important improvements in methodology and data collection. Future research must reconcile the magnitudes of the estimated effects of taxes on consumption with the larger estimated effects of taxes on traffic fatalities.

Young adults are at special risk for alcohol-related problems. While there is evidence that increases in alcohol prices or taxes reduce youth drinking, one study found that this effect may not hold for binge drinking among college students. Further research is needed to clarify whether measures to reduce alcohol consumption might lead to changes—either increases or decreases—in marijuana consumption.

Finally, the benefits and costs of alcohol taxation are being researched from a societal perspective. Recent studies disagree about the level of alcohol taxation that would best balance benefits and costs. The economic approach would provide a useful framework for further discussion and research on this topic.

Continued progress in economic studies of the demand for alcoholic beverages will provide insights into how changes in prices or taxes may affect different groups of drinkers or different kinds of drinking behaviors. Important challenges remain, however, such as the need for improvements in data, including better measurement of the prices of alcoholic beverages. Other challenges are methodological, such as the need to separate the actual effects of alcohol taxes on behavior from spurious associations between tax and price policies and social attitudes toward drinking. With the now-substantial base of knowledge and improved methods of data collection and statistical analysis, future studies

will provide new insights into the connections among alcoholic beverage taxes, prices, and consumption and related consequences.

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Cost Research on Alcoholism Treatment

Although relatively little research has been conducted on the cost of services for alcohol treatment, this field has witnessed important developments in recent years. Some of these developments have grown from enduring interest in certain research questions. One central question has been whether individuals who undergo alcoholism treatment have lower health care expenditures afterwards. Another is whether some treatment settings deliver better outcomes for comparable costs—or comparable outcomes for lower costs—and thus are more cost-effective.

Other developments have arisen as questions not previously addressed have begun to receive attention. One line of inquiry is whether shorter or longer periods of inpatient treatment are more cost-effective. Another is whether treatment cost savings in the short term might lead to a higher probability of relapse, greater readmission to later treatment, and, consequently, greater long-term treatment costs. Above all, the last few years have brought improvements in the methodological tools for analyzing the costs of alcoholism treatment. These improvements hold considerable promise for the further development of the field.

Past Research

Earlier studies on the cost of alcoholism treatment have been summarized by Jones and Vischi (1979), Annis (1986), Holder (1987), Holder et al. (1991), and Finney et al. (1996). The National Institute on Alcohol Abuse and Alcoholism's (NIAAA) national plan for health services research also contains a review of this literature, along with a consensus statement reflecting the future research priorities of the National Advisory Council on Alcohol Abuse and Alcoholism (1997). This literature contains several general themes. One of the oldest is whether treatment for alcoholism leads to reductions in general health care costs, and, if so, whether such reductions would be sufficient to cover the costs of the alcoholism treatment. A net reduction in total health care costs, that is, a decrease in total costs after adjustment for alcohol treatment costs, is referred to as a cost offset. Early studies showed that cost offsets following alcoholism treatment could be demonstrated (Jones and Vischi 1979). Later literature (Holder 1987) continued to support this finding, while also showing that (1) cost offsets can be better studied if longer periods (greater than 1 year) of pretreatment health care costs are examined; (2) people with alcoholism (and their family members) are heavier users of health care services than are nonalcoholic people of the same age and gender; and (3) prior to entering treatment, general medical care costs for those who eventually seek treatment tend to rise (the "ramp-up" effect).

Another early concern raised in the literature on treatment cost was whether there are more effective and cost-effective alternatives to inpatient alcoholism treatment. A review of this literature published in 1986 concluded that (1) inpatient alcoholism programs lasting 4 weeks to a few months showed no higher success rates than did periods of brief hospitalization for a few days; (2) some patients could be safely detoxified without pharmacotherapy and in non-hospital-based environments; (3) partial hospitalization programs ("day hospitalization" with no overnight stays) had results equal or superior to inpatient hospitalization, at one-half to one-third the cost; and (4) in some populations, outpatient programs produced results comparable to those of inpatient programs (Annis 1986).

A recent analysis reviewed 14 additional studies comparing inpatient with outpatient treatment (Finney et al. 1996). Of these, seven studies found no significant differences in treatment outcomes between inpatient and outpatient regimens, five found effects favoring inpatient treatment, and two found effects favoring outpatient treatment. In both of the studies

favoring outpatient treatment, the regimen was a day hospitalization program, an intensive form of outpatient treatment. When the researchers investigated the intensity of therapy across programs, they found that the most intensive therapy almost always produced better treatment results. Because outpatient treatment is substantially less expensive than inpatient treatment, the authors offered the following policy recommendations: "(a) Encourage outpatient treatment for most individuals with sufficient social resources and no serious medical/psychiatric impairment and (b) promote the development and availability of less costly nonmedical residential and intensive outpatient treatment options" (Finney et al. 1996, p. 1793).

Although outpatient settings may be cost-effective for many patients, they may not be appropriate for all patients. The investigators in the study just described (Finney et al. 1996), along with other commentators (Schuckit 1998), have strongly recommended that inpatient treatment be retained as an option available for some patients, particularly those whose conditions are highly resistant to treatment, those with few financial resources, those whose environments may not be conducive to recovery, and those with serious, coexisting medical or psychiatric conditions.

Alcoholism treatment involves a diverse set of services. Researchers have identified some 43 current modalities, or therapeutic approaches, that have been discussed in the alcoholism research literature (Miller et al. 1995). Examples include motivational counseling, marital and family therapy, cognitive-behavioral therapy, skills training, aversion therapy, and psychotherapy. (It should be noted that treatment for alcoholism often entails application of several such modalities within a single treatment program.)

An obvious question is whether any of these modalities can be shown to be more cost-effective than the others. One research team opened up this line of inquiry with a review of 33 treatment modalities for which there had been at least one published clinical trial (Holder et al. 1991). In the review, each modality was rated for the degree of evidence of success, the strength of that evidence, and the cost of each treatment. The general finding was that the modalities with the most evidence of effectiveness were not the most expensive; meanwhile, some of the modalities with the least evidence of effectiveness also had the highest costs. This discomfitting conclusion was accompanied by the observation that the range of treatment costs across settings was enormous, with a high of $585 per day for hospital-based care and a low of $6 per visit at social model, nonresidential programs.

In reviewing these findings, it is important to note the surrounding context of cost studies in health care generally. As one investigative group noted, the number of such studies across all health care fields increased significantly between 1979 and 1990 (Elixhauser et al. 1993). However, the methodological standards for conducting either cost-effectiveness analyses or cost-benefit analyses varied so much from study to study that meaningful comparisons among the costs or benefits documented could not be made (Elixhauser et al. 1993). Hence, progress toward increased knowledge was inhibited by a lack of standardized techniques for measuring health treatment costs. Recent developments, discussed later in this section, have been aimed at reducing this problem.

Recent Studies

Recent studies of alcoholism treatment costs can be divided into two general categories: those that continue the study of issues raised in the earlier literature, and those that examine new research questions that have emerged from earlier work. For convenience, in the next sections the research is divided into studies of "continued issues" and studies of "new issues."

Continued Issues: Cost-Effectiveness of Different Treatment Modalities

A good example of the study of a continued issue is a 1996 reanalysis of the cost-effectiveness literature (Finney and Monahan 1996), a contribution explicitly labeled as a "second approximation" in response to the "first approximation" literature review offered in 1991 (Holder et al.

1991). For the later study, investigators reanalyzed 142 of the 177 studies from the original study, excluding only those studies that were not available in English, were duplicate reports, had unclear treatment modalities, or did not include a comparison group. They added 3 treatment modalities to the original classification scheme, bringing the total to 36, and revised the procedure for assessing outcomes by developing a mathematical formula, or "effectiveness index," that rated the strength of each study's findings on the basis of the research methods used.

Using this refined procedure, the authors of the 1996 review confirmed some of the findings of the original review. In both, some treatment modalities appeared to be effective, such as social skills training, the community reinforcement approach, behavioral marital therapy, and stress management training, whereas others did not, such as residential milieu treatment and general counseling. On the other hand, several treatment modalities received effectiveness ratings under the revised index that were quite different from those received in the original analysis. Brief motivational counseling, self-control training, and use of oral disulfiram (a drug that creates an aversive reaction to alcohol), for example, were rated significantly lower by the newer index.

Overall, the range of effectiveness ratings across all 36 modalities studied was reduced in the newer review. In its main finding, the reanalysis did not show a relationship between effectiveness and cost. When only those 26 modalities that had been documented by three or more studies were included, greater cost was related to lower effectiveness, but this relationship was not statistically significant.

Later research took the next logical step, which was to examine the costs of specific treatment modalities. In one recent study, investigators calculated the costs for each of the three treatments compared in a project called Matching Alcohol Treatments To Client Heterogeneity (Project MATCH) (Cisler et al. 1998). Project MATCH was an 8-year, multisite clinical trial sponsored by NIAAA. The trial tested the hypothesis that patients who were appropriately matched to treatments, based on characteristics of both the patient and the therapy, would have better outcomes than those who were unmatched or mismatched. Specifically, Project MATCH investigated three behavioral treatments: cognitive-behavioral therapy, motivational enhancement therapy, and 12-step facilitation (Project MATCH Research Group 1997).

As it turned out, each of the therapies produced generally comparable treatment outcomes in the Project MATCH trial. Therefore, the question was raised as to whether any of these equally effective treatments could be offered for a lower cost. Findings showed that average per-patient costs for motivational enhancement therapy were the lowest, at $537, compared with $904 for cognitive-behavioral therapy and $956 for 12-step facilitation. It is important to note, however, that the number of patient contact hours differed across therapies: only 4 hours for motivational enhancement therapy, compared with 12 hours for both 12-step facilitation and cognitive-behavioral therapy. When costs were computed per hour of patient contact rather than per patient, motivational enhancement therapy was actually more expensive ($134 per contact hour) than either cognitive-behavioral therapy ($75 per contact hour) or 12-step facilitation ($80 per contact hour). Thus, the therapy that appeared most expensive—12-step facilitation—was actually least expensive per contact hour, and the therapy that appeared least expensive—motivational enhancement therapy—was actually the most expensive per contact hour.

Another study compared treatment costs over a 3-year period for people with alcoholism who chose to attend Alcoholics Anonymous (AA) with costs for those who sought help from a professional outpatient alcoholism treatment provider (Humphreys and Moos 1996). As expected, treatment costs were lower for the AA group over the course of the study. However, outcomes were similar for both groups, indicating that voluntary AA participation may significantly reduce treatment costs without compromising outcomes. The authors cautioned that AA is not a substitute for outpatient treatment in all cases, but it can be effective for many individuals who

choose it. One limitation of this study is that patients selected their own treatment option rather than being randomly assigned. This "self-selection" creates the possibility of bias in the findings because the subjects who are more likely to achieve successful treatment outcomes, such as those with more motivation or less severe conditions, might be more likely to choose one treatment alternative over another.

Continued Issues: Cost Offsets

Recent studies have also continued to investigate cost offsets, or net reductions in health care costs attributable to alcoholism treatment. For example, one research group analyzed health insurance claims from 10 large firms, as generated by some 15,000 employees and dependents who received alcoholism treatment between 1989 and 1991 (Goodman et al. 1997). Results indicated that after the initiation of treatment, health care costs incurred by alcoholics declined, but that differences in these costs from pretreatment levels were relatively modest. The researchers found that cost offsets were greater for clients who initially received inpatient rather than outpatient treatment. Cost offsets were also greater within 6 months of the initiation of treatment than they were later. The authors emphasized that although the estimated cost offset effects were modest, "substance abuse treatment should not depend on whether it 'pays for itself' by offsetting other treatments" (Goodman et al. 1997, p. 938). They noted that substance abuse treatments, like other medical treatments, should instead be justified by the health benefits they provide.

Another research group examined the additional question of whether legal costs would drop, along with health care costs, after alcoholism treatment for patients who had behavioral marital therapy (O'Farrell et al. 1996*a*,*b*). The results can only be taken as suggestive, however, because of the small number of subjects included in the study's two components, a cost offset analysis (36 subjects) and a cost-effectiveness analysis (59 subjects). The cost offset analysis indicated that behavioral marital therapy decreased both health care and legal costs and that the savings exceeded the cost of delivering the therapy. Behavioral marital therapy was not found to be more cost-effective in terms of prolonging abstinence from drinking than was simple individual counseling, which was given to the control group. The two therapies had similar effectiveness in prolonging abstinence, but behavioral marital therapy was substantially more expensive. Behavioral therapy was just as cost-effective as individual counseling in terms of promoting marital adjustment, however. In addition, when special sessions to prevent relapse were added to behavioral marital therapy, improvements occurred in abstinence from drinking and marital adjustment outcomes. The additional relapse prevention therapy did not, however, lead to greater savings in health care or legal costs (O'Farrell et al. 1996*b*).

New Issues: Length of Treatment

Although the relative merits of inpatient versus outpatient treatment continue to receive occasional study (Long et al. 1998), most observers seem to have accepted the conclusions of the study by Finney and colleagues (1996); that is, outpatient treatment should be encouraged for most patients, but access to inpatient treatment should be retained for those patients who need it. The focus of cost-effectiveness research has accordingly shifted from the issue of inpatient versus outpatient care toward consideration of other treatment program dimensions. Prime among these are comparisons of shorter versus longer periods of treatment.

One research group abstracted medical records and surveyed program administrators at 98 U.S. Department of Veterans Affairs (VA) inpatient treatment programs in an attempt to identify the characteristics of the most cost-effective clinics (Barnett and Swindle 1997). Their principal measure of program outcome was whether patients were readmitted to treatment at any VA hospital in the United States within 180 days of discharge. They found that both treatment cost and outcome were related to program size, intended length of stay, ratio of staff to patients, and client treatment histories. In addition, they found that 28-day programs were much more costly and only slightly more effective than 21-day programs. Whereas the average 21-day

treatment costs were $3,754 per patient and had a 75.0-percent chance of successful outcome (within the 180-day window), the longer 28-day treatment programs added $860 to per-patient costs but only improved success rates to 78.3 percent. On this basis, the authors concluded that 21-day programs were more cost-effective than 28-day programs.

Similar findings on length of stay were produced by a 1998 study of 12 inpatient alcoholism treatment facilities for U.S. Navy personnel (Trent 1998). A planned reduction from a 6-week to a 4-week treatment program created an opportunity to conduct a natural experiment of treatment outcomes under the two plans. Results indicated that patients treated in the shorter, 4-week program achieved outcomes similar to those treated by the longer 6-week program in terms of alcohol use, number of negative incidents, retention on active duty status, job performance, and recommendation for reenlistment or advancement. The researchers also noted that participation in aftercare (principally attendance at AA) was the best predictor of treatment outcomes at 1-year follow-up. Although the study did not estimate the costs of the competing programs, clearly, shortening program length by about one-third could generate significant cost savings.

New Issues: Long-Term Costs

Alcoholism is, of course, a chronic disease. It is therefore reasonable to expect that any given individual with alcoholism may experience several episodes of treatment, separated by periods of sobriety, over the course of a lifetime. Thus, it is important that treatment cost research examine the long-term, or lifetime, costs for affected individuals. Such research is valuable for examining whether focusing on potential treatment cost savings in the near term might be shortsighted because such savings lead to greater costs over the long run. For example, while inpatient treatment may not seem cost-effective in the short term, if it reduces episodes of later care, it may compare more favorably with other treatment strategies when viewed from a long-term perspective.

Fortunately, cost researchers are taking the first steps in this direction. One research group has made the distinction between the alcohol treatment costs incurred during the first 6 months of treatment and the costs incurred later (Goodman et al. 1996). One of their studies, involving 879 insured employees and retirees who underwent alcoholism treatment, analyzed whether the patients required additional alcoholism treatment between 6 and 90 months after the initial treatment episode, and estimated the cost of such treatment (Goodman et al. 1996). The researchers examined such variables as the intensity of initial treatment; inpatient versus outpatient setting of the initial treatment; severity of diagnosis (dependence vs. abuse); presence of drug abuse, liver disease, or coexisting psychiatric disorders; and demographic characteristics.

The results indicated that the treatment setting (inpatient vs. outpatient) during the first 6 months had no bearing on either the need for or the total costs of later treatment. Moreover, the intensity of treatment during the first 6 months had no effect on later treatment costs for patients diagnosed as alcohol abusers, although more intense treatments in the initial 6 months slightly reduced later treatment costs among patients diagnosed as alcohol dependent. The patient's diagnosis, however, did influence the probability that treatment would occur after the 6-month mark. Later treatment was more common among alcohol-dependent individuals (as opposed to alcohol abusers) and those who also abused other drugs. Treatment costs beyond the first 6 months were greater for those with drug abuse problems, liver disease, or coexisting psychiatric disorders, largely because these factors increased the likelihood that long-term treatment would occur in an inpatient rather than an outpatient setting.

While these results seem to indicate that near-term savings can be achieved without triggering greater costs in the long run, they run counter to an earlier finding that a return to treatment (over a 2-year window) was less likely among patients initially treated in an inpatient hospital setting than among those attending AA (a less intensive

and less costly option) (Walsh et al. 1991). The tradeoff between near-term and later treatment costs clearly requires continued research attention.

New Developments in Measuring Costs

Perhaps most important of all the new directions that recent studies have taken is the development of improved methodological tools for conducting cost research. Heretofore, treatment cost studies, whether in the alcohol treatment field or in other health care fields, have generally not been based on recognized economic principles for assessing cost. They also have been so idiosyncratic as to preclude judicious comparison of results across studies. Steps toward remedying these conditions hold considerable promise for the advancement of knowledge in the field.

Three significant recent developments in the improvement of cost measurement methodologies have been (1) the guidelines contained in the U.S. Public Health Service's (PHS) *Cost-Effectiveness in Health and Medicine* (Gold et al. 1996; see also Russell et al. 1996; Siegel et al. 1996; Weinstein et al. 1996); (2) the Drug Abuse Treatment Cost Analysis Program (DATCAP) developed by French and colleagues (French and McGeary 1997; French et al. 1997); and (3) the Uniform Accounting System and Cost Reporting for Substance Abuse Treatment Providers, a contract product developed for the Center for Substance Abuse Treatment by Capital Consulting Corporation (Caliber Associates 1998*a,b*).

The PHS guidelines contain a set of recommendations for conducting cost-effectiveness studies (Gold et al. 1996; see also Russell et al. 1996; Siegel et al. 1996; Weinstein et al. 1996). They were developed to promote consistency in economic evaluations of health care programs. To create these guidelines, the PHS commissioned a group of leading experts to reach consensus on a set of standard procedures for conducting cost-effectiveness studies. Among the many guidelines are recommendations to measure costs to the entire society rather than from the perspective of a given treatment-delivering organization; to include a "reference case" in research reports or an analysis conducted according to a common, standard set of economic assumptions to facilitate comparison with other studies; and to identify ethical problems that may arise in the course of analysis. The complexity of the guidelines indicate that considerable expertise in the mathematics of economics would be required to use them. The guidelines were not developed to apply specifically to alcoholism or substance abuse treatment costs, and have yet to be used to study such costs. However, they should be fully appropriate for such analyses.

The DATCAP takes quite a different approach (French and McGeary 1997; French et al. 1997). Its intent is to provide a procedure for measuring substance abuse treatment costs that could be administered without placing a substantial burden on the staff of a typical treatment center. The procedure measures economic costs, that is, the market value of all goods and services expended in providing treatment. Costs are estimated from the perspective of the provider organization rather than from the perspective of the client, of third-party payers (such as insurance companies), or of the society at large. These cost-estimating procedures have been applied to employee assistance programs (Bray et al. 1996; French et al. in press) and to a wide variety of drug abuse treatment programs (French et al. 1996, 1997), but applications specific to alcoholism treatment have not yet appeared in the literature.

The Uniform Accounting System and Cost Reporting for Substance Abuse Treatment Providers was also developed more as a tool for treatment providers than for academic researchers (Caliber 1998*a,b*). Like DATCAP, it measures costs from the perspective of the provider organization. The Uniform System differs from DATCAP by focusing on accounting costs rather than on economic costs. Accounting costs are based on a treatment program's actual expenditures for goods and services used in providing treatment. These can differ from economic costs (market value costs) whenever the treatment provider has access to free or subsidized resources, such as volunteer labor, the use of free or subsidized space, or donated food (Dunlap and

French 1998). In such cases, the accounting costs (actual expenditures for resources) will be lower than the economic costs (market values of resources). Which of the two systems is more desirable depends on the purpose of a study and the perspective of its authors. Most treatment providers would probably be more comfortable with accounting costs, as these most closely resemble the budgets that will be needed to provide the services. Researchers, on the other hand, are more likely to prefer economic costs, since conclusions based on the comparison of costs between programs should not be confounded by uneven access to free or subsidized resources.

By providing templates for the measurement of treatment costs, the above three systems promise to facilitate future research in two ways. First, they will make any cost study easier to conduct by providing model cost-measurement systems built on underlying assumptions that do not need to be reformulated de novo by each researcher who addresses the subject. Second, the standardization they provide should enable and encourage comparison between studies, thereby offering a richer field of evidence from which to draw conclusions, insights, and hypotheses. Given both advantages, these three cost measurement systems hold substantial promise for the near-term development of the field.

In Closing

Research in the field of treatment costs has seen some interesting developments in recent years. Some of these have been based on continued study of earlier research questions, while others have emerged as new themes in the literature. Research on the cost-effectiveness of different treatment modalities has continued to find that the more expensive modalities do not necessarily produce better treatment outcomes. Other research has continued to show that cost offsets are achieved following treatment; that is, reductions in general health care costs for those who have been treated for alcoholism are large enough to compensate for the expense of that treatment. Researchers have continued to conclude that outpatient therapy may be a more cost-effective option than inpatient therapy for many patients (although some patients will require inpatient therapy). Having generally resolved these points, research attention has begun to shift to related topics, such as the relative cost-effectiveness of shorter versus longer inpatient treatment programs, and whether the short-term savings from outpatient treatment are balanced against treatment costs that might be realized in the long term. While probably less interesting to most readers, developments in the standardization of methods for measuring treatment costs should be recognized as significant. These promise to improve future cost research considerably.

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The Economic Costs of Alcohol Abuse

The burden imposed by a disease can be measured in many ways. These measures include the number of deaths attributed to a particular disorder, the total number of cases at a given time, the number of new cases that occur in a given year, hospitalization rates, potential years of life lost to a disease, and more comprehensive measures that combine mortality and quality-of-life information.

Another approach to assessing the burden of disease is to estimate the associated "cost of illness" (COI). Studies of COI provide a framework for expressing in dollar terms the multidimensional impact of a health problem. Typically, a COI study of a particular health problem includes estimates of the costs of health care services, losses in productivity from illness and premature death, and other expenditures and resource losses that can be attributed to the health condition. For many diseases, the COI estimates run well into the billions of dollars. Estimates for different diseases often are not directly comparable to one another, however, because of variations in methods, data sources, and underlying assumptions (National Institutes of Health 1997).

Over the past two decades, five major studies have used the COI framework to estimate the economic costs of alcohol abuse in the United States (Berry et al. 1977; Cruze et al. 1981; Harwood et al. 1984, 1998; Rice et al. 1990). These studies present estimates of the costs of alcohol abuse on the basis of analyses of health care costs, productivity losses, and various additional costs, such as those associated with alcohol-related crime and motor vehicle crashes. In this context, the term "alcohol abuse" refers to any cost-generating aspect of alcohol consumption. This differs from the clinical definition of the term, which involves specific diagnostic criteria. Thus, the costs associated with a single occasion of drunk driving that leads to injury or property damage would be counted in this framework, even though this behavior would not, by itself, meet the clinical criteria for a diagnosis of alcohol abuse.

In the most recent of these COI studies, the research group estimated the overall economic cost of alcohol abuse at $148 billion for 1992, the most recent year for which adequate data were available at the time the study was undertaken (Harwood et al. 1998). Making adjustments for population growth and inflation, the authors also projected their estimates forward to 1995, for which the overall estimated cost was $166.6 billion. A subsequent update further projected the estimates to 1998, for which the overall estimated cost was $184.6 billion (Harwood 2000). This 1998 estimate amounted to roughly $683 for every man, woman, and child living in the United States in 1998. Unless otherwise noted, cost figures reported in this section are drawn from the update for 1998.

More than 70 percent of the estimated costs of alcohol abuse were attributed to lost productivity ($134.2 billion), most of which resulted from alcohol-related illness or premature death. Most of the remaining estimated costs were expenditures for health care services to treat alcohol use disorders and the medical consequences of alcohol consumption ($26.3 billion, or 14.3 percent of the total), property and administrative costs of alcohol-related motor vehicle crashes ($15.7 billion, or 8.5 percent), and various criminal justice system costs of alcohol-related crime ($6.3 billion, or 3.4 percent). A breakout of the estimated costs for 1992 and the associated projections for 1998 is shown in table 1; the percentage distribution is shown in figure 1.

The new estimates and projections are the latest since a 1990 report that estimated the economic costs of alcohol abuse by using data for 1985 (Rice et al. 1990). The estimate by Harwood

Table 1: Estimated economic costs of alcohol abuse in the United States, 1992 and 1998*

Economic Cost	1992 ($ millions)	1998 (Projected) ($ millions)
Health care expenditures		
Alcohol use disorders: treatment, prevention, and support	5,573	7,466
Medical consequences of alcohol consumption	13,247	18,872
Total	18,820	26,338
Productivity impacts		
Lost productivity due to alcohol-related illness	69,209	87,622
Lost future earnings due to premature deaths†	31,327	36,499
Lost productivity due to alcohol-related crime	6,461	10,085
Total	106,997	134,206
Other impacts on society		
Motor vehicle crashes	13,619	15,744
Crime	6,312	6,328
Fire destruction	1,590	1,537
Social welfare administration	683	484
Total	22,204	24,093
Total costs	**148,021**	**184,636**

*The authors estimated the economic costs of alcohol abuse for 1992 and projected those estimates forward to 1998, adjusting for inflation, population growth, and other factors.

†Present discounted value of future earnings calculated using a 6-percent discount rate.

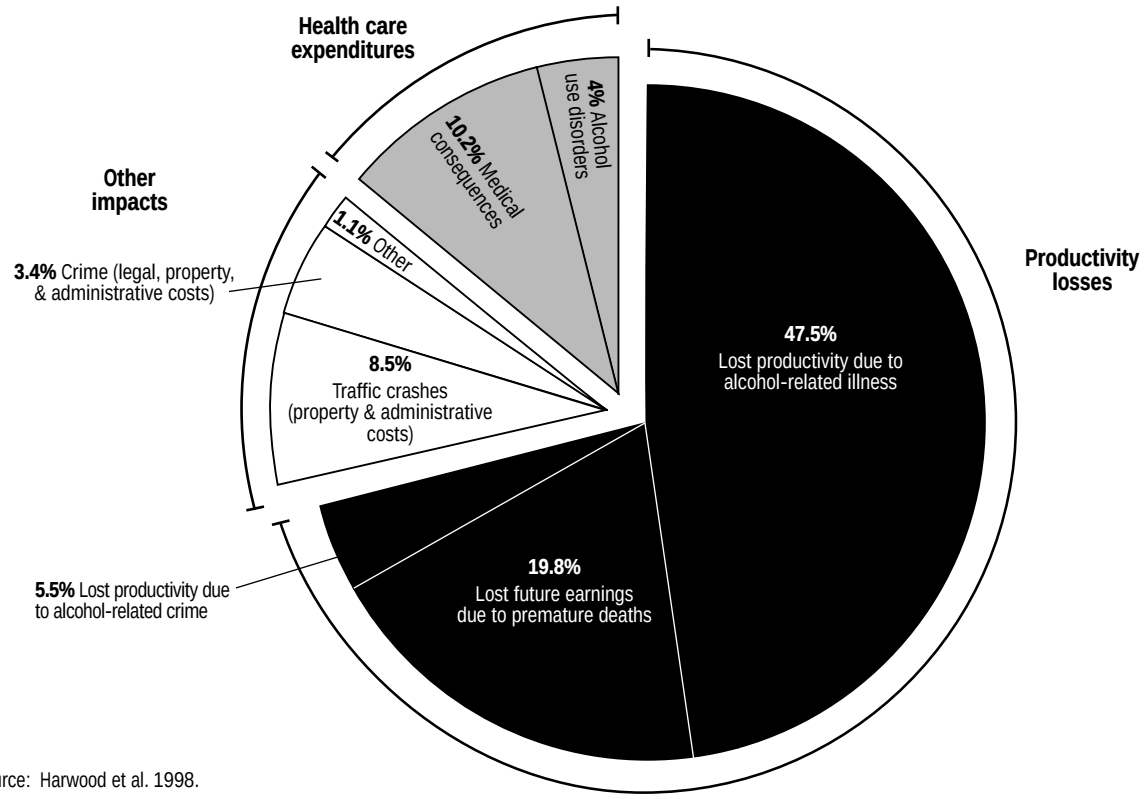
Sources: Harwood 2000; Harwood et al. 1998.

and colleagues for 1992 is 42 percent greater than the estimate by Rice and colleagues, even after accounting for increases that would be expected due to inflation and population growth. However, the estimate for 1992 is almost exactly equal to the average of the estimates from four other major studies, the Rice study included, dating back to 1977 (adjusting each of the earlier estimates for inflation and population growth). Although the estimates for 1985 and 1992 were developed using generally similar approaches, Harwood estimated that more than 80 percent of the increase reported in the newer study could be attributed to differences in data and methodology rather than to real increases in alcohol abuse or its consequences. Methodological and data factors were particularly important in contributing to higher estimates of productivity losses associated with alcohol-related illness and with health care costs for treating the medical consequences of alcohol misuse.

Distribution of the Burden of Costs

An innovative section in the 1998 study by Harwood and colleagues estimated how the burden of the costs of alcohol abuse is distributed across various segments of society (figure 2). This analysis, based on the data for 1992, found that much of the economic burden of alcohol abuse falls on segments of the population other than the alcohol abusers themselves. About 45 percent of the estimated total cost was borne by alcohol abusers and their families, almost all of which was due to lost or reduced earnings. About 20 percent of the total estimated cost of alcohol

Figure 1: Economic costs of alcohol abuse, United States, 1998
(Total estimated cost: $184.6 billion)



Source: Harwood et al. 1998.

abuse was borne by the Federal government and 18 percent by State and local governments. Nearly three-fourths of the costs borne by the Federal government were in the form of reduced tax revenues resulting from alcohol-related productivity losses, and most of the remaining Federal burden was for health care costs. Of the burden on State and local governments, reductions in tax revenue resulting from productivity losses accounted for just over half, while 38 percent was for criminal justice and motor vehicle-related costs. Private insurance arrangements (including life, health, auto, fire, and other kinds of insurance) shouldered the burden for 10 percent of the total estimated cost, primarily in the areas of health care costs and motor vehicle crashes. Six percent of the total cost was borne by victims of alcohol-related crimes (including homicide) and by the non-drinking victims of alcohol-related motor vehicle crashes.

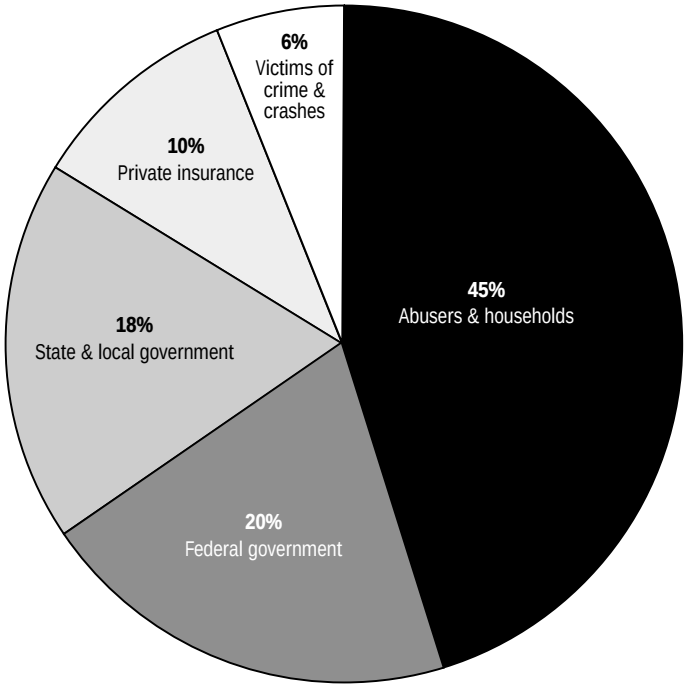
Components of the Costs of Alcohol Abuse

The estimated cost of alcohol abuse was constructed from estimates of numerous smaller categories and subcategories of costs, which were based on a wide variety of methods and data sources. These smaller categories, in turn, fall in three general groups: health care costs, productivity losses, and other impacts. The main issues and findings associated with each of these broad areas are described below, followed by a discussion of some key caveats and limitations associated with the estimates.

Health Care Costs

Health care costs of alcohol abuse were estimated at $26.3 billion for 1998, representing a relatively modest fraction (14.3 percent) of the total estimated cost of alcohol abuse. This category includes both the costs of treating alcohol abuse

Figure 2: Distribution of the costs of alcohol abuse



Source: Harwood et al. 1998.

and dependence, estimated at $7.5 billion, and the considerably greater costs of treating the adverse medical consequences of alcohol consumption, estimated at $18.9 billion. Each of these subcategories comprises a number of components, such as costs incurred in different treatment settings or for different categories of providers, reflecting both the pervasive health consequences of alcohol consumption and the complexity of the Nation's health care system.

The costs associated with treating alcohol use disorders (alcohol abuse and alcohol dependence) include costs incurred in a variety of community-based settings (such as hospitals, residential treatment facilities, outpatient clinics, and physicians' offices), costs incurred in other settings (primarily in facilities operated by the U.S. Department of Veterans Affairs), and expenditures for alcohol abuse prevention efforts. Also included in this category are various support costs, such as training for counselors and other professionals in alcohol abuse prevention and treatment, costs of research on alcohol abuse (estimated as the budget for the National Institute on Alcohol Abuse and Alcoholism), and administrative costs for health insurance associated with these treatment expenses. Collectively, these support costs represented 2.1 percent of the estimated health care costs, or 0.3 percent of the overall estimated cost.

The costs of treating the medical consequences of alcohol consumption—as distinct from the alcohol problems themselves—reflect the variety and seriousness of the health conditions for which alcohol consumption can be an underlying cause. Prominent examples of these conditions include liver disease, various cancers, stroke, and trauma. Because alcohol causes some but not all of the cases for many of these health problems, Harwood and colleagues adjusted the number of hospitalizations for each condition by applying factors called "alcohol-attributable fractions" (AAF's). These AAF's represent the proportion of deaths from various causes that are considered attributed to alcohol (Stinson et al. 1993). For example, AAF's range from 5 percent for diabetes

mellitus, to 20 percent for stomach cancer, to 75 percent for esophageal cancer, to 100 percent for alcoholic liver cirrhosis.

The researchers used the AAF's as a proxy for the proportion of hospitalizations attributable to alcohol for various diagnoses. They recognized that this approximation generated some imprecision in the estimate of hospital costs, because the proportion of hospitalizations for a given condition resulting from alcohol consumption might not equal the proportion of deaths from that condition that are attributable to alcohol. Although admittedly imperfect, this approach was adopted in an effort to reduce the systematic underestimation of these costs inherent in the methodology employed in the 1990 study.

Hospital costs represented about 44 percent of the estimated $18.9 billion spent in 1998 on health care for the medical consequences of alcohol consumption. The remaining costs in this category were associated with Fetal Alcohol Syndrome (FAS) (15 percent), outpatient care (13 percent), nursing homes (5 percent), pharmaceuticals (12 percent), other (nonphysician) health professionals (7 percent), and health insurance administration (5 percent).

Because of public and research interest in FAS, the various health care costs associated with this condition were estimated separately. FAS is a characteristic pattern of birth defects resulting from prenatal alcohol exposure. Symptoms of FAS include pre- and postnatal growth retardation and central nervous system anomalies, such as developmental delays, mental retardation, and skull or brain malformations. Overall costs for FAS include both health care costs and productivity losses attributable to FAS. Of the $2.8 billion in estimated health care costs of FAS in 1998, more than 90 percent was accounted for by the costs of providing home and residential care to adults with moderate to severe mental retardation associated with FAS, and by the costs of special education for children and adolescents with the range of mental impairments associated with FAS.

Productivity Losses

Productivity losses were estimated at $134.2 billion (72.7 percent of the total) for 1998, including losses due to premature deaths, alcohol-related illness, and alcohol-related crime. Estimating these costs presents a particular challenge because they are fundamentally unobservable: there is no direct way to measure the value of goods and services that go unproduced as a result of alcohol problems. Instead, analysts rely on the economic theory of competitive labor markets, which holds that workers' earnings reflect the value of their productive contributions. Following this line of reasoning, lower productivity will result in lower earnings, and the magnitude of the productivity loss may be approximated by the lost or foregone earnings. For example, alcohol-related premature deaths represent a loss of productive potential, and the amount that these individuals would have earned during the remainder of their lives provides an estimate of this loss. Similarly, alcohol use disorders can impair productivity, and the magnitude of this loss is represented by the reductions in earnings sustained by individuals as a result of their alcohol use disorders.

Losses From Illness. Productivity losses resulting from alcohol-related illness were estimated at $87.6 billion for 1998 (65.3 percent of estimated productivity losses and 47.5 percent of the estimated total cost). Nearly all of this estimate ($84.5 billion) represents impaired workplace and household productivity of individuals with a history of alcohol dependence. Of the remainder, lost work time for residential treatment of alcohol use disorders accounted for $1.9 billion, and productivity losses suffered by adults with FAS were estimated at $1.3 billion.

The estimate of impaired workplace productivity was developed using data from the 1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES), a nationally representative data set designed to measure the incidence and prevalence of alcohol abuse and dependence according to well-defined clinical criteria. The researchers applied statistical models to the NLAES data to

estimate lost earnings and excess unemployment among individuals with a history of alcohol dependence. After adjusting the results to account for demographic differences between those with and without a history of alcohol dependence, the researchers found that the only statistically significant losses were for males. Moreover, these losses stemmed only from reduced earnings, not from excess unemployment. A key finding of interest was that earnings reductions among males with a history of alcohol dependence were much larger for those who began drinking before age 15 than for those who began drinking later.

Losses From Premature Deaths. Premature deaths attributed to alcohol consumption resulted in productivity losses estimated at $36.5 billion in 1998 (27.2 percent of estimated productivity losses and 19.8 percent of the estimated total cost). This was based on an underlying estimate of 107,360 deaths attributable to alcohol consumption in 1992. The productivity losses resulting from these deaths were estimated using data on the average expected additional years of life for men and women of different ages, had they not succumbed to an alcohol-related death, and the average expected value of their future earnings and contributions to household productivity.

Expected future earnings were expressed in "present discounted value" terms, a standard technique for expressing values that accrue at different times in comparable terms. Economists frequently disagree about the appropriate discount rate to use in specific applications; a recent expert panel report recommended that cost-effectiveness studies of health interventions use a discount rate of 3 percent (Gold et al. 1996). For the latest estimates, the researchers used a 6-percent discount rate for consistency with earlier studies. If they had used 3 percent instead, it would have increased the estimate of productivity losses due to premature deaths by about 46 percent.

Crime-Related Productivity Losses. Additional productivity losses due to alcohol-related crime were estimated at $10.1 billion (7.5 percent of productivity losses and 5.5 percent of the total). Perpetrators of these crimes who are incarcerated forfeit their productive potential; this loss was estimated at $9.1 billion for 1998. Also, victims of alcohol-related crimes often lose work time as a result of their victimization; these losses were estimated at $1.0 billion for 1998.

Other Impacts

Other impacts of alcohol abuse generated costs in two particularly important categories. Alcohol-related motor vehicle crashes generate various administrative and property damage costs in addition to their enormous costs in terms of deaths and injuries. The estimate for these property and administrative (insurance and legal) costs was $15.7 billion for 1998 (8.5 percent of the total cost estimate). In addition to its effects on productivity, alcohol-related crime burdens the criminal justice system, consuming police, legal, and corrections services. Based on estimates from a variety of sources that alcohol plays a causal role in 25 to 30 percent of violent crimes and 3 to 4 percent of property crimes, these additional costs of alcohol-related crime were estimated to be $6.3 billion for 1998 (3.4 percent of the total).

Limitations and Caveats

As with earlier studies of economic costs, the latest research in this area confirms that alcohol abuse imposes a heavy burden on society. Although estimates of the economic costs of alcohol abuse attempt to be as comprehensive as possible, and although the magnitude of costs revealed in these estimates is undeniably enormous, there are several important caveats that apply to the interpretation of these estimates.

First, the estimates should not be considered precise. For many of the areas in which costs are incurred, good data are not readily available. Some components—most notably the productivity losses—reflect quantities that are fundamentally unobservable. In these cases, the magnitude of costs must be based on theoretical reasoning and statistical inference. Many components of the total cost were estimated quite roughly using convenient approaches to

approximating costs. In addition, the estimation procedures employed do not permit the usual indicators of statistical precision for most of the components. These considerations suggest that the cost estimates—the total as well as the various components—are best thought of as indicators of the general magnitude of these costs and not as precise measures.

Second, there are several significant aspects of the burden of alcohol problems that are not captured in these estimates. Perhaps most important, alcohol problems exact a heavy toll in terms of human suffering. Failed marriages, anguished families, stalled careers, criminal records, and the pain of loved ones killed or disabled from alcohol-related causes are aspects of this suffering that cannot be accounted fully in a COI framework. In addition, secondary effects of alcohol problems on economic market outcomes are not reflected in estimates of the economic cost of alcohol abuse. For example, worries about alcohol-related crime and motor vehicle crashes may induce people to spend more on security and safety measures than they otherwise would, and these costs are not counted in the COI framework. Similarly, alcohol problems are known to contribute to workplace accidents and absenteeism, thereby increasing the cost of labor to businesses, with potential effects on total employment and production over and above the effects on individuals' productivity. The overall magnitude of such secondary economic consequences of alcohol problems is unknown, but the aggregate effect could be substantial.

Third, estimates of the economic costs of alcohol abuse reflect only adverse consequences. However, in addition to generating the large costs described above, alcohol consumption also confers some benefits. Most obviously, many people value the enjoyment they obtain from consuming alcoholic beverages. Evidence for this includes purchasers' decisions to spend $94.5 billion on alcoholic beverages in 1997 (Putnam and Allshouse 1999), in the process generating $18.2 billion in Federal, State, and local tax revenues (Distilled Spirits Council of the United States 1999). In addition, evidence is accumulating that moderate consumption of alcoholic beverages is associated with certain health benefits (see the section "Measuring the Health Risks and Benefits of Alcohol" in the first chapter of this report). In part because COI studies do not consider any benefits associated with alcohol consumption, estimates of the economic costs of alcohol abuse, such as those presented in the recent report by Harwood and colleagues, should not be interpreted as indicators of the net loss to society resulting from use of alcoholic beverages.

Finally, estimates of the economic costs of alcohol abuse—however large they may be—do not provide sufficient information by themselves to justify the use of any particular policies that might be suggested as ways to reduce those costs. Any specific policy intended to reduce the adverse consequences of alcohol consumption must be evaluated in terms of the costs and benefits associated with that particular policy. The tools of cost-benefit analysis and cost-effectiveness analysis can be used as frameworks to evaluate the impact that a particular policy might have on reducing the costs of alcohol abuse, and how expensive it would be to achieve that impact.

In light of these limitations, COI studies may be most useful at the initial stage of the policy development process. Estimates of the various components of the economic costs of alcohol abuse can help direct attention to the most costly adverse consequences of alcohol consumption. Scientists, clinicians, and policy makers can use this information in their search for strategies to address these problems.

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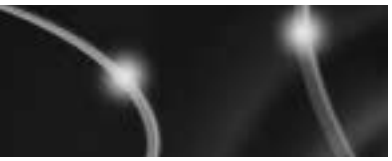
Prevention Research



In recent years, research on strategies to prevent alcoholism and alcohol abuse has expanded greatly and shifted in emphasis. While studies 10 to 15 years ago focused almost exclusively on education-based prevention approaches, more recent research has evaluated a wider range of prevention measures, including laws and policies to reduce alcohol-related problems at local, State, and national levels.

As just a few examples, at the local level, recent studies have examined the effects of community-based programs that generate new policies to reduce underage drinking and alcohol-related traffic crashes. At the State and national levels, research has evaluated the effects of laws that set the minimum legal drinking age and the maximum blood alcohol concentration for drivers, as well as alcohol taxes. Although no longer the principal focus, research on educational approaches continues as well, with, for example, studies of programs that teach children to resist peer pressure to use alcohol, that challenge their misperceptions about the benefits and pervasiveness of alcohol use, and that train them to critically evaluate alcohol advertising.

Gauging the effectiveness of these and other prevention strategies can be complicated by a wide range of factors, such as cultural and economic variability in the study populations or activities at the community or State level that may influence the study outcomes. Using rigorous statistical methods, however, investigators are tackling the challenge of measuring the impact of critical intervening variables and accounting for extraneous factors. As a result, they are producing more robust results that can be generalized to populations beyond the study groups, thus offering new understandings of how programs and policies can reduce the toll of alcohol-related problems.

For example, as noted in the section "Reducing Alcohol-Impaired Driving," thousands of young lives have been saved by increasing the legal drinking age to 21 and by passing "Zero Tolerance" laws that lower the maximum legal blood alcohol levels in young drivers to 0.02 percent. Findings from econometric studies also indicate that raising taxes on beer (the drug of choice among youth) could further reduce deaths caused by alcohol-impaired driving.

In addition, as described in the section "Community-Based Prevention Approaches," school-based programs that are closely linked to other community activities and to parent involvement have been shown to reduce rates of alcohol use among middle school students. Other programs have successfully mobilized communities to lower the incidence of alcohol

sales to minors and to reduce the number of traffic crashes involving alcohol.

Prevention researchers have also pursued answers to the questions of whether alcohol advertising increases alcohol consumption and related problems and whether it predisposes children and adolescents to drink. In general—as noted in the section "Alcohol Advertising: What Are The Effects?"—research based on economic analyses shows that alcohol advertising seems to encourage people to switch brands or beverage preferences without increasing consumption rates. At the same time, survey studies of children and adolescents show links between alcohol advertising and favorable beliefs about alcohol, greater intentions to drink, and a greater likelihood of drinking. Although these results offer grounds for both reassurance and concern, the study methods used thus far are limited in their ability to generate firm conclusions about cause and effect.

As with other areas of scientific inquiry, prevention investigators are challenged both by the demands of the questions under study and by the constraints of the available research methods. As such, each of the sections in this chapter includes details not only about recent prevention strategies and results, but also about the strengths and limitations of the research methods employed.

Studies indicate that many prevention efforts can reduce harmful drinking and its consequences, while others have little or no effect. Having this knowledge is helping policy makers and program planners to make significant reductions in our Nation's alcohol-related problems. Guidance will be further enhanced by future research that not only delineates which programs seem most effective overall, but also defines in detail which components of those programs are most critical to their success.

Reducing Alcohol-Impaired Driving

Alcohol-impaired driving is a major public health problem in the United States. Traffic crashes involving alcohol killed more than 16,000 people in 1997 alone (National Highway Traffic Safety Administration [NHTSA] 1998*b*) and injure a million more each year (Blincoe 1996). Fatal traffic crashes, the leading cause of death for those aged 1 through 24, involve alcohol 4 times out of 10 (NHTSA 1998*b*; U.S. Department of Health and Human Services 1997).

The good news is that annual traffic deaths related to alcohol have dropped by more than one-third since the early 1980's. The bad news is that the dramatic decline in fatalities seen in the early 1990's has leveled off, while the number of people killed and injured each year remains staggeringly high. (More statistical information can be found later in this section and in the box below.)

Why Did the Fatality Rates Drop So Significantly?

Although many safety improvements have occurred since 1982—such as air bags, laws requiring the use of child restraints in all 50 States, and laws mandating the use of seat belts in 49 States—these improvements do not explain the major reduction in alcohol-related crashes. According to an analysis of the annual number of traffic fatalities that occur Nationwide for every 100 million vehicle miles traveled, the traffic fatality rate dropped both for alcohol-related deaths and for other fatalities between 1982 and 1996 (NHTSA 1997*b*). Alcohol-

Facts About Alcohol-Impaired Driving

- How Many Deaths and Injuries? In 1997 alone, alcohol-related crashes killed more than 16,000 people—an average of one death every 32 minutes (National Highway Traffic Safety Administration [NHTSA] 1998*b*). In addition, an estimated 1 million more people are injured each year in alcohol-related crashes (Blincoe 1996).
- What Are the Chances? About 3 out of every 10 Americans will be involved in an alcohol-related traffic crash at some point in their lives (NHTSA 1998*b*).
- Who Are the Victims? Alcohol-impaired driving often harms the innocent: in 1996, 40 percent of those killed in crashes involving drinking drivers were people other than the drinking driver. Most of these victims were passengers in the drinking driver's vehicle (23 percent of all fatalities), followed by occupants of vehicles struck by the drinking driver (12 percent), and pedestrians (5 percent) (NHTSA 1997*a*).
- Who Are the Drivers? According to the Behavioral Risk Factor Survey of 102,263 adults aged 18 and older (Liu 1997):
  - More men than women (4 vs. 1 percent) reported alcohol-impaired driving. The highest rate was reported by males aged 21 through 34 (7 percent), followed by males aged 18 through 20 (5 percent).
  - The highest rate of impaired driving was reported by white males (4.4 percent), compared with 3.1 percent for Hispanic males and 2.8 percent for black males.
  - Among those who reported "binge" drinking (defined in the study as consuming at least five drinks at a single sitting in the past month), 14.6 percent reported driving while impaired; this rate was thirty-fold higher than that reported by those who did not report binge drinking.
- How Many Are Arrested? In 1996 alone, 1.5 million people were arrested for driving while intoxicated (NHTSA 1998*b*). This has been the leading category of arrests over the past decade, accounting for nearly 10 percent of all arrests.
- What Are the Financial Costs? Alcohol-related traffic deaths and injuries cost the Nation more than $45 billion in lost economic productivity and hospital and rehabilitation costs (Blincoe 1996).

Research on the Effects of Laws and Programs: Methodological Considerations

When designing evaluations of efforts to reduce alcohol-impaired driving, researchers are challenged by constraints relating both to the nature of the law or program under study and to the research methods (De Jong and Hingson 1998). The optimal research design would be a true experimental design, with large numbers of communities or States randomly assigned either to a treatment group that is exposed to the intervention, or to a control group that is not. Clearly, however, random assignment of laws to States or communities is politically and financially unrealistic.

To follow are brief descriptions of alternative methods used to test the impact of community or State initiatives. (See also the discussion of "Methodological Concerns" in the section in this chapter on "Community-Based Prevention Approaches.")

Quasi-Experimental Design

In studies with "quasi-experimental" designs, researchers compare outcomes for treatment communities or States with similar nontreatment ("control") jurisdictions. Unlike the classic experimental design, the designation as a treatment or control community is not always random. Challenges for these studies include matching the intervention site with its control site on variables that might influence study outcomes, as well as teasing apart the effects of multiple laws or programs initiated within a relatively short time. These studies also need to account for shifts in legislation or law enforcement that might affect driving behaviors over the course of the study.

Time-Series Design

This research option involves the analysis of survey data or crash indicators over an extended period of time, both before and after the introduction of an intervention. When reliable and valid data are available over a lengthy time period, this design can be used to evaluate national, regional, or local campaigns. The design is most easily used when the occurrence of a single event can be precisely defined in time, thus enabling clear before-and-after comparisons.

In many cases, however, the only data available are broad indicators, such as statistics on alcohol-related traffic fatalities, or proxy measures, such as single-vehicle nighttime crashes, which are three times more likely than other crashes to involve alcohol. Using only this type of data can introduce imprecision in evaluating the effects of legislation or other programs, especially in short-term studies involving small jurisdictions (Heeren et al. 1985).

Crash Characteristic Comparisons

These methods were developed by analyzing the characteristics of crashes that involve alcohol in States that test blood alcohol levels in a high percentage of drivers in fatal crashes (Klein 1986). When available, alcohol test results are used for fatal crash analyses. When alcohol test results are not available, however, the characteristics of the crashes, in terms of how they compare to crashes involving alcohol, can be used to develop projections of alcohol involvement. The NHTSA has used this approach, called imputational methodology, to estimate annual alcohol involvement in fatal crashes at the national and State level. These estimates may be problematic when used for smaller subgroups, such as cities, specific age and gender groups, or at different times of the day or days of the week.

Using these methodological approaches, with cognizance of the strengths and limitations of each, researchers have been able to draw conclusions, as described in this section, about the effects of various legislative and programmatic interventions to reduce alcohol-impaired driving.

related fatalities fell significantly more, however, down 56 percent versus only 11 percent for other traffic fatalities.

One likely contributor to the drop in alcohol-related crashes is the reduction in drinking since the early 1980's. Nationwide, the annual per capita alcohol consumption has declined nearly 20 percent during this time period (Williams et al. 1996).

In addition, part of the alcohol-related traffic fatality decrease can be attributed to the passage of State-level legislation. This legislation includes "general deterrence laws" aimed at the population at large, such as raising the minimum legal drinking age to 21 or allowing police officers to immediately confiscate drivers licenses of drivers whose blood alcohol concentrations (BAC's) exceed the legal limit. Other legislation includes "specific deterrence laws" aimed at persons already

convicted of alcohol-impaired driving. These include lower legal BAC limits for convicted offenders, mandatory license suspension, mandatory treatment and rehabilitation, dedicated detention and probation, and actions against vehicles and tags. Research on the effectiveness of these and other deterrence laws is described later in this section.

Once laws are enacted, there is no guarantee that they will be observed. Active enforcement of, and education about, these laws at the community level has been critical to their success. As described later, publicity and police enforcement efforts such as well-publicized sobriety checkpoints can significantly enhance the benefits of State-level legal changes.

Reductions in alcohol-related crashes have also resulted from large-scale prevention programs at the community level. In recent years, researchers have begun exploring the potential of these comprehensive intervention programs, which combine the efforts of multiple departments of city governments with those of private citizens. A brief description of these programs is included in this section; for more information, see also the section "Community-Based Prevention Approaches" later in this chapter.

Other factors that have influenced the alcohol-related traffic fatality rates include policies such as alcohol taxation rates and State monopoly systems, which can influence alcohol availability, particularly to young drivers. Moreover, individual-level initiatives, such as personal interventions to prevent alcohol-impaired driving and designated driver strategies, also may reduce impaired driving. Each of these topics is described within.

Why Have the Rates Leveled Off in Recent Years?

It is too soon to know why the fatality rates have leveled off since the dramatic drops of the late 1980's and early 1990's. One contributing factor may be a drop in police enforcement, as drunk driving arrests Nationwide have decreased 23 percent since 1983 (Hingson 1996*a*). In addition, questions have been raised as to whether public pressure to reduce drunk driving has dropped in recent years. (These topics are discussed in more detail later in this section.) In the meantime, continued research is needed to monitor and analyze the trends and to expand the range of approaches for reducing alcohol-related traffic fatalities.

Recent Trends in Alcohol-Related Traffic Fatalities

The remarkable progress in decreasing alcohol-related traffic fatalities has been documented by National Roadside Surveys conducted in 1973, 1986, and 1996, in which drivers were stopped between 10:00 p.m. and 3:00 a.m. on Friday and Saturday nights, when most drinking occurs (Voas et al. 1997*c*). The researchers used similar sites and sampling procedures in each survey.

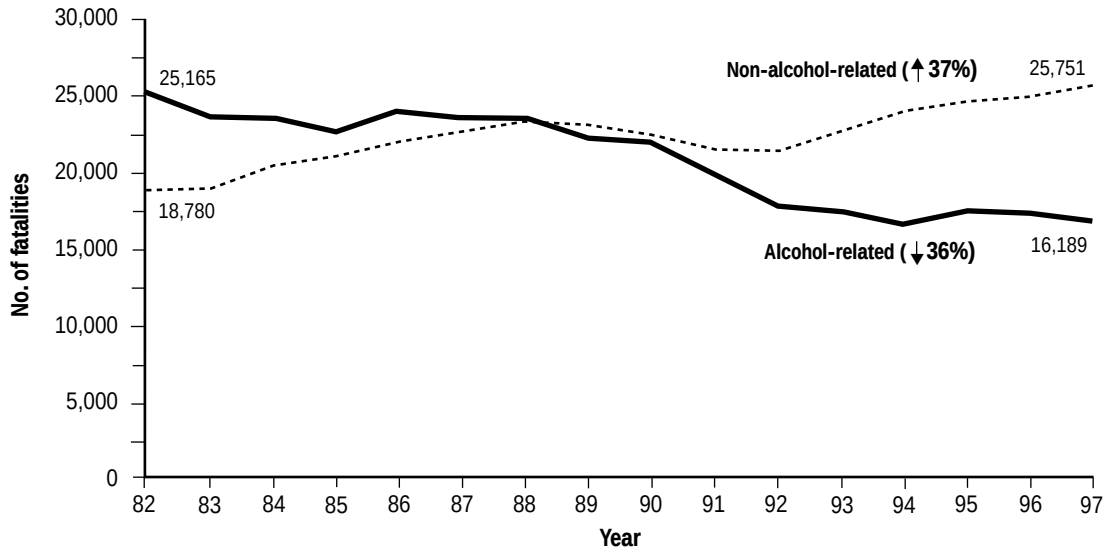
The surveys revealed the following changes in drinking and driving statistics from 1973 through 1996:

- Changes in Drinking and Driving in General: A 53-percent drop in the proportion of drivers with positive BAC's (from 36 percent in 1973 to 17 percent in 1996). The decline was greatest for drivers with lower BAC's, in the range of 0.005 to 0.049 percent.

- Changes by Age Group: A 92-percent drop in the proportion of drivers under age 21 with 0.10-percent BAC (from 4.1 to 0.3 percent of drivers in this age group). By 1988, it was illegal to sell alcohol to individuals under 21 years of age, which may account in part for this decline, the largest in any age group. The smallest reduction by age group was still substantial—a 33-percent drop in the proportion of drivers aged 21 through 25 with 0.10-percent BAC (from 5.7 to 3.8 percent).

- Changes by Gender: A 50-percent drop in the proportion of female drivers at 0.10-percent BAC (from 3.0 to 1.5 percent of female drivers) and a 36-percent drop in the proportion of male drivers at 0.10-percent BAC (from 5.5 to 3.5 percent of male drivers).

Figure 1: Trends in alcohol-related and non-alcohol-related traffic fatalities, United States, 1982–1997



Sources: National Highway Traffic Safety Administration 1997*a*, 1998*b*.

- Changes by Race/Ethnicity: A 55-percent drop in the proportion of white drivers with positive BAC's (from 5.1 to 2.3 percent of white drivers) and a 40-percent drop in the proportion of black drivers with positive BAC's (from 6.0 to 3.6 percent of black drivers). At the same time, the proportion of Hispanic drivers with positive BAC's more than doubled (from 3.3 to 7.5 percent of Hispanic drivers). This is a worrisome finding, since the proportion of surveyed drivers who were Hispanics increased sevenfold during the study period (from 1.4 to 10.3 percent).

In addition, as mentioned previously, data from fatal crashes, first collected nationally in 1982, confirm the overall declines in alcohol-impaired driving. Between 1982 and 1997, alcohol-related traffic fatalities dropped 36 percent, from 25,165 to 16,189 fatalities (NHTSA 1997*a*, 1998*b*) (figure 1). The greatest reductions were among youth aged 15 through 20, whose alcohol-related traffic deaths dropped 59 percent, from 5,380 to 2,209 per year (NHTSA 1997*a*, 1998*a*) (figure 2).

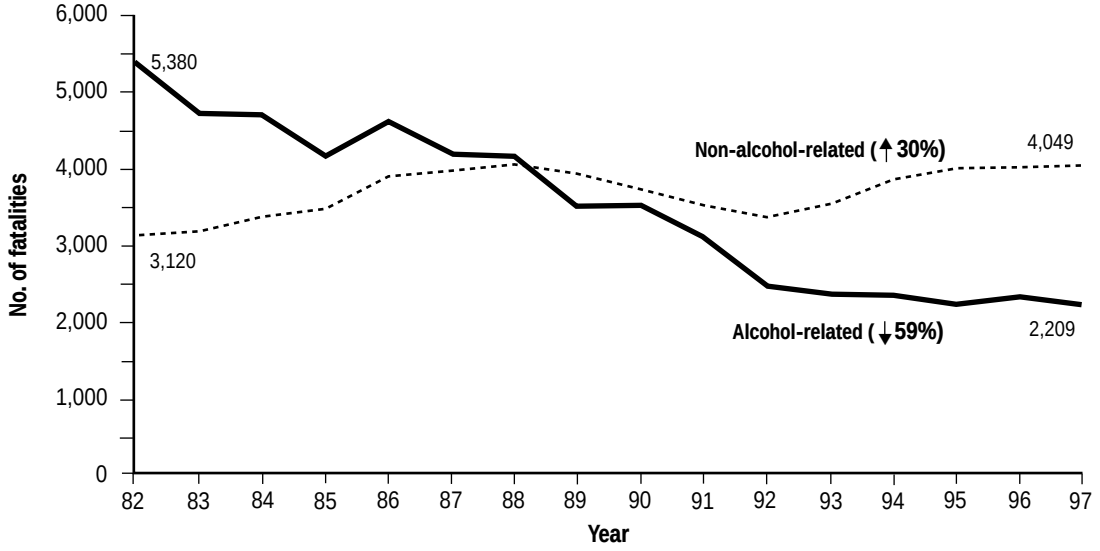
Legislative Efforts To Reduce Alcohol-Impaired Driving

Legislative efforts to reduce alcohol-impaired driving have emphasized laws that deter violations by applying swift, certain, and severe penalties when warranted. The punishment's severity is considered less of a deterrent than is its quick and unavoidable administration (Ross 1992).

Most of this legislative activity has been stimulated at the State level, although Federal initiatives did promote the passage of laws forbidding drinking, and driving after drinking, for those under age 21. The passage of Federal and State-level legislation has been spurred by grassroots citizen activist groups, such as Mothers Against Drunk Driving and Remove Intoxicated Drivers, and the political coalitions they have formed with medical, public health, community, and business groups.

As mentioned previously, laws to deter drunk driving fall into two categories: laws aimed at the general public, and laws aimed specifically at those already convicted of "driving under the influence" (DUI). (Note: As used throughout this section, DUI also refers to driving while intoxicated [DWI], a term used in some States.) Although convicted DUI offenders have a higher than average likelihood of further arrests and crashes, most drivers in fatal crashes involving alcohol have never been previously convicted. In 1997, for example, 89 percent of fatally injured drivers with a BAC of 0.10 percent or

Figure 2: Trends in alcohol-related and non-alcohol-related traffic fatalities, persons aged 15 through 20, United States, 1982–1997



Sources: National Highway Traffic Safety Administration 1997*a*, 1998*a*.

higher did not have a DUI conviction during the 3 years prior to the crash (NHTSA 1998*b*). In addition, among those arrested for DUI, two-thirds have never been arrested before (NHTSA 1995). Thus, laws and programs need to deter both first-time offenses and repeat offenses.

Many studies have been undertaken to evaluate the effectiveness of both general and specific deterrence laws. Highlights from recent research are described next.

General Deterrence Laws

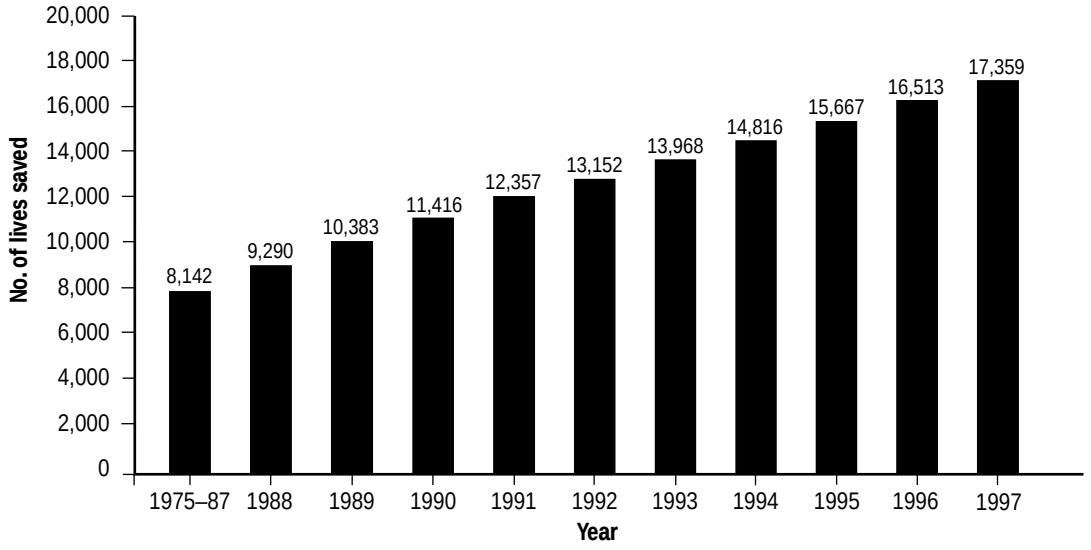
Minimum Legal Drinking Age. In 1984, when the National Minimum Drinking Age Act was passed, half of the States had a legal drinking age of 21. By 1988, all States had a minimum legal drinking age of 21. Of the 29 studies performed since the early 1980's that evaluated the effects of increases in the minimum legal drinking age, 20 showed significant decreases in traffic crashes and crash fatalities (Toomey et al. 1996). Only three clearly found no change in traffic crashes involving youth; the remaining six studies had equivocal results

According to NHTSA, States that adopted a minimum legal drinking age of 21 in the early 1980's experienced a 10- to 15-percent drop in alcohol-related traffic deaths among youth, compared with States that adopted the law later (Blincoe 1996). Overall, NHTSA estimates that imposing a minimum legal drinking age of 21 has prevented more than 17,300 traffic deaths since 1976, or approximately 700 to 1,000 deaths each year for the past decade (NHTSA 1998*b*) (figure 3).

In the years since these laws were enacted, the proportion of high school seniors who reported drinking in the previous month has declined substantially, from 72 percent in 1980 to 51 percent in 1999, according to the annual Monitoring the Future Study (Johnston et al. 1999). The proportion who consumed five or more drinks on at least one occasion in the previous 2 weeks declined from 41 to 31 percent (figure 4). Minimum legal drinking age laws not only have reduced drinking among people under 21, but they also have reduced drinking among people aged 21 through 25 who grew up in States with a minimum legal drinking age of 21 (O'Malley and Wagenaar 1991).

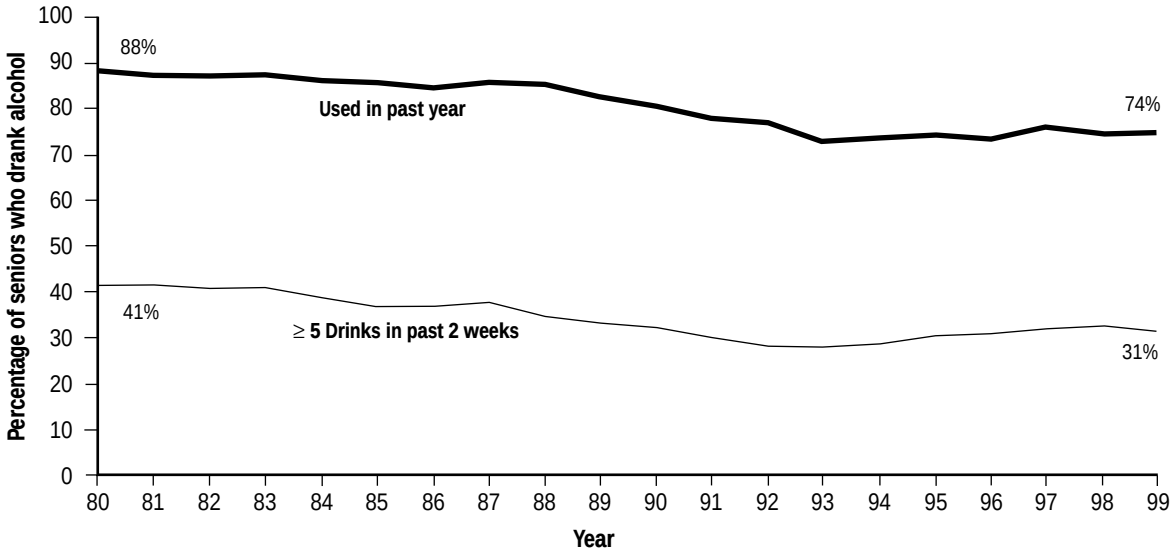
Although U.S. laws prohibit the sale to, or possession of alcohol by, individuals younger than 21, this age group can still obtain alcohol from many sources. Buyers who appear to be younger than

Figure 3: Cumulative estimated number of lives saved by the minimum legal drinking age laws, 1975–1997



Source: National Highway Traffic Safety Administration 1998*b*.

Figure 4: Alcohol use by high school seniors, 1980–1999



Source: Johnston et al. 1999.

21 can successfully purchase alcohol from licensed establishments without showing age identification in 50 percent or more of their attempts (Forster et al. 1994, 1995; Preusser and Williams 1992). An analysis of attempts by youth who appeared underage to purchase alcohol at 100 outlets in 28 Minnesota communities revealed that liquor stores were more likely than bars to sell to minors (Wolfson et al. 1996). Bars without managers present at all times were more likely to sell to minors, as were those where staff received no formal server training.

In addition, although many youth purchase alcohol themselves, most indicate that they generally obtain alcohol through social contact with persons over age 21 (Wagenaar et al. 1996). Laws prohibiting the sale and provision of alcohol

to minors are not well enforced (Wagenaar and Wolfson 1995). For every 1,000 minors arrested for alcohol possession, criminal penalties are faced by only 130 of the establishments that sell alcohol to minors and only 88 of the adults who purchase alcohol for minors. According to one estimate, only 5 out of every 100,000 incidents of minors' drinking result in a fine, license revocation, or license suspension of an alcohol establishment (Wagenaar and Wolfson 1994).

Heightened enforcement of drinking age laws can, however, reduce youth access to alcohol. One study demonstrated dramatic reductions in alcohol sales to minors following an enforcement campaign involving three sting operations in which underage males attempted to purchase alcohol (Preusser et al. 1994). Over the course of a year, sales to minors dropped from 59 to 26 percent, during which time store owners were informed about the results of the initial sting, impending stings, and potential penalties for selling to minors.

Other measures that might further enhance compliance with the age 21 law include: (1) use of distinctive and tamper-proof licenses for drivers under age 21, (2) "use and lose" laws that impose driver's license penalties on minors who purchase or are found in possession of alcohol, (3) keg registration or other limits on large container sales, and (4) increased penalties for illegal service to minors, including laws that entitle injured parties to sue for damages. Research is needed to establish whether these proposals would significantly reduce alcohol consumption and driving after drinking (De Jong and Hingson 1998).

Zero Tolerance Laws. When most States raised the legal drinking age to 21, they did not simultaneously make it illegal for persons under age 21 to drive after drinking. In the fall of 1995, the U.S. Congress amended the National Minimum Drinking Age Act by mandating withholding of Federal highway funds from States that did not adopt laws that make it illegal for those under 21 to drive after drinking any alcohol. At that time, only half the States had these "Zero Tolerance" laws, which set legal BAC limits of zero to 0.02 percent. As of April 1998, 50 States and the District of Columbia had passed Zero Tolerance legislation.

The impact of these laws has been significant. One recent study compared the first 12 States that lowered the legal BAC's for drivers under 21 with 12 nearby States that did not. The study found that the States adopting Zero Tolerance laws experienced a 20-percent decline in the proportion of crashes that are most likely to involve alcohol (single-vehicle, nighttime fatal crashes) among drivers under 21, compared with the States that did not lower BAC's. States that adopted BAC limits of 0.04 or 0.06 percent had no significant declines (Hingson et al. 1994).

Some States, however, have found it difficult to achieve broad awareness of the Zero Tolerance law. Studies in California and Massachusetts found that 45 to 50 percent of young drivers were unaware of the law (Martin and Andreasson 1996).

Administrative License Revocation. Forty States have administrative license revocation (ALR) laws that allow a police officer or other official to confiscate immediately the license of a driver whose BAC exceeds the legal limit. ALR laws permit punishment to occur at the time of infraction and, because the court system is bypassed, the punishment is more swift and certain. One Nationwide study found that ALR was associated with a 5-percent decline in fatal crashes and a 9-percent decline in single-vehicle, nighttime fatal crashes (Zador et al. 1989).

A more recent national study examined the effect of ALR laws by analyzing, within the States that adopted these laws, the difference in fatal crash rates before and after the legislation was enacted. To exclude the effects of other Statewide changes that could influence crash rates, such as safety belt laws and highway improvements, the researchers tracked changes in the rates of fatal crashes that did not involve drinking drivers as well as those that did. They found that regardless of changes in overall fatal crash rates, States that adopt ALR laws witnessed annual declines of 13 percent in

the proportion of fatal crashes involving drivers with BAC's of 0.10 percent or higher (Voas and Tippetts 1999).

These laws have faced some challenges for allegedly imposing "double jeopardy" on a driver who subsequently is convicted of DUI and receives additional penalties, but no State supreme court has upheld such a challenge. Questions have also been raised as to whether ALR laws create economic hardship for offenders whose licenses are suspended. Recently, however, a survey of 579 first-time offenders and 233 multiple offenders in four States with varying ALR laws found that ALR does not have a major impact on a DUI offender's job or income (Knoebel and Ross 1997).

Reducing Legal Limits for Blood Alcohol Concentration. Every State except Massachusetts and South Carolina has adopted laws that make it a criminal offense to drive with a BAC above the State's legal limit, which in most States is 0.10 percent. The laws include a provision that the driver's BAC in and of itself, or "per se," is enough to demonstrate impairment, so prosecutors do not have to introduce other evidence and thus can make convictions more easily.

Seventeen States have lowered the legal BAC limit from 0.10 to 0.08 percent. Massachusetts has set the BAC for its ALR law at 0.08 percent. A number of studies have found that after States adopt a 0.08-percent law, they experience significant decreases in alcohol-related fatal crashes (Hingson et al. 1996*a*; Johnson and Walz 1994; NHTSA 1991). Often, however, the States implemented ALR laws after the 0.08-percent laws, which made it difficult to separate the effects of each law (NHTSA 1991; Rogers 1995).

New research has shown, however, that 0.08-percent laws do have independent effects, but the lower limits work best when enacted in combination with ALR. In a recent analysis, researchers examined data on fatal crashes for six States that adopted 0.08-percent laws in 1993 and 1994 and six nearby States with higher BAC limits (Hingson et al. in press). Over the study period, the States with lower limits experienced a 26-percent drop in the proportion of drivers in fatal crashes with BAC's of 0.10 percent or higher, which was significantly greater than the 20-percent decline observed in the comparison States. The 26-percent reduction was also significantly greater than the declines observed in all other States that did not have 0.08-percent laws during the same period.

In this study, four of the States with 0.08-percent laws also had ALR laws, but the ALR laws had been in place prior to most, if not all, of the analysis period. Hence, the ALR laws could not have explained the decreases in alcohol-related fatal crashes. The researchers concluded that independent effects of the 0.08-percent law occurred in these States, although they noted that stronger effects had been shown in other studies of States that adopted 0.08-percent and ALR laws at the same time or nearly the same time (Hingson et al. 1996*a*; Rogers 1995).

Another new investigation, a national study conducted over a 16-year period, found that upon enacting 0.08-percent laws, States can expect, on average, an annual 8-percent decline in the proportion of drivers involved in fatal crashes who have positive BAC's (Voas and Tippetts 1999). The reduction attributed to the 0.08-percent laws was observed for drivers at all BAC's and it was distinct from the effects of other DUI laws, safety belt laws, and potentially confounding trends in alcohol consumption and demographic, economic, and seasonal factors. In addition, an 11-State study examined the effects of 0.08-percent legislation in each State before and after the laws were enacted (Apsler et al. 1999). The researchers found that the 0.08-percent laws, alone and in conjunction with ALR laws, were associated with significant declines in alcohol-related fatalities in seven States, as well as with significant declines attributed solely to the 0.08-percent laws in five of those States.

Currently 10 States have adopted neither 0.08-percent laws nor ALR laws. Meanwhile, many other nations have set much lower legal blood alcohol limits than the United States. The limit in Canada, Austria, Switzerland, and the United Kingdom is 0.08 percent. In Australia, the legal

limit ranges from 0.05 to 0.08 percent. The Netherlands, Finland, France, and Germany have 0.05-percent legal limits. Sweden's limit is 0.02 percent, and Japan's is 0.005 percent.

The feasibility of reducing legal limits depends heavily upon public support. In the United States, a recent survey shows that many people do not think that drinking five drinks in 2 hours guarantees unsafe driving (Jones and Boyle 1996). On average, with this level of drinking on an empty stomach, a 165-lb man would reach a BAC of 0.08 percent, which increases the risk of having a fatal crash by about 11 times (see the box "The ABC's of BAC's"). In this national survey of more than 4,000 drivers, however, 75 percent believed that at least half of all drivers would be dangerous if they drove after five drinks in 2 hours, but only 28 percent thought all drivers would be unsafe (Jones and Boyle 1996).

Specific Laws To Deter Repeat Offenders

Once convicted of alcohol-impaired driving, a DUI offender is more likely than other drivers to be arrested again for driving while intoxicated and to be involved in alcohol-related crashes (NHTSA 1996*a*). Repeat offenders account for approximately one-third of drivers arrested or convicted for DUI each year and for one-sixth of drivers with positive blood alcohol levels who are killed in traffic crashes (NHTSA 1995; Voas et al. 1997*c*). Specific deterrence laws seek to reduce this recidivism through such measures as actions against vehicles and tags, lower legal blood alcohol levels for convicted DUI offenders, treatment programs, jail sentences, victim impact panels, probation, detention dedicated to DUI offenders, and a combination of these actions. To follow are highlights of recent research in these areas.

Actions Against Vehicles and Tags. Although license actions have been shown to reduce recidivism, many people with suspended licenses continue to drive. Unlicensed drivers can be apprehended only when police have probable cause to stop their vehicle. Washington and Oregon have enacted legislation that allows police to seize the vehicle registration of drivers caught driving after suspension, leaving the motorist with a temporary, 60-day registration. A sticker on the vehicle tag gives the police probable cause to stop the vehicle and ask to see the driver's license. This law has been effective in Oregon but not in Washington, where it was enforced less often (Voas et al. 1997*a*).

In another recent study, researchers examined the effects of a 1993 Ohio law that permits immobilization of vehicles belonging to people caught driving while their licenses were suspended for a DUI offense (Voas et al. 1997*b*). The immobilization period was 30 days for a first offense, 60 days for a second offense, and 180 days for a third offense. Third- and fourth-time offenders were also subject to vehicle forfeiture. In a 2-year follow-up study, the researchers noted reductions in incidents of driving with a suspended license and of repeat DUI offenses among those whose vehicles were immobilized or impounded. This held true both before and after the offenders reclaimed their vehicles. The research team also evaluated a somewhat different application of the same law in a different part of Ohio and obtained similar results (Voas et al. 1998).

Another approach uses ignition interlock devices to prevent vehicle operation when a measurement of the driver's breath alcohol level exceeds a designated limit. This technique temporarily reduces recidivism, which may rise once the device is removed. In Maryland, 1,380 multiple-DUI offenders with suspended or revoked drivers licenses were randomly assigned to either a treatment program or an experimental interlock program when their licenses were reinstated (Beck et al. 1997). One year later, the alcohol-related traffic violation rate was significantly lower for participants in the interlock program.

Lower Legal Blood Alcohol Concentration Limits for Convicted DUI Offenders. Although persons convicted of DUI have increased chances of further DUI arrests or crashes, almost all States allow the same legal BAC for these drivers as for those never convicted of DUI. One exception is Maine. In 1988, the State set the legal limit at

The ABC's of BAC's

The proportion of alcohol to blood in the body is expressed as the blood alcohol concentration (BAC), which is determined by a person's drinking rate as well as the body's absorption, distribution, and metabolism of the alcohol. To follow is a brief introduction to BAC's and their consequences for driving.

Absorption and Distribution

When alcohol is consumed, it passes from the stomach and intestines into the bloodstream. As it circulates in the bloodstream, alcohol distributes itself evenly throughout all the water in the body's tissues and fluids. Thus, the alcohol level can be measured not only by testing the blood, but also by testing the urine, saliva, or water vapor in the breath.

In cases of traffic fatalities involving alcohol, blood testing must, of course, be used to estimate alcohol levels; otherwise, law enforcement agencies primarily use breath testing. Breath-test results are often converted to equivalent blood alcohol measurements, however, because early drunk driving laws set limits based on blood tests (National Highway Traffic Safety Administration [NHTSA] 1990).

In the United States, blood alcohol measurements are based on the amount of alcohol, by weight, in a set volume of blood. For example, a BAC of 0.10 percent—a level at which it is illegal to drive in the United States—is equivalent to 0.10 grams of alcohol per 100 milliliters of blood. This translates, by weight, to a proportion of just under 1 gram of alcohol for every 1,000 grams of blood in the body (Jones et al. 1998).

Breakdown in the Body

Within a few seconds after ingestion, alcohol reaches the liver, which begins to break it down, or metabolize it. Any BAC measurement therefore reflects not only a person's drinking rate but also his or her rate of metabolism.

Alcohol is metabolized much more slowly than it is absorbed, so the concentration of alcohol builds when additional drinks are consumed before prior drinks are metabolized.

How any one person absorbs and metabolizes alcohol varies depending on factors such as, age, gender, whether or not food is eaten with the alcoholic beverage, and the proportion of body mass that is fatty tissue.

Although individual rates can vary widely, on average, a 165-lb man who has four drinks in an hour on an empty stomach, or a 135-lb woman who has three drinks under similar conditions, would reach a BAC of 0.08 percent (NHTSA 1992). This is the legal limit for driving in 17 States; other States have a 0.10-percent BAC limit (See pp. 382–383 for further discussion on legal BAC limits).

Consequence: Crash Risk

Drinking even a little alcohol can change an individual's ability to respond to the demands of driving. For example, a driver's ability to divide attention between two or more sources of visual information can be impaired by BAC's of 0.02 percent or lower (Howat et al. 1991; Moskowitz 1985; Starmer 1989). Starting at BAC's of 0.05 percent or higher, consistent impairment occurs in eye movements, glare resistance, visual perception, reaction time, certain types of steering tasks, information processing, and other aspects of psychomotor performance (Finnigan et al. 1992; Hindmarch et al. 1992; Howat et al. 1991; Starmer 1989).

Research has documented that the risk of a motor vehicle crash increases as BAC increases (Howat et al. 1991; Starmer 1989; Zador 1991) and that the more demanding the driving task, the greater the impairment caused by low doses of alcohol (Starmer 1989). Increases in blood alcohol levels cause the risk of fatal crashes to rise dramatically (table 1). For drivers under 21 years of age, the fatal crash risk increases to an even greater degree as BAC rises (Zador 1991). Alcohol consumption enhances the dangers unique to young drivers, who have less driving experience and tend to take more risks.

Table 1: Compared With Drivers Who Have Not Consumed Alcohol—

If You Drive With Blood Alcohol Concentration (BAC) in This Range:	Then Your Chances of Being Killed in a Single-Vehicle Crash Increase by:
0.02–0.04 percent	1.4 times
0.05–0.09 percent	11 times
0.10–0.14 percent	48 times
0.15 percent and above	380 times

Source: Data are from Zador 1991.

0.05 percent for drivers previously convicted for DUI, lower than the 0.08-percent limit for other drivers. Convicted drivers have their licenses reinstated on the provision that if they are caught driving with BAC's above 0.05 percent, their licenses will be immediately suspended.

A new study shows that the law significantly reduced fatal crashes involving drivers previously convicted of DUI (Hingson et al. 1998). During the 6 years after the law was enacted, the proportion of fatal crashes involving drivers previously convicted of DUI dropped by 25 percent, while it rose in the rest of New England. In addition, the proportion of crashes involving fatally injured drivers with prior DUI convictions and illegal alcohol levels declined by nearly a third. Most of the later decline was due to a reduction in alcohol-related fatalities of previously convicted drivers with BAC's of 0.15 percent or higher at the time of the fatal crash. Because of the benefits shown by this law, Maine adopted a Zero Tolerance Law for Convicted DUI Offenders in 1995.

Treatment. Treatment to rehabilitate DUI offenders reduces the incidence of repeat offenses by up to 9 percent compared with standard sanctions such as jail or fines, according to an analysis of research on this topic (Wells-Parker et al. 1995). Treatment strategies that combine punishment, education, and therapy with follow-up monitoring and aftercare appear to be more effective than any single approach for first-time as well as repeat offenders, according to the analysis. For example, combining treatment with a licensing action—such as suspension, revocation, or a daytime-only driving permit—was more effective than either tactic alone. In addition, weekend intervention programs that evaluate alcohol and other drug abuse and that create individualized treatment plans produced lower recidivism rates than jail, suspended sentences, or fines.

Jail Sentences. Although jail sentences may have some short-term deterrent effects, mandatory jail sentences tend to negatively affect court operations and the correctional process by increasing the demand for jury trials and plea bargains and by crowding jails (NHTSA 1996*a*). Within the past decade, Norway and Sweden abandoned mandatory jail sentences for people driving above the legal BAC limit. In both countries, traffic deaths decreased after the reforms, which raises questions about the general deterrent effects of jail sentences (Ross and Klette 1995).

Victim Impact Panels. A Victim Impact Panel (VIP) is a group of three or four speakers who were seriously injured or who had a loved one killed in a DUI crash. The panelists present their stories to DUI offenders with the goal of reducing DUI recidivism. In one study, the rates of repeated DUI incidents among 2,000 offenders who attended VIP's were compared with an equal number of DUI offenders who were not ordered to attend the sessions. The study included drivers matched by age and gender in two States; in Oregon those who attended a VIP had a lower rate of recidivism than those who did not, but in California no differences between the two groups were observed (Shinar and Compton 1995).

Probation. According to a 1996 review of sentencing options, probation may slightly reduce recidivism among drivers at low risk for being repeat offenders (NHTSA 1996*a*). However, probation alone does not reduce recidivism among those at high risk for another DUI citation. In one study, the effects of intensive, supervised probation involving both treatment and in-home confinement with electronic monitoring resulted in significant decreases in recidivism relative to comparison groups (Jones and Lacey 1996).

Dedicated Detention. Detention facilities maintained specifically for DUI offenders can offer both incarceration and supervised rehabilitation services. One program of this type, in Prince Georges County, Maryland, reduced recidivism among both first-time and repeat offenders (Harding et al. 1989).

Enforcement of Impaired-Driving Laws

The extent to which drunk driving laws are enforced can influence their impact on impaired driving. Drunk driving arrests increased dramatically between 1978 and 1983, from 1.3 to 1.9 million, but have dropped since then, to 1.5 million in 1996 (NHTSA 1998*b*). The general public may sense this drop in enforcement, as suggested by a 1995 national survey of 4,000 drivers. The survey respondents believed that people who drink and drive are more likely to be in a crash than to be stopped by the police (Jones and Boyle 1996).

Several studies have demonstrated that sobriety checkpoints serve not only to enforce laws, but also to deter drunk driving. In a California study, the use of sobriety checkpoints reduced alcohol-related crashes regardless of the number of officers present or the number of locations used (Stuster and Blowers 1995). In Tennessee, an extensive Statewide sobriety checkpoint program was implemented from April 1994 through March 1995. More than 150,000 drivers were stopped at 900 checkpoints widely publicized on television, on radio, and in newspapers. The program yielded a 22-percent reduction in alcohol-related fatal crashes, compared with five adjacent States during the same time period (Lacey et al. 1997). Publicity appears to have been a crucial element in the effort.

Declining arrest rates may reflect the reduction in the number of intoxicated drivers on the road. Even so, plenty remain to be caught, as only one driver is arrested for every 300 to 1,000 drunk driving trips (Voas and Lacey 1988). It is also possible that arrests have dropped because public pressure has declined. An important area for future research is whether the public views the alcohol-impaired driving problem as less urgent than it did in the early 1980's and how to sustain public concern about this major health problem.

In summary, many different legal approaches have been used in an attempt to reduce the incidence of DUI, with varying degrees of success. The NHTSA (1996*a*) sentencing guide identifies several other sentencing approaches that researchers have not yet systematically evaluated, including financial sanctions, publication of offenders' names in newspapers, victim restitution programs, and court-ordered visits to emergency rooms.

Comprehensive Community Programs

Citing the long-term success of community-based approaches in confronting other public health problems, the Institute of Medicine of the National Academy of Sciences has recommended comprehensive, multistrategy community interventions to reduce alcohol-related problems (Institute of Medicine 1989). One program is described below; a more comprehensive discussion of recent community programs can be found in the section "Community-Based Prevention Approaches" later in this chapter.

In Massachusetts, the Saving Lives Program began in March of 1988 in six cities that had a combined population of 318,000 (Hingson et al. 1996*b*). The communities not only attempted to reduce alcohol-impaired driving, but also targeted other risky driving behaviors in which alcohol-impaired drivers are more likely to engage, such as speeding, running red lights, not yielding to pedestrians in crosswalks, and not wearing seat belts.

In each of the six cities, a full-time coordinator from the mayor's or city manager's office organized a task force of concerned private citizens, organizations, and officials representing various city departments, such as education, health, police, and recreation. Active membership in these task forces ranged from 20 to more than 100 individuals, and included an average of 50 organizations. For funding, each community received about $1 per resident annually from the program.

To reduce drunk driving and speeding, the communities introduced media campaigns, business information programs, speeding and drunk driving awareness days, speed watch telephone hot lines, police training, high school peer-led education, Students Against Drunk Driving chapters, college prevention programs,

alcohol-free prom nights, beer keg registration, and increased liquor outlet surveillance. To increase pedestrian safety and seat belt use, the communities conducted media campaigns and sobriety checkpoints, posted crosswalk signs warning motorists of fines for failure to yield to pedestrians, added crosswalk guards, and offered education programs for preschool children and training for hospital and prenatal clinic staff.

Fatal crashes in these six cities decreased 25 percent compared with the rest of the state, dropping from 178 in the 5 years before the program to 120 during the 5 program years. Fatal crashes involving alcohol declined by 42 percent, from 69 to 36, and fatally injured drivers with positive BAC's dropped 47 percent, from 49 to 24. Visible injuries per 100 crashes declined 5 percent, from 21 to 17. The program also cut in half both the proportion of vehicles observed speeding and the proportion of teenagers who reported driving after drinking.

The results from this and other programs indicate that comprehensive community initiatives that combine the forces of multiple city departments and private citizens can reduce driving after drinking, related driving risks, and traffic deaths and injuries. A major question is whether these changes can be sustained without support from initial funding sources.

Alcohol Control Policies

In addition to laws that seek to deter drinking and driving, a number of laws and policies have attempted to reduce alcohol-related driving deaths by controlling the availability of alcohol as a means of discouraging drinking, particularly among persons under 21. Among the actions described below are raising taxes on alcoholic beverages, mandating training of alcoholic beverage servers, restricting sales through government-run monopolies, and limiting the number and location of alcohol outlets.

Taxes

Studies have consistently found that increases in beer taxes are linked with lower rates of alcohol-related traffic fatalities (Chaloupka 1993; Cook 1981; Saffer and Grossman 1987*a*,*b*). One recent study found, for example, that for every 1-percent increase in the price of beer, traffic fatality rates would be expected to drop by nearly the same proportion, or 0.9 percent (Ruhm 1996). The study found that higher beer taxes are linked most strongly with lower rates of traffic fatalities that occur at night or among those aged 18 through 20.

Another recent study questioned the reliability of the estimated relationship between taxes and traffic fatality rates (Dee 1999). The results showed that the effect on daytime fatalities, although smaller than the effect on nighttime fatalities by about one-fourth, was still statistically significant and of substantial magnitude. The researcher found this result implausible, because alcohol is far more likely to be involved in nighttime fatalities than daytime fatalities.

Results of one study suggested that raising alcoholic beverage prices may have little effect on consumption by the most heavily drinking persons (Manning et al. 1995). The findings showed that the most heavily drinking individuals (the top 5 percent of drinkers in terms of consumption) were significantly less likely than more moderate drinkers to alter their consumption in response to price changes. Although the study showed no significant effects of price changes on consumption among the most heavily drinking persons, it found significant responsiveness to prices among drinkers up through the 90th percentile of consumption levels, with the greatest responsiveness found among drinkers at the 50th percentile.

Estimates of lives saved help to give a concrete picture of the effects of higher alcohol taxes. In estimating the potential effects of the 1991 national alcohol tax increase, one research team started by analyzing motor vehicle fatalities in the 48 contiguous States from 1982 to 1988 (Chaloupka 1993). The investigators estimated that had the tax of 33¢ per six-pack been in effect throughout that period, 1,744 fewer people would have died each year, of whom 671 would have been 18- to 20-year-olds.

Moreover, if the beer tax had been set higher, at 81¢ per six-pack from 1982 to 1988 (based on a tax of 25¢ per ounce of pure alcohol), the researchers estimated that 7,142 fewer people of all ages would have been killed in traffic crashes each year. Of this number, 2,187 would have been youths and young adults. These estimates suggest that raising the tax on alcohol could have saved the lives of considerably more 18- to 20-year-olds than can be attributed to setting the minimum legal drinking age to 21. (See also the discussion in the section "Effects of Changes in Alcohol Prices and Taxes" in the chapter on economic and health services perspectives.)

Server Training, Sanctions, and Liability

When legally impaired drivers take to the road, they are more likely to have just left a bar or restaurant than any other single departure point (McKnight 1993). Between one-third and one-half of intoxicated drivers consumed their last alcoholic beverage at these locations, as reported by drivers in roadside surveys (Palmer 1988; Foss et al. 1990). Breath tests given to patrons leaving bars indicate that about one-third have BAC's above the legal limit (Stockwell et al. 1992; Werch et al. 1988). These findings point to a need for server training programs to help waiters, waitresses, and bartenders to avoid serving alcohol to people who are already intoxicated, as well as manager training to focus additionally on service policies.

During the 1980's, when server training programs proliferated, some communities and States made training a condition of licensing. Evaluations of these programs produced mixed results, but some studies show that such training can modify serving practices to help reduce the rate and amount of alcohol consumed by patrons. After training, servers usually are more likely to intervene with intoxicated customers (Geller et al. 1987; McKnight 1987) and in some instances, patrons have lower BAC's (Hennessy and Saltz 1990; Saltz 1987).

As a result of a server training law passed in Oregon in 1985, some 36,000 servers and 6,000 owner-managers completed a State-approved training course by the end of 1988. All beverage service license holders in the State had completed training by 1991, and 13,000 new servers receive training each year. In the first 6 months of the law, single-vehicle, nighttime crashes likely to involve alcohol decreased by 4 percent (Holder and Wagenaar 1994). This crash rate dropped by a total of 11 percent after the first year, 18 percent after the second year, and 23 percent at the end of the third year. Unfortunately, the researchers did not have direct evidence of changes in alcohol server behavior, although 68 percent of those who completed the course self-reported changes in their behavior (Holder and Wagenaar 1994). Therefore, it is difficult to assess whether all of this substantial 23-percent reduction can be directly attributed to this specific legislation.

All States have either criminal or civil sanctions against serving patrons who are obviously intoxicated; active enforcement of these laws can enhance the effects of server training laws. As one example, after introduction of an enforcement effort in Washtenaw County, Michigan, investigators found that refusals of alcohol service to "pseudo-patrons" (people hired by the researchers to simulate intoxication) rose from 18 to 54 percent (McKnight and Streff 1994). In addition, the percentage of people arrested for drunk driving who had come from bars declined by 25 percent.

All but seven States recognize some form of server liability. These regulations permit individuals to sue for damages incurred as a result of service to a minor or intoxicated patron. In an analysis of the effects of a variety of public policies on mortality rates by State and year, researchers found that server liability laws significantly reduced traffic mortality rates, while mandatory minimum jail sentences and fines did not (Sloan et al. 1994).

State Monopoly Versus Privatized Sales Outlets

Eighteen States have some form of monopoly control over the sale of alcoholic beverages, which influences both the availability and price of alcohol. Compared with States that issue licenses to private retail sellers, in monopoly

states spirits are less available, beer is more available, and alcoholic beverages cost more (Gruenewald et al. 1993).

Relatively little research has examined the effect of State-regulated alcohol sales on alcohol use or related problems. One study documented that a State policy change regarding sales was associated with a significant increase in alcohol-related crashes and single-vehicle, nighttime crashes (Blose and Holder 1987; Holder and Blose 1987). Both types of crashes rose 16 to 24 percent after North Carolina allowed the sale of spirits by the drink in bars and restaurants instead of requiring spirits to be purchased by the bottle at markets and other off-site establishments.

The conversion of Iowa and West Virginia from monopoly to license States resulted in increased sales of alcoholic beverages in both States (Holder and Wagenaar 1990; Wagenaar and Holder 1991). Unfortunately, these analyses did not examine the effect of increased sales on alcohol-related traffic crashes.

Outlet Density

More than a decade ago, researchers established the connection between the density of outlets in an area and fatal traffic crashes (Dull and Giacopassi 1988). The investigators examined alcohol control regulation and outlet density in 95 counties of Tennessee. After controlling for population size, urbanization, and race, they found that both higher outlet density and the absence of restrictions on alcohol sales were associated with increased motor vehicle mortality.

More recently, another research team reported that regions with greater outlet density and higher ratios of outlets to people had higher alcohol sales (Gruenewald and Ponicki 1995). In this study, a 10-percent increase in outlet density resulted in a 4-percent increase in sales of spirits and a 3-percent increase in sales of wine. This team also analyzed crash data from 38 States over 12 years and found that the rates of single-vehicle, nighttime fatal crashes were more strongly related to sales of beer than to sales of spirits and wine. In addition, they explored the question of whether reducing outlet density might lead to increases in fatal crashes as a result of people driving further to obtain alcohol. The researchers found that reductions in the availability of alcohol did not appear to increase the fatal crash rate.

Individual Actions

Designated Drivers

The use of designated drivers has been widely promoted in the United States since 1988, when Jay Winsten at the Harvard School of Public Health initiated a national campaign with the television industry. For 6 years, more than 160 prime-time U.S. television networks, with audiences of 45 million people, showed subplots, scenes, and dialogue in their regular programs as well as 30- and 60-minute episodes supporting the designated driver campaign. The major networks, ABC, NBC, and CBS, also aired public service messages promoting the designated driver concept (Winsten 1994).

Two Roper Organization surveys (1991) showed strong recognition and acceptance of the concept: 93 percent of Americans thought the use of designated drivers was an excellent or good idea, and 46 percent of drinkers reported being a designated driver in 1991 versus only 35 percent in 1987. However, recent national surveys (Voas et al. 1997*c*) revealed a drop from 42 percent in 1993 to 39 percent in 1995 in the percentage of drivers 16 through 64 years of age who said they had been a designated driver. Whether this change reflects reductions in drinking is not clear.

In 1996, the National Roadside Survey stopped drivers at 211 locations in 24 cities or counties on weekend nights, when drinking is most likely to occur. Of the 6,480 drivers stopped, nearly all of whom were breath tested, 24.7 percent reported being designated drivers (Fell et al. 1997). This is a sharp increase from 5 percent who were self-reported designated drivers in a similar survey in 1986 (Lund and Wolfe 1991).

In the 1996 study, most of the designated drivers (82 percent) had BAC's between zero and 0.02 percent. In all, about a third of

designated drivers consumed some alcohol before driving, but most (95 percent) remained at BAC's below the legal limit of 0.08 percent. Also of note in this study, a far greater proportion of non-designated drivers left bars with BAC's of greater than 0.10 percent, compared with designated drivers (8.0 percent of non-designated drivers vs. 1.5 percent of designated drivers).

Whether or not the impaired, non-designated drivers in this study had passengers in their vehicles was not reported. It is quite possible that passengers in vehicles driven by a "designated driver" who has a BAC of 0.08 percent are generally unaware that the driver has consumed that much alcohol. It may be particularly difficult for passengers who themselves have been drinking heavily to discern whether the designated driver has been drinking excessively too.

One recent study of 109 injured pairs of drivers and passengers at a trauma center revealed that more than 4 in 10 drivers and passengers had positive BAC's (Soderstrom et al. 1996). In nearly two-thirds of cases when alcohol had been consumed by the driver, a passenger, or both, the person with the higher BAC was driving.

Thus, many more people now use designated drivers, and most designated drivers in roadside surveys do not exceed the legal BAC limit. However, designated drivers who do exceed the legal limit, like any driver who does so, are at greater risk of crashing. Rather than protecting their passengers, these designated drivers endanger them.

Personal Interventions To Reduce Alcohol-Impaired Driving

Few studies have examined the effectiveness of personal interventions to dissuade impaired people from driving. One recent study of young men who drink heavily, however, found that personal interventions, particularly by wives or girlfriends, can have a high degree of success (Kennedy et al. 1997).

The research team surveyed a random sample of 730 men aged 21 through 35 from areas of the country where a disproportional number of fatal alcohol-involved crashes had occurred. More than half of these men reported having been the target of an intervention to prevent them from drinking and driving. Of the respondents, 41 percent had consumed 10 or more drinks, and another 40 percent had consumed 6 to 10 drinks. Those who intervened were usually friends (51 percent) or wives or girlfriends (36 percent). Most of the respondents (85 percent) reported that the most recent intervention prevented them from driving after drinking. Those who consumed 10 or more drinks were most likely not to drive, and wives or girlfriends were most successful in preventing drinking and driving.

A smaller college survey in California revealed that 73 percent of interventions prevented impaired driving among that population. Assertive interventions were more likely than passive ones to achieve success. Generally, the older and more sober the person who was intervening, the greater the likelihood of success (Newcomb et al. 1997). Systematic programs to increase personal intervention behavior have not been tested, and they warrant consideration.

Safety Belt Laws

People who drive after heavy drinking and passengers who ride with heavily drinking drivers are less likely to wear safety belts, according to studies conducted by observations (Foss et al. 1994) and telephone interviews (Hingson et al. 1996*b*). Both of these studies found that legally intoxicated drivers are about one-third less likely to wear seat belts than are other drivers.

The use of safety belts reduces the risk of crash fatality and serious injury requiring hospitalization by 45 to 50 percent (Voas et al. 1997*c*). However, laws enforcing the use of safety belts have not had that much additional impact, as they reduce injuries and fatalities by only 5 to 10 percent (Campbell and Campbell 1988). One important reason for these smaller than anticipated effects is

that the people most likely to be involved in traffic crashes, such as young males who drive after drinking, have been significantly less responsive to safety belt use laws (Dee 1998). Efforts to combine safety belt laws and drunken driving law enforcement should be considered, particularly in "primary" safety belt law States where police can stop motorists simply because they are not wearing safety belts. Such strategies may hold promise both in reducing driving after drinking and increasing safety belt use.

In Closing

While the overall reduction in alcohol-related traffic deaths since 1982 is a remarkable achievement, progress has slowed in recent years. The current level of 16,000 deaths and more than 1 million injuries in alcohol-related traffic accidents each year demonstrates the need for continuing attention to this major public health problem. Further reductions could be achieved if all States adopted ALR, Zero Tolerance laws for youth, 0.08-percent "criminal per se" laws for adults, and mandatory treatment, if needed, for convicted offenders. These laws would have the greatest benefits if they were actively publicized and enforced at the community level through checkpoints and comprehensive community programs that involve multiple city government departments, organizations, and private citizens.

In the early 1980's, the formation of citizen groups like Mothers Against Drunk Driving reflected a sense among the public that private citizens could participate in identifying more effective solutions to the problem of drinking and driving. Indeed, many important legislative reforms at the State level were enacted. Stimulating public concern and developing new ways to engage private citizens to work with local government departments will be key challenges for the next decade.

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Community-Based Prevention Approaches

In the last decade or so, researchers, community organizers, and funding agencies have shown a heightened interest in community-based prevention programs. This increasing interest has been spurred by the convergence of two subtle but distinct approaches to prevention programs, each of which has evolved to the point where the local community is the "target" of a prevention effort.

In one approach, the community represents an area within which program designers can reach individuals, usually with a health promotion message, in an attempt to change behavior. In this "catchment area" perspective, program staff often define the community in terms of a media market and take advantage of efficient mechanisms for disseminating messages, such as electronic media or billboards.

An alternative approach, sometimes called the public health or "environmental" perspective, tends to focus on formal laws, policies, and practices that affect the production, distribution, sales, and marketing of alcoholic beverages, or formal mechanisms that affect the drinkers themselves, such as drunk driving laws. These prevention programs generally promote policy changes by working through community institutions such as planning commissions or licensing authorities, rather than aiming messages at the general population.

The growth of interest in community programs probably reflects the desire by program planners to combine appealing features from both approaches: the efficient means of reaching individuals in the catchment area approach, and the policy changes at the smallest formal legislative or regulatory setting, such as a city or county, in the environmental approach. Not surprisingly, current prevention programs often blend elements of these two approaches in various ways, as can be seen in the studies described later in this section.

This section presents some fundamental issues underlying community prevention efforts, as well as findings from some recent studies. Earlier community-based prevention studies can be found in a review by Gorman and Speer (1996). Additional sources of information on alcohol prevention projects can be found in Holder and Howard (1992), Greenfield and Zimmerman (1993), Farquhar and Fortmann (1992), and Giesbrecht et al. (1990).

Community Prevention for Heart Disease and Health Promotion: A Precedent

Researchers in the field of cardiovascular disease (CVD) set the precedent for community-based prevention programs. The first of these studies, carried out almost 20 years ago in clinical and work site settings, successfully reduced smoking, dietary fat intake, and other risk factors among individuals who were at high risk of developing CVD (Benfari 1981; Kornitzer et al. 1980). Later studies took a broader approach, targeting entire communities with strategies that combined community organization and health education (Carlaw et al. 1984; Farquhar 1978; Farquhar et al. 1990; Lasater et al. 1984; Murray 1986; Puska et al. 1985).

Some early CVD programs emphasized the power of the individual to alter one's own behavior. For example, the Multiple Risk Factor Intervention Trial (MR. FIT) required clinic patients to sign contracts with program staff stating that they would stop smoking, start exercising, and adopt other healthy habits to reduce their risk of CVD (Benfari 1981). Later programs at the community level targeted similar health behaviors, but instead of individual contracts, their strategies included community organization and the use of social marketing tactics to broadcast health messages (Farquhar et al. 1985).

While researchers in the field of alcohol abuse prevention can build upon the technical expertise and practical experience of these CVD programs, they face different challenges and opportunities in designing alcohol programs. One fundamental difference is that these CVD studies aim to alter a medical endpoint, that is, reducing heart attacks and strokes, by changing people's behaviors. In contrast, a program on alcohol abuse prevention will not have such a narrowly defined, clinical endpoint. Reducing traffic accidents and other problems associated with drinking, for example, but not necessarily the incidence of drinking, is a legitimate goal.

In addition, researchers in alcohol prevention programs must take into consideration that excess alcohol consumption can lead to trauma far more quickly than excess fat consumption or other risk factors can lead to CVD. They also must take into account the fairly complicated social standards associated with drinking that generally do not exist with eating fatty foods or other health habits that contribute to CVD. Alcohol researchers have the advantage, however, of many ready-made opportunities to develop prevention efforts by tapping into local regulatory systems that address alcohol safety issues.

For these and other reasons, community-based alcohol programs require links between public education, community organizations, and agencies involved in regulatory and environmental policies. Hence the strategies used in the studies described below required innovations beyond those used in the CVD studies.

Methodological Concerns

In community prevention research, by definition, whole communities form the intervention and control groups, rather than individuals within those communities. These larger samples may allow researchers more precision in estimating some outcomes, such as the likelihood of becoming intoxicated, or may permit them to capture relatively rare events, such as alcohol-related injuries.

Determining how many communities are required for a study presents a challenge due to the year-to-year variability in alcohol-related problems at the community level, as well as differences in community sizes and growth trends (Saltz et al. 1992). Ideally, one would recruit a large number of communities, with half of the communities receiving the intervention and the other half serving as controls. Because conducting an intervention in just one community can be costly, researchers must decide where to put their resources. They must choose whether to maximize the prevention program activities, or the scope and precision of the evaluation, or the number of communities involved, the latter of which is particularly difficult since the number needed for finding statistical significance is uncertain. Each research team must find the best balance of these competing claims on resources.

Choosing communities to recruit into a study is also problematic. The selection of communities is often related to proximity to the research team rather than any strong theoretical rationale. There seems, too, to be an implicit selection of smaller, and likely more manageable, communities over large cities or districts. Moreover, the choice of outcome measures—such as single-vehicle, nighttime crashes—may dictate selection of communities, because of jurisdictional constraints on collecting and reporting data.

Conventional wisdom would argue that adopting the classic experimental design, that is, randomly assigning communities to be either the intervention (treatment) group or the control group, would maximize the validity of results (Wagenaar et al. 1994). Some researchers have taken a different position, however, in that they purposely select intervention communities that appear most accommodating or ready to adopt the treatments the researchers are evaluating (Holder et al. 1997). They argue that if an arbitrary selection of communities produced no impact, one could not be sure if the intervention itself was without merit, or if it would have worked in a community that was more supportive. The merit of this argument would seem to depend first on whether

a community's "readiness" can be assessed, and second on one's conception of an "intervention." Some might argue, for instance, that getting the community ready should be part of the intervention itself.

Finally, a range of other methodological issues arise in community intervention studies, including:

- How to adjust for the fact that when data are collected from intact social units, they are more homogeneous than one might find in a purely random sample (Murray and Wolfinger 1994).
- How to design and conduct evaluations in dynamic environments (Goodman and Wandersman 1994; Pentz 1994; Stout 1992).
- How to evaluate interventions as they evolve in different ways at different sites (Hansen and Kaftarian 1994).
- How to maintain the scientific integrity of the research design within the context of working with communities (Howard and Barofsky 1992).

An excellent overview of study design and other methodological issues can be found in a set of papers from a 1995 Symposium on Community Intervention Trials published in the *American Journal of Epidemiology* (Donner 1995; Fortmann et al. 1995; Green et al. 1995; Koepsall et al. 1995; Murray 1995).

Recent Research Results

A review of recent literature reveals results from three major community-based studies in the last 3 years to prevent alcohol problems. The first, Project Northland, builds upon school-based prevention programs but extends beyond the classroom into the community. The second, Communities Mobilizing for Change on Alcohol, focuses on reducing youth access to alcohol. Finally, the Community Trials Project targets alcohol-related trauma through integrated interventions focusing on community laws and policies. (An additional community project, the "Saving Lives Program," is described in the section "Reducing Alcohol-Impaired Driving" earlier in this chapter.)

Preventing the Onset of Adolescent Drinking: Project Northland

As school-based prevention programs have become more refined and informed by research, they have expanded from a focus on the individual to a broader approach that includes environmental influences, in particular the effects of peers. Whereas early programs may have emphasized the physical effects of alcohol or an individual's decision-making skills, current programs tend to have students examine their perceptions of alcohol use among peers, learn to resist peer influence, or take part in activities that involve peer education and events outside the classroom.

Project Northland, which focused on high-risk, relatively heavily drinking communities in northern Minnesota, is representative of this general trend. Starting in 1991, the project team surveyed approximately 2,000 students who were in sixth grade and tracked them for 3 years (Perry et al. 1996). The researchers combined school districts to form a sample of 20 sites, then randomly assigned 10 sites to the intervention, or treatment program. The other 10 sites, which served as a comparison set, continued whatever programs they had in place.

The project team developed three different treatment programs, one each for grades six through eight. Each program included components not only for students, but also for parents and the larger community. Thus, the students were subject to a "multiyear, multilevel" intervention. The sixth-grade curriculum, for example, combined classroom sessions with homework exercises that involved the children's parents. In addition, the intervention included forming communitywide task forces that developed policies related to underage drinking.

Similarly, the seventh-grade program comprised an 8-week, peer-led classroom curriculum with peer-directed, alcohol-free activities outside the classroom, home program booklets, and newsletters to parents. In addition, the intervention communities mobilized to pass local ordinances and resolutions to limit alcohol availability to youth. Businesses and schools provided incentives for students who pledged to be alcohol- and drug-free.

The eighth-grade curriculum encouraged students to look specifically at individuals and organizations that influenced adolescent alcohol use. Students collected information from various community members through interviews, then formulated model alcohol policies in a simulated town meeting. Parents attended student-produced plays with an alcohol prevention theme. As in the prior year, eighth-grade peers led alcohol-free "alternative" activities. At the same time, the task forces continued intensified efforts to develop local alcohol-related policies.

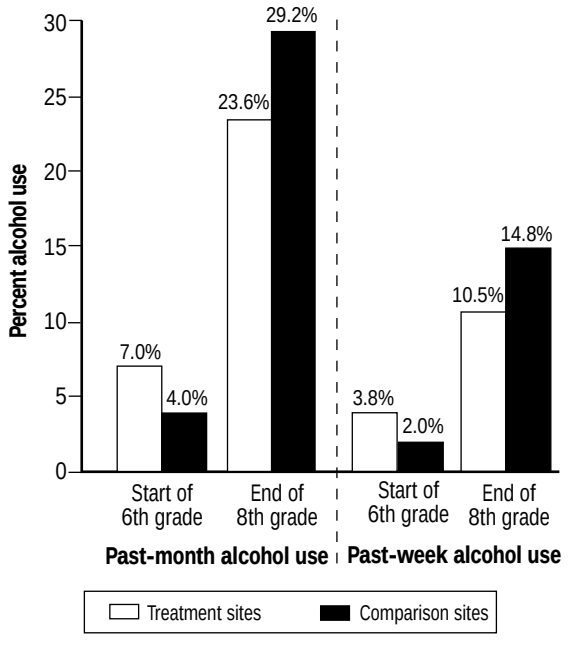
From grades six through eight, the materials and activities moved from a focus on the self to interactions with parents, peers, and the community at large, thus engaging the students in expanding "concentric circles of influence." By the eighth grade, the students were involved in the larger community in ways that would presumably foster both their own and the community's ability to change the environmental influences on adolescent drinking. More details on the program, including measures of participation, can be found in Williams et al. (1995) and Komro et al. (1994).

The researchers surveyed 2,350 students at the beginning of the study, then conducted follow-up surveys at the end of each of the 3 school years. They managed to retain 1,900 students for survey purposes throughout the entire study period, with most of the attrition due to students moving from the area. The surveys focused primarily on the use of alcohol (past month and past week), tobacco (cigarettes and smokeless tobacco), and marijuana. The researchers assessed the "tendency to use alcohol" by creating a scale that combined certain survey responses, such as linking a student's actual use of alcohol with his or her intentions to use it. In addition, the project team measured peer influence, self-efficacy, perception of access to alcohol, and mediating factors such as communication with parents.

By the eighth grade, students in the treatment sites had lower rates of alcohol use, both in the past month and past week, as well as lower scores on the "tendency to use alcohol" scale. These statistically significant differences were observed despite the fact that the intervention sites, though selected at random, had higher alcohol use rates at the beginning of the study.

For example, at the start of the study, sixth graders in the treatment sites had almost double the rate of past-month alcohol use of those in the comparison sites (7.0 vs. 4.0 percent) (figure 1). By the time they reached eighth grade, however, students at the treatment sites had a significantly lower rate of past-month use (23.6 vs. 29.2 percent). Similarly, in sixth grade, the intervention group had nearly double the rate of past-week use (3.8 vs. 2.0 percent), but by eighth grade their rate was again significantly lower

Figure 1: Results from Project Northland



than the comparison group (10.5 vs. 14.8 percent). No significant differences were observed for cigarette, smokeless tobacco, or marijuana use—which were not targets of the program—except for a higher initial rate for cigarette use in the intervention sites (6.9 vs. 4.7 percent).

On the measure of general peer influence, students in the intervention sites had lower scores in the eighth grade than did those in the comparison sites (at the start of the study there were no significant differences between the sites). No significant differences were observed between the treatment and comparison schools in terms of students' self-efficacy, perceived access to alcohol, or communication with parents.

Because the intervention sites started at somewhat of a disadvantage, in that more students used alcohol when the study began, the research team analyzed the data in terms of student alcohol use at the start of the study. When they looked only at students who were not drinking at the beginning of the study, the researchers found not only lower alcohol use by eighth grade in the treatment sites (15.3 vs. 21.2 percent in past month), but also lower use of cigarettes (15.5 vs. 24.6 percent) and marijuana (3.1 vs. 6.2 percent). In contrast, none of the rates of use changed among students who were already "users" at the study's beginning.

The overall implication for the study was that the program affected those students who had not yet begun to use alcohol, but had little or no impact on those students who were already drinking.

This study focused on adolescents and their use of alcohol and other drugs, rather than on the effects the programs may have had on the larger community and its alcohol consumption or related problems. As with most community prevention studies, the effect of the community-level activities such as plays for parents and community task forces could not be estimated separately from the other program elements. Some findings suggest, however, that these activities outside of the classroom may have had limited impact on the community as a whole. For example, at the end of the study, the students in the intervention sites and comparison sites showed no significant differences in their perceptions of alcohol availability or the consequences of driving after drinking. Future research could test the efficacy of these other activities by systematically excluding them from the overall program to see if they are necessary or not, or if there is an important interaction between the classroom activities and these other elements.

Underage Access to Alcohol: Communities Mobilizing for Change on Alcohol

This community-organizing effort was designed to reduce drinking and drinking-related problems among 15- to 20-year-olds by reducing their access to alcohol. Communities Mobilizing for Change on Alcohol (CMCA) aimed to build the capacity of communities to change their own policies and practices related to alcohol access (Wagenaar et al. 1994). It was hoped that the intervention would better equip the communities to handle not only a wider range of alcohol-related problems, but also other health and social problems.

The CMCA project team identified five focus areas: (1) influences on community policies and practices, including community action to change policies, pressure on enforcement agencies to enforce existing policies, and influences on parents and others to support these efforts; (2) the policies and practices themselves, in particular formal laws against serving minors and informal practices related to enforcing those laws; (3) youth access to alcohol, that is, the relative ease or difficulty with which minors could obtain alcoholic beverages, which was thought to affect the final two components; (4) youth alcohol consumption; and (5) youth alcohol problems.

The researchers recruited 15 communities in Minnesota and western Wisconsin, each of which had a school district with at least 200 ninth graders. The researchers formed seven pairs of communities, plus one group of three communities, by matching for their size (the populations ranged from 8,000 to 65,000), State, proximity to

a college or university, and baseline data from an alcohol purchase survey. Each set of communities had one intervention site that had been selected at random and one or two comparison sites.

The researchers sought to organize the communities to develop their own specific interventions to influence underage access to alcohol. As determined by each community, any number of activities could be included, such as using decoy operations (in which underage buyers attempt to purchase alcohol at selected outlets), citizen monitoring of outlets selling to youth, requiring keg registration, developing alcohol-free events for youth, shortening hours of sale for alcohol, initiating responsible beverage service (RBS) training, and developing educational programs for youth and adults (Wagenaar and Perry 1994). To coordinate the activities, the CMCA project hired, trained, and supervised a part-time local organizer from within each community.

The researchers gathered evaluation data before the interventions began and again 2.5 years later, focusing on questions about alcohol use, purchasing behavior, perceptions of availability, and other measures. They conducted surveys of 9th-grade students at baseline, 12th-grade students at baseline and follow-up, 18- to 20-year-olds, alcoholic beverage merchants, and outlets in which 21-year-old women who appeared to be younger attempted to purchase alcohol without showing identification. Other methods included monitoring mass media and collecting process-oriented data to capture how the intervention moved ahead and how the staff and communities surmounted obstacles in reaching their objectives.

The results of the intervention were mixed. After the 2.5-year program, merchants checked more frequently for age identification, reduced their likelihood of sales to minors, and reported more care in controlling sales to youth (Wagenaar et al. 1996). The telephone survey of 18- to 20-year-olds showed lower frequency of providing alcohol to other minors and decreased likelihood of buying and consuming alcoholic beverages themselves. Disappointingly, these results were not, in themselves, statistically significant. The researchers argue, however, that progress was made consistently in all seven of the intervention sites. Future analyses of these data or replication of the study may help to discern whether the results indicate a meaningful impact.

Meanwhile, the baseline data from CMCA is providing insights into the nature of underage drinking, with a number of papers published in the past 3 years. As one example, an analysis of the baseline data on 12th graders showed that the young men tended to drink more if they had heavily drinking peers, liberal drinking norms, the perception that alcohol was readily available, and the sense that parents and school officials were unlikely to catch them drinking (Jones-Webb et al. 1997). The pattern was similar for female 12th graders, except that their consumption was not influenced by their perceptions about availability.

Preventing Injuries and Deaths Related to Drinking: The Community Trials Project

The Community Trials Project (CTP) differed from the previous two studies in two important respects: first, the project aimed to reduce injuries and deaths related to drinking rather than alcohol consumption itself, and second, it sought to reduce trauma over the entire population rather than in adolescents exclusively (Holder et al. 1997; Treno and Holder 1997*a*). The project was conducted in three areas—northern California, southern California, and South Carolina—each containing one experimental community matched with one comparison site. Five interacting project components, with the goals and actions listed below, were successfully implemented in all three experimental communities.

- "Community Knowledge, Values, and Mobilization" Component: Included developing community coalitions to address local problems, increasing the community's

awareness of the problems, and obtaining support for project activities through media events and other means (Holder and Treno 1997; Treno and Holder 1997b,*c*; Treno et al. 1996).

- "Responsible Beverage Service Practices" Component: Primarily sought to reduce the risk of intoxicated and underage customers in bars and restaurants by training a substantial number of managers and servers (Saltz 1997*a,b*; Saltz and Stanghetta 1997).

- "Reduction of Underage Drinking" Component: Placed pressure on retailers to reduce sales to underage youth and included the implementation of police stings (Grube 1997*a,b*; Grube and Voas 1996).

- "Risk of Drinking and Driving" Component: Aimed to reduce the incidence of driving under the influence (DUI) of alcohol, and resulted in significant increases in police enforcement activity against drunken driving (Voas 1997; Voas et al. 1997).

- "Access to Alcohol" Component: Attempted to reduce the availability of alcohol, which led to community action directed at regulating alcohol outlets (Gruenewald 1997; Gruenewald et al. 1996*a,b*; Millar and Gruenewald 1997; Reynolds et al. 1997).

On the basis of their preliminary findings, Holder and colleagues (1997) characterize the CTP as successful in several respects. The primary outcome of interest, alcohol-involved traffic crashes, was estimated to have dropped by about 10 percent annually over the 28-month intervention period for which data were available. The community mobilization effort carried out the interventions successfully and with significant community support, especially when the participants understood the research base for the strategies. Media coverage of alcohol-related trauma and control policies increased as a result of training community members. And finally, sales of alcoholic beverages to underage decoys were reduced. To follow are some details about the five project components, their strategies, and the results.

Community Knowledge, Values, and Mobilization. This component aimed to help the communities become aware, concerned, and organized enough to develop and implement their own action plans for addressing local problems. Creating a core of effective program staff was a critical first step. In all three experimental communities, local program staff were hired during the first project year. A project coordinator, who was a trained and experienced community organizer, provided regular on-site technical assistance to all three communities.

Keeping local staff and coalitions informed was a top priority. Early in the first project year, orientations were held in each community to provide details to local staff, coalition members, and community leaders about the project goals and components. During the second project year, local staff received training in "media advocacy" to help gain media coverage for project messages and activities. Also during the second year, the scientific staff provided training on project research rationales and component designs to local staff and coalition members. Additional guidance was provided by a professional advisor on political and legislative action, alcohol problem prevention, and community organization and activism.

As the communities mobilized, the broad-based coalitions provided general support for project goals, while task forces developed specific strategies and intervention plans. Among the strategies that were developed and implemented by one or more of the communities are the following: increased arrests for DUI, establishment of police stings, adoption of alcohol outlet density regulations, training for clerks and those holding licenses to sell alcohol, implementation of RBS standards at community events, and introduction and use of passive DUI breathalyzers. (The sections that follow provide details about some of these strategies.)

On the basis of the study results, the researchers identified six points as essential in mobilizing communities to support prevention programs:

- It is important to explain the research base for the interventions to the community participants.
- Existing community coalitions may take their own lead and require only project staff guidance when considering specific interventions.
- Preexisting community support for project interventions is essential to developing intervention programs rapidly.
- Existing support for project interventions among community leaders may be used to focus mobilization efforts.
- Community events such as local festivals may provide opportunities for intervention and to galvanize public support.
- Media events may generate project enthusiasm.

These experiences were seen to parallel those of community intervention efforts in other countries (Gorman and Speer 1996; Midford et al. 1995) as well as in the United States (Hingson et al. 1996; Wagenaar and Perry 1994).

Responsible Beverage Service Practices. The goal of this component was to reduce the likelihood of customer intoxication at licensed bars and restaurants by implementing RBS practices (Saltz 1997; Saltz and Stanghetta 1997). Specifically, these practices were (1) to monitor customer consumption of alcohol and pace the more heavily drinking patrons to prevent intoxication, (2) to prevent intoxicated patrons from driving or engaging in other risky behaviors, (3) to serve drinks in standard serving sizes, (4) to promote consumption of food and nonalcoholic beverages, and (5) to avoid price promotions for alcoholic beverages, such as "two-for-one" sales and "happy hours."

The experimental communities met these objectives through several tactics. They obtained support from local and State hospitality organizations for RBS training, then provided the training, using a standard curriculum, to managers and servers at licensed alcohol outlets. In addition, they increased enforcement of laws regarding service to intoxicated customers, obtained endorsement of RBS from civic bodies and organizations, and explored the use of local licensing or zoning authority to require RBS practices.

To evaluate this component, the research team sent trained associates to a sample of establishments and had them order enough drinks to require intervention on the part of the server. Since the researchers were looking for effects of this component at a *community* level in the experimental sites, the sample included some establishments that had undergone voluntary training and others that had not. Although prior research has demonstrated that RBS training improves server practices in a given establishment, this study suggests that voluntary training in a *portion* of a community's establishments has little effect on the community as whole. This conclusion is supported by a preliminary analysis, in which no significant differences in server intervention were observed between experimental and comparison sites (Saltz and Stanghetta 1997).

Reduction of Underage Drinking. This component made use of three intervention strategies: enforcement of underage sales laws, clerk training and outlet policy development, and media advocacy (Grube 1997*a*,*b*; Grube and Voas 1996). As part of this effort, local police sent warning letters to all outlets informing them that routine enforcement of underage sales laws was being initiated. The letters were followed by a series of decoy operations in which the police had underage buyers attempt to purchase alcohol at selected outlets. Outlets selling to the decoy buyers were cited. To further increase perceptions of enforcement, warning letters reminding off-license owners and managers about ongoing decoy activities were regularly sent to all outlets. These activities were combined with a media advocacy campaign designed to elicit community support and to raise awareness of increased enforcement among owners and managers of

businesses like liquor stores and markets that sell alcohol for consumption off-site.

The researchers found that prior to the intervention, randomly selected outlets in the experimental sites were about equally likely as those in comparison sites to sell alcohol to an apparent minor. After the intervention, however, experimental community outlets were about half as likely as those in comparison sites to sell alcohol to an apparent minor.

Risk of Drinking and Driving. This component also used three intervention strategies: expansion of DUI news coverage, implementation of sobriety checkpoints, and use of a special breath-testing program (Voas 1997; Voas et al. 1997). Expanded DUI news coverage was achieved through the media advocacy efforts of community coalition members, who worked with the media consultant and police department leadership. Releases to the news media reported changes in DUI enforcement, covering topics such as the novelty of new breath sensors; the use of DUI "sweeps"—intensive efforts on a single night with multiple roadblocks; and the development of special patrols. Police departments established sobriety checkpoints for random breath testing of motorists in each of the experimental sites. In two of the three sites, a special breath-testing program was initiated in which DUI police patrols were staffed with additional officers and provided with breath testers concealed in flashlights. These additional enforcement efforts significantly increased arrests for DUI within these two sites.

The activities of this component had a statistically significant impact upon traffic crashes involving alcohol. The overall reduction in alcohol-involved crashes, compared with control sites, was 78 crashes over a 28-month intervention period; this represents an annual reduction of 10 percent.

Access to Alcohol. The final component used three intervention strategies as well: mapping and publicizing the connections between the geographic availability of alcohol and alcohol-related problems, developing local planning and zoning policies to regulate the density of alcohol outlets, and encouraging community action to revoke licenses from problem outlets (Gruenewald 1997; Gruenewald et al. 1996*a*,*b*; Millar and Gruenewald 1997; Reynolds et al. 1997).

Early in the intervention, researchers made maps of the experimental communities that displayed the denser pattern of alcohol-related crashes around the areas with higher concentrations of outlets. Guided by the maps, community coalitions and planning and zoning departments developed policies that increased the distance requirements between outlets and strengthened regulation of problem outlets. Community groups joined in these efforts by overseeing license renewals and staging protests against problem outlets. Ultimately this component led to greater local input in license renewal; new regulations regarding special event permits, such as banning alcohol at some public activities; and successful protests of licenses that eliminated sales of alcohol from problem outlets.

Commentary and Future Research Needs

While none of these community-based alcohol prevention studies has reported substantially large impacts on their chosen targets, a real effect may be seen in all of them. Each described study was predicated on the belief that working at the community level could produce a synergism not observed with smaller scale interventions—that is, with a communitywide effort, the final outcome would be greater than merely a sum of the individual parts. However, individual aspects of these studies—such as Project Northland's curriculum materials and the DUI enforcement campaign of the CTP—were so well developed that the observed impact might have been achieved even without the benefit of other community activities.

Researchers in the field of CVD prevention (Koepsell et al. 1995) raised a related question regarding their experiences with community-based interventions. They describe the effects of these programs as "quite modest" even though

great effort and funds were expended on them. These authors go on to say:

> Such questions point out a need for future community prevention studies to incorporate cost-benefit analysis along with measures of program impact. Policy makers and communities are not typically swayed solely by the fact that some reduction in a given problem can be achieved. Rather, they want to know how much such a reduction will cost and how that would compare to other alternatives to improving the community's health. (p. 598)

These cautionary comments raise the additional issue of making generalizations about the outcomes of these community studies. A particular impact demonstrated by a study may not be detected in other settings where implementation may be less intense, where evaluation data may not be available, or where the program does not benefit from a "halo" derived from academic involvement. Thus, neither the costs nor the benefits of conducting an intervention in one community will necessarily transfer to other communities.

A related concern is how to sustain the impact of community interventions. The impact may depend on large infusions of resources, or fade in time as the novelty of the interventions wears off. These concerns are perhaps more relevant to educational or awareness campaigns that require continuous sources of money rather than, for example, zoning law changes, which would presumably continue in force with lower maintenance costs. Even law enforcement, however, requires a commitment of will and money to be sustained over the long run.

Not all community-based alcohol interventions are expensive, however. The CMCA intervention entailed one half-time staff member per community with some support from a university. Another relatively inexpensive program, of the Addiction Research Foundation in Toronto, Canada, has been working to help communities in Ontario develop municipal alcohol control policies by disseminating model policies and making brief presentations to municipal officials (Gliksman et al. 1995).

Moreover, progress may be hastened if, in addition to conducting large, comprehensive intervention studies—which by their sheer cost will be limited in number—the field develops smaller studies that break community interventions into component parts for closer study. This strategy and other important topics for future research efforts are described below.

Closer Investigations

Our understanding of comprehensive interventions would be enhanced if more were known about how to model specific components of the interventions. To take a relatively simple example, we would like to know how much effort it takes to make a community aware of something: How many messages are needed? Of what type? Over what time frame? And how do environmental factors such as newspaper readership and community size interact with the process?

In a different arena, one might ask about the impact of law enforcement "stings" of outlets. How many does it take to get other owners' attention? What accelerates or impedes the diffusion of information to those businesses, given that some are very small-scale operations and some have owners and staff with limited proficiency in English? Does an environmental change reach its greatest impact immediately, or does it have its greatest influence on the generation that comes to drinking age after the change is in place?

These questions are not only a pursuit of answers for their own sake but would also inform the more comprehensive studies as well. Apart from the tradition of "time-series" modeling, in which the time, intensity, and duration of the intervention must be specified, the field does not usually address the question of how best to model an intervention. Usually, there is an implicit

pretest versus posttest comparison, as though the intervention were a discrete event falling in between those two time points. Greater knowledge of individual intervention processes may enable the use of more powerful analytic tools tailored either to interventions that are cumulative over time or to studies better characterized as relatively short "blips" or spikes, such as law enforcement campaigns.

Mobilization Strategies

In the area of community mobilization, researchers have attained much practical experience and have made their knowledge available though guidebooks and case studies. As a topic of formal research, however, community mobilization remains underdeveloped. Among the studies described herein, the CMCA study most strongly emphasized community organization as a central component rather than a supporting activity. Although the researchers reported some measure of success, it would have been helpful to compare their approach with competing models of community organization to see where a given strategy worked best and least well. This was beyond the scope and budget of the CMCA project, but future research could address these specific strategy questions directly, without entering into matters of overall design or final impact.

To look at but one major issue bearing upon community mobilization, there is an underlying, implicit divergence of perspectives running through discussions on intervention strategies. This issue has to do with whether a community is considered a homogeneous collection of individuals moving together in some way, or whether the community comprises a complex mix of individuals with different values, knowledge, and ability to influence public affairs. Of course, the latter is closer to the truth, yet most discussions of community interventions treat the community as though it had one set of values or moved in concert toward an increased level of awareness.

An alternative approach could focus on identifying various community players and, like a political campaign, enhance the support of those who are already "loyal" to the goals of the intervention, avoid mobilizing those who are in opposition, and work on the "swing votes." This "political campaign" strategy is not necessarily the superior approach, but without some kind of formal investigation, community-based interventions will continue to be dominated solely by conventional wisdom regarding the place and value of task forces, collaborations, and coalitions.

Novel Interventions

Another important area of future effort is the development of novel interventions. The scope of current community-based interventions is rather narrow. All three of the studies described previously, for example, aimed to reduce adolescent access to alcohol. In part, this strategy reflects an understandable conservatism to employ more conventional interventions in large-scale projects. Smaller studies, however, could explore more unusual strategies while still operating at the community level. For example, collaborations could be developed with alcohol retailers to promote low-alcohol and alcohol-free beverages, or local fees could be used to support closer monitoring of alcohol licensees, as some communities are initiating on their own.

The call for novelty might also involve the targets chosen for prevention. Compared with underage drinking, for example, very little has been designed to reduce alcohol-involved violence. In part, this merely reflects a less developed understanding of the incidence and sources of violence in the community. Still, some existing interventions, such as reducing teenage access to alcohol and enforcing RBS practices, could cut a community's level of violence. Indeed, a community initiative in Australia's Gold Coast employed a combination of RBS and community policing that appears to have reduced alcohol-related violence in one notorious tourist center (Homel et al. 1997). (For more information on alcohol and violence, see the first chapter in this report.)

In Closing

Although community-based prevention research is in its early development, interest in full-scale community studies of the kind described here should be complemented with a range of smaller studies to allow better identification of potentially powerful interventions and the best ways of implementing them. This approach would require peer reviewers, policy makers, and funding agencies to recognize the value of such modest studies even where a "final" answer regarding impact is not forthcoming.

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Alcohol Advertising: What Are the Effects?

Does alcohol advertising increase the overall level of alcohol consumption? Does it predispose children and adolescents to drinking? Although these and other related questions have been raised by public health advocates and echoed in public opinion surveys, the evidence from research to date is mixed and far from conclusive. In general, studies based on economic analyses suggest that advertising does not increase overall consumption, but instead may encourage people to switch beverage brands or types. At the same time, research based on survey data indicates that children who like alcohol advertisements intend to drink more frequently as adults. While these findings might offer some grounds for both reassurance and concern, the limitations of the research methods that have been used hinder the ability to draw firm conclusions about cause and effect in either case.

In recent years, public health advocates have called for strict regulation or elimination of alcohol advertising (Mosher 1994), and community-level action has focused on reducing local alcohol advertising (Woodruff 1996). Particular attention has been devoted to how alcohol advertising might affect young people (Atkin 1993) and to the targeting of minority communities (Abramson 1992; Alaniz and Wilkes 1995; Scott et al. 1992). A poll of public attitudes found that 57 percent of the public support prohibiting alcoholic beverage advertisements on television, 64 percent support advertising to counteract alcohol advertisements, and 41 percent support prohibiting sports sponsorship by the alcohol industry (Kaskutas 1993).

As described in this section, researchers have examined the effects of alcohol advertising through four main types of studies: experimental research in controlled settings; econometric analyses, which apply economic research techniques; surveys; and intervention studies of "media literacy" programs that encourage skepticism about advertisements. In general, experimental studies based in laboratory settings provide little consistent evidence that alcohol advertising influences people's drinking behaviors or beliefs about alcohol and its effects (Kohn and Smart 1984; Kohn et al. 1984; Lipsitz 1993; Slater et al. 1997; Sobell et al. 1986). In addition, econometric studies of market data have produced mixed results, with most showing no significant relationship between advertising and overall consumption levels (Fisher and Cook 1995; Gius 1996; Goel and Morey 1995; Nelson and Moran 1995).

Survey research of children and adolescents, however, provides some evidence of links between alcohol advertising and greater intentions to drink, favorable beliefs about alcohol, and a greater likelihood of drinking (Austin and Meili 1994; Austin and Nach-Ferguson 1995; Grube 1995; Grube and Wallack 1994; Wyllie et al. 1998*a*,*b*). Still, the survey study designs employed thus far have not been able to establish whether, for example, the advertisements caused the beliefs and behaviors, or whether preexisting beliefs and behaviors led to an increased awareness of the advertisements. Media literacy training may increase the ability of children and adolescents to offer counterarguments to messages in alcohol advertisements (Austin and Johnson 1997*a*,*b*; Slater et al. 1996*a*), but studies have not yet measured whether these effects persist beyond a short term.

The following is a review of the evidence, from each of these research areas, about the effects of alcohol advertising on alcohol consumption, alcohol-related problems, and drinking-related beliefs and attitudes. Studies have been drawn from such diverse fields as drug and alcohol studies, communications, psychology, sociology, marketing and advertising, and economics.

Background: The Frequency and Content of Advertising Messages

Concerns about alcohol advertising stem at least in part from its pervasiveness. The alcohol industry spent $1.03 billion on alcohol advertising in 1996, with the expenditures concentrated on television commercials and beer advertising (Besen 1997). Thus alcohol advertising, especially for beer, appears relatively frequently on television. Moreover, this advertising tends to appear most often during sports programming. While about one alcohol commercial appears in every 4 hours of prime-time fictional programming, one appears for every 25 minutes of programming for major professional sports (football, baseball, and basketball) and one for every 50 minutes of college sports programming (Grube 1993, 1995; Madden and Grube 1994). Overall, alcohol commercials make up 1.5 percent of all advertisements on prime-time television and 7.0 percent of all advertisements in sports programming.

Standard commercials, however, are not the only way in which alcohol is marketed on television. Alcohol advertisers use other types of promotions embedded in sports programming to place their product names, slogans, and symbols before the television viewing audience. Stadium signs, brief sponsorships (such as "This half-time report is brought to you by…"), and on-site promotions (such as product symbols and names on race cars) are broadcast to the television viewing audience at a rate of 3.3 per hour in major professional sports programming, 3.0 per hour in other professional sports programming, and 0.3 per hour in college sports programming (Grube 1993, 1995; Madden and Grube 1994).

The engaging images and messages in alcohol commercials may add to the perception, among critics, that advertisements contribute to increased drinking and drinking problems. What is engaging about the advertisements? Although no recent research has investigated this question, older content analysis studies of alcohol advertisements show that alcohol ads link drinking with highly valued personal attributes, such as sociability, elegance, and physical attractiveness, as well as with desirable outcomes, such as success, relaxation, romance, and adventure (see, for example, Atkin and Block 1980; Strickland et al. 1982).

Researchers have been particularly interested in the degree to which children and adolescents pay attention to these commercials. In one survey of fifth- and sixth-grade children, 59 percent of the children could correctly identify the brand of beer being promoted from an edited, still photograph taken from a television commercial featuring Spuds McKenzie (Grube 1995). A vast majority of the children (82 percent) in the same survey correctly matched the advertising slogan, "Spuds McKenzie, the original party animal," with Budweiser.

Alcohol advertising with celebrity endorsers, humor, animation, and rock music has been shown to be especially appealing to adolescents (Atkin and Block 1983; Grube 1995). In addition, a study of adolescent boys confirmed that they were particularly attracted to alcohol advertisements depicting sports (Slater et al. 1996*c*, 1997). In one recent study, adolescents perceived that a significant number of alcohol advertisements portray people under 21 years of age (Slater et al. 1996*b*). Other research has indicated, however, that adolescents' identification with the actors in the ads, or their desire to be like the actors, is relatively low (Austin and Meili 1994). Lifestyle- or image-oriented alcohol advertising has been shown to be more appealing to both adults and adolescents than is alcohol advertising that promotes only product quality (Covell et al. 1994).

Besides the frequency of advertisements and their appeal to minors, concerns have also stemmed from advertising content that raises safety questions. One study found that 33 percent of television beer advertisements (16 of 49) contained scenes of people drinking and either driving or engaging in water activities such as swimming or boating (Grube 1995). Moreover, messages to drink safely and moderately (such as "Know when to say when") appear in less than 1 percent of alcohol advertisements and have been criticized for not clearly defining responsible drinking (DeJong et al. 1992).

Does Alcohol Advertising Affect Drinking or Drinking Problems?

Earlier reviews have concluded that the effects of alcohol advertising on people's drinking beliefs and behaviors are limited, at best (Atkin 1995; Calfee and Scheraga 1994; Fisher 1993; Smart 1988). More recent research has not markedly changed this conclusion.

The two key questions that frame most of the current studies are whether alcohol advertising (1) increases overall drinking and drinking problems in the population or (2) increases drinking among children and adolescents or favorably predisposes them toward alcohol. A third important question about the possible effects of alcohol advertising on minority populations, who have been targets of advertising for particular alcohol products, has received little or no quantitative research to date and therefore is not covered in this review.

In the descriptions below, alcohol advertising research is grouped into four types of studies: experimental studies, econometric studies, survey research, and media literacy interventions.

Experimental Studies

Experimental studies have investigated how short-term exposure to alcohol advertising affects people's drinking beliefs and behaviors under controlled conditions. Typically, a group of participants is exposed to one or more alcohol advertisements embedded in a television program, among a series of neutral advertisements, or, in the case of print advertising, in a booklet or magazine. The investigators then compare the experimental group's beliefs or behaviors related to drinking with those of a control group that views the same items without the embedded alcohol advertisements. The results of earlier experimental studies have been mixed, with some studies finding no effects (Kohn et al. 1984; Sobell et al. 1986) and others finding small or short-term effects for some study participants (Kohn and Smart 1984).

A later study applied this approach to examine the effects of television beer advertising on the drinking beliefs of young people who were not regular drinkers (Lipsitz et al. 1993). The researcher showed three groups of fifth- and eighth-grade students videotapes containing 40 television commercials. One group saw videotapes containing 5 beer commercials scattered among 35 other commercials. Another group saw videotapes with the same five beer commercials plus two antidrinking public service announcements (PSA's). The control group saw videotapes with five soft-drink commercials in place of the beer commercials. The remaining 35 commercials were the same for all groups and advertised a variety of products, such as foods and automobiles.

After viewing the videotapes, the children completed a memory task that showed they attended to the advertisements and remembered seeing the beer and soft-drink commercials. Then they completed an "alcohol expectancy" questionnaire that measured the extent to which they believed drinking would lead to a number of desirable outcomes, such as enhancing social behavior or promoting relaxation. Neither exposure to the beer advertisements nor to the antidrinking PSA's affected the children's expectancies about the outcomes of drinking.

More recently, an experimental study examined young people's responses to variations in the placement of alcohol advertisements. The researchers exposed a sample of 244 high school students to videotaped television beer advertisements embedded in either a sports program or an entertainment program (Slater et al. 1997). The researchers asked the students to complete a questionnaire that measured their reactions after viewing each advertisement. The research team also asked the students about their present alcohol use and their future drinking intentions.

The responses were split along gender lines. The female students responded more negatively to the beer advertisements and offered more counterarguments than did the male students, particularly when the programs they watched had sports content.

In addition, adolescents of Anglo-American descent who responded favorably toward the beer advertisements were more likely to report current drinking and future intentions to drink. This finding might be interpreted as suggesting that alcohol advertising increases drinking predisposition. The effects were relatively small, however, and the finding did not hold for Latino students. Moreover, the design of this study did not allow the researchers to determine whether a favorable orientation toward alcohol advertisements predisposed the young people to drinking, or whether being predisposed to drinking made the young people more favorable toward alcohol advertisements. Nevertheless, the Latino-Anglo difference is an interesting finding. Although the Latino students liked the advertisements, they may have seen them as less personally relevant. Factors such as identification or perceived similarity with actors in television advertisements may influence the relationship between a person's attitude toward alcohol advertisements and his or her beliefs and behaviors related to drinking.

Experimental Studies: Methodological Considerations. Overall, the results of these experimental studies offer only limited support, at best, for effects of alcohol advertising on drinking beliefs and intentions (Atkin 1995; Grube and Wallack 1994; Lastovicka 1995; Thorson 1995). Although laboratory experimental studies can control for extraneous factors and can allow for strong causal inferences, they often lack realism. In a typical study, respondents are exposed to alcohol advertising in an artificial setting such as a schoolroom. The stimulus advertisements are often embedded among a very large number of "neutral" advertisements shown one after another. This style of presentation does not reflect the natural situation in which viewers are usually exposed to advertising. As a result, it is difficult to draw conclusions about the "real world" effects of alcohol advertising on beliefs and behaviors on the basis of these laboratory studies.

Furthermore, advertisers target specific audiences with particular advertisements (Thorson 1995). If the stimulus advertisements do not contain images, themes, or music that appeal to the participants in a specific study, it is less likely that any effects will be observed. In most cases, including the study described previously involving third and fifth graders (Lipsitz et al. 1993), the stimulus advertisements are not described in enough detail to ascertain if they were appropriate for the experimental participants. Additionally, these laboratory experiments can only address the effects of short-term exposure to a limited number of alcohol advertisements. The relevance of such studies for understanding the cumulative effects of exposure to hundreds or thousands of alcohol advertisements over many years is questionable. This research paradigm may be most relevant to understanding which ads appeal to viewers and whether or not exposure to alcohol advertising elicits immediate and short-term increases in consumption among those already favorably predisposed to drinking (Kohn and Smart 1984).

Econometric Studies

A number of studies have applied the theoretical and statistical techniques of economic research to analyze issues relating to alcoholic beverage advertising. Generally these econometric studies have focused on the relationship between the advertising expenditures of the alcohol industry and the average amount of alcohol consumed per person (per capita consumption) or the amount of alcohol sales, with price and other factors taken into account. A few studies have investigated whether alcohol advertising affects rates of traffic fatalities and other alcohol-related problems such as liver cirrhosis.

Overall, the econometric studies conducted to date provide little consistent support for a relationship between alcohol advertising and alcohol consumption and related problems. They do provide indirect support, however, for the hypothesis that alcohol advertising leads to changes in brand or beverage preferences without increasing total consumption. To follow is a summary of recent studies as well as criticisms related to methodological issues.

The Question of Consumption. The overall conclusion from econometric studies conducted prior to 1990 is that alcohol advertising exerts a negligible effect on overall alcohol consumption (for reviews, see Calfee and Scheraga 1994; Fisher 1993; Saffer 1995*a*,*b*, 1996). These early studies suggest that a 1-percent decrease in alcohol advertising would be associated, at most, with a 0.1-percent decrease in consumption (Godfrey 1994).

Since then, two econometric studies have departed from the previous findings in that they reported substantive and statistically significant effects of alcohol advertising on alcohol-related problems (Saffer 1991, 1997). The first of these studies reported that countries with restrictions on broadcast alcohol advertisements had lower rates of both alcohol consumption and traffic fatalities (Saffer 1991, 1993*b*). Using data from 17 European and North American countries for the years 1970 through 1983, the researcher determined that countries with partial restrictions on television alcohol advertising, such as prohibitions on commercials for liquor, had 16-percent lower alcohol consumption rates and 10-percent lower motor vehicle fatality rates than did countries with no restrictions. In turn, countries with complete bans on television alcohol advertisements had 11-percent lower consumption rates and 23-percent lower motor vehicle fatalities rates than did countries with partial restrictions.

Controversy about these findings arose with the publication of a reanalysis (Young 1993) that criticized the original study (Saffer 1991) on a number of grounds. The reanalysis indicated that countries with low rates of alcohol problems were more likely to adopt bans on alcohol advertising because of preexisting, conservative drinking styles and attitudes. The reanalysis also suggested that partial alcohol advertising bans might actually *increase* alcohol consumption, a counter-intuitive outcome. Questions about these findings, in turn, were raised by the author of the original study, who reported that the reanalysis suffered from methodological flaws that rendered the results inconsistent (Saffer 1993*b*).

More recently, another study reported significant advertising effects on drinking problems (Saffer 1997). The study has a number of methodological strengths and, although it cannot establish causation, it offers the strongest econometric evidence to date that alcohol advertising might influence drinking problems. The researcher looked at the relationship between motor vehicle fatalities and variations in local alcohol advertising in the top 75 media markets in the United States from 1986 through 1989. Alcohol advertising was represented as the sum of industry expenditures for producing and broadcasting television, radio, and outdoor advertisements, weighted for their relative impact based on the estimated number of people exposed to each.

After accounting for regional price differences and population variables such as income and religion, the researcher found that increases in alcohol advertising were significantly related to increases in total and nighttime vehicle fatalities. The effects appeared to be greater for older drivers than younger drivers (18 through 20 years old). On the basis of these analyses, the researcher estimated that a total ban on alcohol advertising might reduce motor vehicle fatalities by as much as 5,000 to 10,000 lives per year.

A separate analysis examined how variations in prices paid by the alcohol industry for advertising might influence rates of motor vehicle fatalities. The researcher found that higher advertising prices were associated with lower fatality rates, apparently because higher prices reduced the amount of advertising and consequently the rate of alcohol consumption. These results indicated that eliminating the advertising tax credit for the alcohol industry would reduce motor vehicle fatalities by as many as 1,300 lives per year (Saffer 1997).

The divergence of the findings of this study from some earlier econometric studies may, in part, be a result of improvements in methodology. Investigating local variations in advertising and adjusting for the relative impact of different media types are two important innovations that have not been duplicated in other econometric

studies. Nonetheless, establishing a cause-and-effect relationship based on this study is problematic. Even though important background and demographic variables were controlled, the possibility that the observed relationship between alcohol advertising and motor vehicle fatalities resulted from some third variable, such as social norms, cannot at this point be discounted.

Reallocating Market Shares. All of the remaining recent econometric studies produced primarily negative findings, and they support earlier conclusions that alcohol advertising has little or no effect on overall consumption levels.

In the most thorough econometric investigation of alcohol advertising to date, researchers used U.S. data from 1970 through 1990 to analyze changes in per capita consumption as a function of changes in advertising. In addition, they looked for "cross-sectional associations," or links between consumption and advertising at specific, narrow time frames over the two decades (Fisher and Cook 1995).

Considering the cross-sectional links first, the researchers found that increased alcohol industry expenditures for magazine advertisements were associated with increased liquor consumption. This finding is consistent with the fact that liquor advertising in the United States occurs primarily in magazines. Although alcohol consumption dropped overall during the two decades, the researchers found that the years with higher total wine and liquor advertising (across all media) also had higher relative consumption levels not only for wine and liquor, but also for beer, and thus, total alcohol. Interestingly, increases in total beer advertising were associated with decreased liquor consumption, as would be expected if market shares were being shifted. These cross-sectional findings provided some support for the effects of advertising on alcohol consumption.

When the researchers analyzed the data using method that accounted for changes over time rather than a static, cross-sectional model, however, there was no evidence that changes in advertising were related to changes in consumption. The reanalysis did indicate that increased advertising of spirits was linked to a drop in the market share for wine. Overall, the findings of this study provide little or no evidence that alcohol advertising increases overall alcohol consumption, although they suggest that such advertising may realign market share.

Other studies have taken different paths to arrive at similar conclusions. One team used four different estimation procedures on annual U.S. data from 1964 through 1990 to investigate the effects of "real"(that is, inflation-adjusted) advertising expenditures for beer, wine, and spirits on the consumption of these beverages (Nelson and Moran 1995). The researchers examined "same-beverage effects," such as the effects of beer advertising expenditures on beer consumption, as well as "cross-beverage effects," such as the effects of beer advertising expenditures on wine consumption. They found that alcohol advertising expenditures were unrelated to total alcohol consumption once the researchers accounted for differences in price, population, income, and age and for advertising for all other goods. Their results also supported the claim that advertising reallocates market shares among brands and, to a lesser degree, beverage types.

Another study examined the effects of brand-level advertising on spirits consumed in the United States from 1976 through 1989 (Gius 1996). Advertising for a given brand of spirits was positively related to consumption of that "own brand" of spirits, whereas rival-brand advertising was not significantly related to own-brand consumption. This pattern was interpreted as indicating that alcohol advertising does not change overall consumption of spirits but rather leads simply to a reallocation of market shares.

It is not clear, however, that this conclusion necessarily follows from the pattern of findings. If own-brand advertising *increases* own-brand consumption but does not significantly *reduce* rival-brand consumption, then it might be having an overall market effect of increasing total

consumption of spirits. This is a concern especially because successful advertising campaigns may elicit extensive counteradvertising by rival brands. Additional research would be needed to bear this theory out, as well as to investigate whether such campaigns build brand loyalty among underage drinkers that is then associated with underage consumption.

An additional study investigated the effects of advertising on alcohol and tobacco consumption in selected States for the years 1959 through 1982 (Goel and Morey 1995). The researchers found mixed results for the effects of advertising on consumption. Some of their findings showed that either the current or the previous year's advertisements for alcohol appeared to *decrease* consumption. As a possible explanation for this counterintuitive finding, the authors suggested that advertising might induce brand switching without increasing overall demand, which may force firms to advertise more to maintain their market shares. Other studies support the proposition that advertising may be a function of sales, as well as sales a function of advertising (Saffer 1995*b*, 1996). The models used in this study (Goel and Morey 1995), and in most econometric studies of alcohol advertising conducted to date, do not capture these potential reciprocal effects.

Econometric Studies: Methodological Considerations. Econometric studies on alcohol advertising have been criticized on a number of grounds (Calfee and Scheraga 1994; Fisher 1993; Saffer 1995*a*,*b*). One recurring limitation is that the studies tend to combine, or aggregate, the advertising data across the different media types, which prevents researchers from detecting the effects of individual media types. In a related issue, the use of data that are aggregated at the yearly level may hide the short-term effects of "pulsed" advertising campaigns that have peaks and valleys in the concentration of advertisements over the year (Saffer 1995*a*). It has also been argued that econometric studies have not taken into consideration the possible cumulative effects of advertising over many years; as a result, they could underestimate advertising effects (Saffer 1995*a*).

Another important caution in interpreting these studies concerns conclusions about cause and effect. Some of the studies have relied on cross-sectional analyses, which take a "snapshot" of the status of many variables at specific, narrow points in time. With this method, even if significant links were to be found between advertising and other variables, it is not possible to draw strong conclusions about cause-and-effect relationships. Although researchers strive to adjust the data for the key factors that might cloud the findings, an apparent relationship between two variables may actually be due to a third, omitted variable in the model. Moreover, the causal direction may be the opposite of that assumed.

Finally, another limitation of the existing econometric studies is that they have focused on per capita consumption, problems, or sales rather than on individuals. As a result, interpretations of results from these studies are susceptible to the "ecological fallacy," that is, erroneously drawing conclusions about individuals on the basis of aggregated data. Thus, the finding that alcohol advertising has no *aggregate* effect on consumption does not mean that there is no effect for any *individual*. Not enough is known about how alcohol advertising might affect specific populations that may be more susceptible or more exposed to the advertising. In particular, it has been argued that young people may be especially influenced by alcohol advertisements (Atkin 1993) and that minority populations have been specially targeted by alcohol advertising (Abramson 1992; Scott et al. 1992). In addition, studies have yet to explore whether advertising has a greater impact on individuals during the initiation or early stages of drinking behavior than after drinking patterns have been established.

Survey Studies

For the most part, survey studies of alcohol advertising have focused on children and adolescents. Many of the early survey studies found significant, positive relationships between exposure to or awareness of alcohol advertising and drinking beliefs and behaviors among young

people (Aitken et al. 1988; Atkin and Block 1980; Atkin et al. 1983, 1984). These effects were small, however, and a few studies found no significant relationships (Adlaf and Kohn 1989; Strickland 1982, 1983).

More recent studies using survey or questionnaire methods, described below, have continued to find significant, though still small, associations between alcohol advertisements and drinking beliefs and behaviors. Almost all of the studies are cross-sectional snapshots of the study groups, however, so they can show associations between variables but cannot confirm cause-and-effect relationships.

Awareness of Alcohol Advertising. One relatively large study looked into connections between children's awareness of alcohol advertising and their knowledge and beliefs about drinking (Grube 1995; Grube and Wallack 1994). In this study, based on a random sample of 468 fifth and sixth graders, the researchers ascertained the students' awareness of alcohol advertising by presenting the students with a series of still photographs taken from television commercials for beer. In each case, all references to product or brand were blocked. The researchers asked the children if they had seen each advertisement and, if so, to identify the product being advertised.

The investigators found that the children who were more aware of advertising had increased knowledge of beer brands and slogans as well as more positive beliefs about drinking. In addition, those with higher levels of awareness of alcohol advertising were slightly more likely to say that they intended to drink as an adult.

The positive links between awareness of advertising, knowledge of beer brands and slogans, and beliefs about drinking were maintained even though the researchers accounted statistically for the possibility that prior beliefs and knowledge could affect the children's awareness of the advertising. The researchers thus suggested that awareness of alcohol advertising predisposes young people to drink, rather than the other way around. The investigators were careful to note, however, that longitudinal studies, which track changes in a group over time, would be necessary to establish the causal nature of the relationship with more certainty.

One study of 677 New Zealand teenagers represented an advance in methodology in that it used a longitudinal design that tracked a random sample of teens over several years (Connolly et al. 1994). One finding was that young men who, at age 15, could recall more alcohol commercials (mostly beer advertisements) drank greater quantities of beer when they turned 18 than did those who could recall fewer commercials at age 15. Conversely, the women who could recall more alcohol advertising at age 15 reported drinking less at age 18 than those who could recall fewer at age 15. Despite the longitudinal approach, the study is problematic for a number of reasons. Most important, it did not account for drinking status or predispositions to drinking at the earlier stages of the study. Thus, it is unclear whether attention to alcohol advertising increased drinking among the young men or whether those who were predisposed to drink paid more attention to the alcohol advertising. Moreover, the fact that recall of advertising was related to decreased drinking in the young women further obscures the interpretation of this study.

Like It or Not: Feelings About Alcohol Advertising. A number of studies have attempted to find out whether children and adolescents who like alcohol advertisements have different drinking beliefs and behaviors than those who do not like the advertisements. In one study of 213 children aged 7 through 12, the more the children liked alcohol advertisements, the more likely they were to have experimented with alcohol (Austin and Nach-Ferguson 1995). Although this effect was relatively robust, the study sample was not selected at random, which limits the ability to generalize about the findings. In a similar study with 154 at-risk preadolescents, the researchers found that the more the children identified with the content of the alcohol commercials, the more likely they were to have positive expectations regarding drinking (Austin and Meili 1994).

In a more recent study of 500 New Zealand children aged 10 through 17, researchers found that the degree to which the children liked a set of beer advertisements influenced how much they expected to drink at age 20 (Wyllie et al. 1998*a*). The researchers showed each child a written description of three television beer commercials as well as a still photograph from each. The children were then asked how often they had seen each advertisement and how much they liked each of them. The results showed that the more the children liked the ads, the higher their expected frequency of drinking at age 20. Liking the advertisements had a relatively large effect on their intentions to drink, but the effect was more modest on current drinking behaviors and only marginally significant. Moreover, the researchers concluded from a statistical analysis that, while liking alcohol advertising influences current drinking status and intentions, the reverse does not seem to be true.

In a similar study of an older age group, the same research group reported stronger results in 1,012 randomly selected 18- to 29-year-olds from New Zealand (Wyllie et al. 1998*b*). In this case, the more the respondents liked the alcohol advertisements, the more likely they were to drink at greater rates and to agree with positive belief statements such as "Drinking is a good way to escape from the hassles of everyday life." Most important, the more they liked the advertisements, the more they reported drinking problems such as getting into a physical fight because of drinking. As with the study just mentioned, the researchers applied a statistical model to conclude that alcohol advertising and responses to alcohol advertising influence drinking beliefs, behaviors, and problems rather than the other way around.

Survey Studies: Methodological Considerations. Although survey studies consistently find significant associations between alcohol advertising and drinking beliefs and behaviors, these relationships tend to be modest. Moreover, a number of these studies have used small and nonrepresentative samples, which raises questions about the ability to generalize the findings to the population at large. In addition, as mentioned previously, because of the cross-sectional designs of most of these studies, as well as the failure to control for previous drinking in the single longitudinal study, conclusions cannot be drawn about causality.

Media Literacy Interventions

Many school-based education programs involve "media literacy" or "resistance to social influence" curricula designed to increase students' ability to think analytically about advertising, including to some extent alcohol advertising (Botvin et al. 1990; Ellickson and Bell 1990; Ellickson et al. 1993; Hansen et al. 1988; MacKinnon et al. 1991). Unfortunately, media literacy or resistance training is most often embedded in curricula with multiple components, and very few evaluations have considered their independent effects. As a result, studies of these broad programs shed little light on the specific effects of teaching young people about the effects of alcohol advertising on drinking beliefs or behaviors.

Recently, a few studies have focused exclusively on providing media literacy education to children and adolescents as a means of countering the potential effects of alcohol advertising. These studies are important for two reasons. First, they may provide evidence about the effectiveness of such interventions for preventing or delaying drinking by children and adolescents. Second, they also may provide indirect evidence about whether or not alcohol advertising affects young people. If such countermeasures lead to socially desirable changes in drinking beliefs or behaviors, it may be implied that alcohol advertising does, in fact, influence young people.

One research team has performed two controlled studies looking at the results of providing general or alcohol-specific media literacy education to young children (Austin and Johnson 1997*a*,*b*). For the first study, which involved 225 third graders, they divided the sample into three groups. One group viewed a "general media education" video designed to promote skepticism toward advertising (Austin and Johnson 1997*a*). This group critiqued sample advertisements taped from network television about food and nonalcoholic drinks. A second group viewed

an "alcohol-specific media education video" and critiqued advertisements for beer and soft drinks. A third group saw neither video and served as a control group.

Afterwards, to obtain a measure of "predrinking" behaviors in these young children, the researchers had the children choose various toys and other products that included equivalent alcohol- and non-alcohol-related pairs. For example, two toys looked like a soft drink or a beer can that danced when switched on. For each pair, the children chose their favorite product. In addition, the children responded to a series of questions about their understanding of the persuasive intent of advertising, their perceptions of advertising realism, their perceptions of the actors in the advertisements, and their expectancies about the desirability of drinking. The researchers collected two sets of this data: one immediately after the intervention, and another 3 months later.

The intervention had both immediate and delayed effects. In the immediate posttest, the children who had received media literacy education showed a decrease in their desire to be like the actors portrayed in advertisements and viewed these actors as less similar to them and as less desirable. They also showed a decrease in their expectations about the positive effects of drinking and were less likely to choose alcohol-related products and toys. These intervention effects were maintained at the 3-month posttest. The analyses also indicated that the alcohol-specific intervention was more effective on these measures than the general media literacy intervention was, and that the interventions influenced girls more than it did boys (Austin and Johnson 1997*a*). In the second study by this team, the researchers followed the same procedures with 246 third graders and their results generally paralleled those of the previous study (Austin and Johnson 1997*b*).

In another study, researchers asked 83 adolescents, aged 12 through 18, about the last time that they were in an alcohol education class, if at all, and to recall the amount of discussion concerning alcohol advertisements that took place in that class (Slater et al. 1996*a*). The research team found that students with prior exposure to alcohol education classes who recalled discussions of alcohol advertising were more likely to offer counterarguments to beer advertisements. After the researchers accounted for the effects of gender, age, and race/ethnicity, two factors—how recently the alcohol education had taken place and the extent to which alcohol advertising had been discussed—emerged as independent predictors of the likelihood of counterarguing. The researchers concluded that exposure to alcohol-specific media literacy education may increase resistance to alcohol advertising months or even years later.

Media Literacy Studies: Methodological Considerations. Although the two experimental studies with third graders just described (Austin and Johnson 1997*a*,*b*) suggest positive effects of alcohol-specific media literacy training, they are limited in important ways. Most notable, the results were somewhat inconsistent between experimental groups and at different measurement periods. In addition, the ability to generalize the results to a broad population is limited because both studies used "convenience samples," which, as the name suggests, were readily available to the researchers but not representative of the population at large. Finally, because the follow-up period was only 3 months, the effects of these childhood interventions on initiation of drinking or drinking frequency in later adolescence are unknown. This is particularly important because the relationship between expectations about drinking and later rates of actual drinking has not been delineated.

The value of the study of adolescents (Slater et al. 1996*a*) is also limited because it used a small, nonrandom sample, and because the relationship between the alcohol education variables and drinking behaviors was not considered. In addition, it is possible that the young people who were less predisposed to drink paid more attention in the alcohol education class and thus were more likely to recall the media literacy component.

Overall, these studies of alcohol-specific media literacy education suggest that such interventions may increase young people's resistance to alcohol advertising and may affect alcohol beliefs and behaviors. Unfortunately, they have yet to investigate effects on actual drinking. Further research with larger and more representative samples, longer follow-up periods, and more inclusive measures of drinking is necessary to establish the effectiveness of media literacy education.

In Closing

When all of the studies are considered, the results of research on the effects of alcohol advertising are mixed and not conclusive.

Overall, experimental studies have produced little consistent evidence that alcohol advertising affects drinking beliefs and behaviors. These studies address short-term exposure to a limited number of alcohol advertisements. The number of advertisements that respondents view in such studies is small compared with ongoing exposure in the natural environment. By their nature, these studies provide little insight into the cumulative effects of exposure to alcohol advertising over many years and may be incapable of producing measurable effects against the background of alcohol advertising occurring in the real world.

Experimental studies are most important for understanding audience reactions to different types of advertisements or for investigating immediate effects, such as an increased interest in use of alcohol that may result from short-term exposure to alcohol advertisements. Large-scale field experiments that block alcohol advertising from reaching selected communities or households could provide stronger evidence regarding the effects of alcohol advertising (Atkin 1995). Such studies are yet to be undertaken, however, and it would be difficult to eliminate all print, outdoor, and national alcohol advertising for such a study.

Similarly, and with a few exceptions (such as Saffer 1997), recent econometric research using aggregated market data provides very little consistent evidence that alcohol advertising influences per capita alcohol consumption, sales, or problems. The bulk of this research supports the claim that alcohol advertising reallocates consumption among brands or beverage types. Interpretation of these studies is limited, however, by difficulties in drawing causal inferences based on the data and analytic methods, aggregation of advertising data across media types, failure to account for reciprocal effects between advertising and sales or consumption, and exclusion of the effects of "pulsed" advertising and the cumulative effects of advertising (Saffer 1995*a*,*b*).

Despite the limitations of any individual studies, however, the overall conclusion drawn from current econometric research is that alcohol advertising has little, if any, effect on total levels of alcohol consumption and related problems. This conclusion is consistent with earlier reviews of this literature (Calfee and Scheraga 1994; Fisher 1993; Smart 1988).

In contrast to experimental and econometric studies, survey research on alcohol advertising and young people consistently indicates small but significant connections between exposure to and awareness of alcohol advertising and drinking beliefs and behaviors. Children and adolescents who view, or are made aware of, alcohol advertisements hold more favorable beliefs about drinking, intend to drink more frequently as adults, and are more likely to be drinkers than are other young people. They also have greater knowledge of alcohol brands and slogans.

Although these effects on young people are small, they may be important. The small effects may reflect the fact that individual differences in exposure to advertising are relatively slight given the high frequency of advertising in the environment (Saffer 1995*b*). Because the environment is saturated with alcohol advertising, most people are exposed to many advertisements each year, with very little variation in individual exposure. In addition, as the number of exposures increases over time, the incremental impact of each single, additional advertisement

diminishes. That is, the incremental effect of any single advertisement is greater if, for example, it is only the tenth advertisement to which a person has been exposed as opposed to the hundredth advertisement, which, in turn, would have a greater impact than the thousandth. These considerations suggest that research on the effects of alcohol advertising should include studies of young children who have had little exposure to it and for whom the greatest impact can be expected.

Taken as a whole, the survey studies provide some evidence that alcohol advertising may influence drinking beliefs and behaviors among children and adolescents. This evidence, however, is far from conclusive. The cross-sectional design of most of the published studies limits the ability to establish cause-and-effect relationships. Although alcohol advertising may predispose young people to drink, the reverse may be true instead. That is, young people who look favorably on drinking may seek information about alcohol and thus be more attentive to alcohol advertisements. Although longitudinal or sequential studies that track samples of young people from childhood to late adolescence would be particularly useful in investigating these possibilities, no such studies have been published that adequately control for past drinking behaviors and predisposition.

Further research, particularly longitudinal studies addressing at-risk populations such as children and targeted minorities, is necessary before firm conclusions can be reached about the effects of alcohol advertising.

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Treatment Research

Every day, more than 700,000 people in the United States receive treatment for alcoholism. In recent years, much progress has been made in understanding how both psychological approaches (such as cognitive-behavioral therapy, motivational enhancement therapy, and 12-step programs such as Alcoholics Anonymous) and medications can help these patients achieve sobriety.

A major change in the alcohol field has been the growing acceptance of the need for research on alcohol treatment. Today's professionals in the fields of both alcoholism treatment and managed care expect to have scientifically validated screening, assessment, and treatment options. As described in this chapter, research in this area has led to several important advances, including the development of effective "brief intervention" by primary care physicians for people at risk of alcohol problems, the rigorous analysis of traditional screening and treatment approaches, and the development of new medications for treating alcoholism.

One in 5 men and 1 in 10 women who visit their primary care providers meet the criteria for at-risk drinking, problem drinking, or alcohol dependence, according to a recent study (Manwell et al. 1998). Many of these patients do not consult alcohol treatment specialists on their own, so their primary health care providers have an important opportunity to identify and treat potential or existing drinking problems. The section "Screening and Brief Intervention for Alcohol Problems" describes a number of alcohol screening instruments that have been tested and validated in clinical settings.

When patients are found to be at-risk or problem drinkers but not alcohol dependent, health care providers can significantly reduce alcohol use and related problems by providing brief interventions. Brief interventions can take many forms, but basically consist of feedback and advice from the health care provider and agreement by the patient on a course of action. Although research has shown that brief interventions can be effective in a variety of populations, providers have not yet widely implemented this approach, at least in part because of a lack of adequate training and the complexity of the current health care system.

For patients who are alcohol dependent, numerous inpatient and outpatient treatment options are available. In recent years, escalating health care costs have propelled a shift from inpatient to outpatient treatment for most patients for all stages of recovery, although inpatient care remains more appropriate for patients with serious cooccurring medical or psychiatric conditions or who have social environments that are not supportive of recovery.

Whether inpatient or outpatient, the treatment can involve psychological approaches, medications, or a combination of the two.

An important task for the scientific community has been to evaluate the effectiveness of the many psychological therapies currently used to treat alcoholism. As described in the section "Treatment of Alcohol Dependence With Psychological Approaches," research progress in recent years has led to a number of important findings, including the following: (1) matching broad categories of client characteristics to different types of treatments does not substantially improve overall treatment outcomes; (2) professional treatments based on 12-step approaches can be as effective as other psychological approaches and may actually achieve more sustained abstinence; (3) supportive ancillary services can be effective in remediating common problems that cooccur with alcoholism; and (4) higher intensity outpatient treatment may help patients gain control over drinking more quickly.

Although psychological therapies can help many alcohol-dependent persons reduce their drinking and maintain abstinence, these approaches alone are not effective for all patients. Advances in neuroscience have helped identify many of the mechanisms underlying addiction, paving the way for improved treatment options through the use of medications. The section "Treatment of Alcohol Dependence With Medications" describes new pharmacotherapy approaches for alcoholism treatment that operate at the molecular level of brain processes that promote and control addiction. Used in combination with psychological approaches, these targeted medications may offer more effective treatment for millions of alcohol-dependent persons. The section describes recent advances in pharmacotherapy research in two areas: (1) medications specifically used to treat alcohol dependence, and (2) medications used to treat some patients who suffer not only from alcohol dependence but also from psychiatric disorders, primarily depression.

Continued research to refine therapies for alcoholism will have widespread benefits for alcohol-dependent individuals who face the realistic fear of relapse, for their families, and for society as a whole, which bears the weight of the enormous economic and social costs of problem drinking.

Reference

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Screening and Brief Intervention for Alcohol Problems

A significant proportion of problems related to alcohol use—including motor vehicle crashes, other injuries, health problems, and family difficulties—occur in persons who are not alcohol dependent (Institute of Medicine 1990). In fact, estimates suggest that alcohol dependence is found in only one in four persons seen in primary care settings who drink above recommended limits of alcohol use (for men, more than two drinks per day or four per occasion; for women, more than one drink per day or three per occasion) (Manwell et al. 1998; National Institute on Alcohol Abuse and Alcoholism [NIAAA] 1995; U.S. Department of Health and Human Services 1996).

The recognition that alcohol-related problems are not limited to those who are alcohol dependent has important implications for the health care system in our Nation. It suggests that health care professionals need to switch from an exclusive focus on identifying and treating persons who are alcohol dependent to the inclusion of persons who are "at-risk" and problem drinkers.

In general patient care, the process of screening allows health care professionals to identify individuals who have, or who may be at risk for developing, particular health-related problems. Once a problem—or a level of increased risk—is found, steps can be taken to help the patient minimize or prevent future problems. Often this intervention takes the form of advice or counseling to encourage the patient to alter behaviors that are contributing to the problem. Such an intervention may be brief—taking only a few minutes—or may require more time to convey a number of health messages.

Screening for alcohol-related problems usually involves asking the patient questions about drinking through structured interviews or self-report questionnaires; it may also involve laboratory tests to detect abnormalities associated with excessive alcohol consumption. When alcohol-related problems are identified, more detailed assessments are needed to specify the nature and extent of the problems so that appropriate treatment can be undertaken.

If the screening and assessment results indicate that a patient is an at-risk or problem drinker but not alcohol dependent, a brief intervention on the part of the health care provider can significantly reduce alcohol use and associated problems (Bien et al. 1993; Fleming et al. 1997; Wallace et al. 1988; Wilk et al. 1997). Although used most often with patients who are not alcohol dependent, brief interventions may also hold promise as part of a "stepped-care" approach that involves specialized treatment settings (Drummond 1997). This section summarizes recent developments in screening for alcohol-related problems and in using brief interventions to reduce patients' risks for further problems.

Screening for Alcohol Problems

A number of alcohol screening instruments have been tested and validated in clinical settings, including brief, structured interviews that contain questions on the quantity and frequency of drinking, questionnaires that can be self-administered or used in an interview by a health professional, and clinical laboratory tests. Although alcohol screening tests, like any screening tests, are not 100-percent accurate, the better instruments have high "sensitivity" and "specificity." Sensitivity is a measure of an instrument's accuracy in detecting persons with the problem in question. A tool with high sensitivity only rarely gives a "false-negative" result for someone who is actually positive. Conversely, specificity is a measure of how well the tool excludes people who do not have the problem; a tool with high specificity only rarely gives "false-positive" results. The strengths and weaknesses of a variety of alcohol screening interviews, questionnaires, and laboratory tests are briefly described.

Interviews: Quantity-Frequency Questions

Currently, the standard of practice for most clinicians is to ask patients how much and how often they drink. To make the responses to these "quantity-frequency" questions uniform, a standard drink is defined as 12 grams of pure alcohol, which is equivalent to one 12-ounce beer or wine cooler, one 5-ounce glass of wine, or 1.5 ounces of 80-proof distilled spirits.

Quantity-frequency questions allow the clinician to estimate a patient's risk directly. These types of questions are also easy to score and can be included as part of an office visit with minimum cost and effort. Examples of quantity-frequency questions are as follows:

- On average, how many days per week do you drink alcohol?
- On a typical day when you drink, how many drinks do you have?
- What is the maximum number of drinks you had on any given occasion during the last month?

The level of alcohol consumption that poses a risk for developing alcohol-related problems is different for men and women (NIAAA 1995). Whereas men may be at risk if they have more than 14 drinks per week or more than 4 drinks on one occasion, women's risk is increased with more than 7 drinks per week or more than 3 drinks per occasion (NIAAA 1995).

Questions about the quantity and frequency of drinking have been shown to have high sensitivity in detecting persons who drink above recommended limits (Adams et al. 1996). Furthermore, physicians can use the patient's response (for example, "I usually drink five or six beers a night") to express drinking risks to patients in a straightforward and easily understood manner. For example, a physician can tell a man who reports drinking four or more standard drinks per day that he has twice the risk for developing stroke and liver failure compared with a man who consumes one or two standard drinks per day (Anderson et al. 1993).

The primary problem with quantity-frequency questions is that patients may understate their drinking, especially if they are alcohol dependent or are intoxicated at the time of the interview. Physicians can minimize this problem with drinkers suspected to be at high risk of alcohol problems by using appropriate interview techniques, such as taking a direct, nonjudgmental approach; corroborating reported behaviors by asking family members or reviewing medical records; and using laboratory tests (the latter is discussed later in this section).

Questionnaires

The limitations of quantity-frequency questions have led to the development of screening questionnaires designed for use in the primary care setting. Most of these questionnaires focus on the consequences of patients' drinking and their perceptions of their drinking behavior (U.S. Preventive Services Task Force 1996). Six questionnaires whose effectiveness has been examined are described briefly below.

CAGE. The CAGE instrument is easy to use. It has been shown to be both sensitive and specific for identifying persons who meet criteria for alcohol abuse and dependence (Buchsbaum et al. 1991; Soderstrom et al. 1997). It consists of the following four questions; one or more "yes" answers increases the risk of alcohol-related problems in both genders:

In the past year,

C Have you ever felt you should Cut down on your drinking?

A Have people Annoyed you by criticizing your drinking?

G Have you ever felt bad or Guilty about your drinking?

E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (Eye opener)?

The CAGE may be limited by its tendency to miss some at-risk drinkers (Adams et al. 1996). In addition, one study found that physicians prefer their own personal screening methods or clinical tests to the CAGE questions (Townes and Harkley 1994).

AUDIT. The Alcohol Use Disorders Identification Test was developed from a World Health Organization (WHO) collaborative project drawing from six countries (Allen et al. 1997; Saunders et al. 1993). Designed to detect hazardous alcohol consumption, the AUDIT is a 10-item questionnaire that inquires about patients' alcohol consumption, drinking behavior, and alcohol-related problems over the past year. Three of the questions in the AUDIT are drawn from the CAGE questionnaire (CAGE questions C, A, and E); the other seven questions concern the frequency and quantity of drinking, binge drinking (defined as having six or more drinks on a single occasion), blackouts, receiving advice from a health care professional regarding alcohol use, alcohol-related injury, and neglect of responsibilities due to alcohol use.

The AUDIT has a sensitivity of 50 to 80 percent; this means that, if 10 persons who have alcohol problems are screened, the test will most likely identify 5 to 8 of them. The test's sensitivity varies, however, depending on the study population and the cutoff score used (Barry and Fleming 1993; Bohn et al. 1995). One limitation of the AUDIT is that it may be less effective for detecting alcohol problems among people who barely meet the criteria for at-risk drinking. These include individuals who have two to three drinks per day and engage in binge drinking once or twice per week (Schmidt et al. 1995). In addition, the AUDIT definition of binge drinking—six or more drinks on one occasion—is well above current at-risk drinking levels (more than four drinks per occasion for men and more than three drinks per occasion for women) (NIAAA 1995). Finally, the length of the AUDIT may make its administration cumbersome for some physicians or patients. Because of these limitations, the AUDIT may be less useful as a primary screening tool and more useful for assessing patients after a possible problem has been discerned by other methods.

Health Screening Survey and Questionnaire. The Health Screening Survey (Fleming and Barry 1991a) and the Health Screening Questionnaire (Wallace and Haines 1985) include questions about alcohol use as well as other health questions (for example, on smoking, weight, exercise, and depression). Researchers have tested both the survey and the questionnaire in primary care settings and have found both instruments to have adequate sensitivity and specificity (Cutler et al. 1988; Fleming and Barry 1991a).

PRIME-MD. A relatively new instrument, the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al. 1994), includes the four CAGE questions and two questions on alcohol consumption. Clinicians use the PRIME-MD to screen patients for mental health and alcohol use disorders. A recent study evaluated telephone-assisted computer administration of the PRIME-MD, in which patients responded to questions over the telephone through the use of interactive voice-response technology (Kobak et al. 1997). The authors concluded that telephone-assisted computer administration of the PRIME-MD is more sensitive than face-to-face administration by a clinician.

Trauma Scale. The five-question Trauma Scale (Skinner et al. 1984) has been found to be more sensitive than laboratory tests in detecting genuine cases of problem drinking. The instrument is also specific in ruling out "social," non-problem drinkers. The questions on the Trauma Scale concern fractures or dislocations, involvement in motor vehicle crashes, head injury, and injuries sustained in assaults or fights or after drinking. Clinicians can better identify cases of excessive alcohol use with this scale by adding a few questions on alcohol abuse and performing some laboratory studies.

T-ACE and TWEAK. The T-ACE (Sokol et al. 1989) and the TWEAK (Russell et al. 1994, 1997) tests were developed specifically to screen for alcohol problems in pregnant women. (See Table 2 of the

section "Issues in Fetal Alcohol Syndrome Prevention" in the chapter on prenatal exposure to alcohol.) Both tests have been validated separately and have been found to be more sensitive than the CAGE questionnaire, in that they are capable of identifying more than 80 percent of women who are drinking above recommended limits (Chan et al. 1993; Chang et al. 1997).

Laboratory Tests

Physicians can uncover patients' drinking problems through the use of biological analyses such as blood and breath tests, although such tests are often underused in clinical settings (Cherpitel 1989). Obtaining blood alcohol concentrations is particularly important in emergency departments, trauma centers, and other acute care settings for confirming patient self-reports and for managing patients who are to undergo surgery. For screening purposes in primary care settings, however, laboratory tests have not been found to be sensitive or specific, in that they identify only about 10 to 30 percent of problem drinkers (Hoeksema and de Bock 1993; U.S. Preventive Services Task Force 1996).

Blood can also be tested for concentrations of an enzyme called gamma-glutamyltransferase (GGT; an indicator of liver injury) and for mean corpuscular volume (an estimate of the volume of red blood cells), which is often elevated in alcohol-dependent persons. These blood tests are not recommended for routine screening, however, because they may not be accurate enough for use in general clinic populations (Beresford et al. 1990; Bernadt et al. 1982).

Another blood test, the carbohydrate-deficient transferrin (CDT) assay, helps to identify men who have been drinking more than five standard drinks per day for a year or more. This assay may also help to monitor a patient's abstinence (Huseby et al. 1997). However, the test is not widely available and it has been found to perform poorly in women (Gronbaek et al. 1995; Stauber et al. 1996), binge drinkers (Lott et al. 1998), people with liver disease (Stauber et al. 1995), and those who have been drinking intermittently in the past 12 months (Anton and Bean 1994). For these reasons, the CDT assay may be more useful for monitoring relapse among high-risk patients than in routine screening of general clinical populations.

For persons who screen positive through a questionnaire, interview, or laboratory test, several psychological assessment methods can be used by clinicians to develop a treatment plan. A number of pencil-and-paper questionnaires are available to assess alcohol-related problems and physical dependence; two examples are the Short Michigan Alcoholism Screening Test (S-MAST) (Selzer et al. 1975), a 13-question instrument widely tested in clinical settings (Fleming and Barry 1991*b*), and the Short Alcohol Dependence Data Questionnaire (SADD) (Davidson and Raistrick 1986), a 15-item assessment of dependence severity that has been widely used in alcohol treatment studies. In addition, patients with alcohol problems should be assessed for mental health disorders (Helzer and Pryzbeck 1988), because the prevalence of depression, anxiety disorders, and other mental heath problems is high among people with alcohol dependence, especially women (Barry et al. 1997; Rowe et al. 1995).

Brief Intervention

Brief interventions are time-limited counseling strategies that are especially useful in busy, high-volume health care practices, where physicians are often pressed for time and have multiple priorities. These techniques can be used to reduce alcohol use in patients who drink but who are not alcohol dependent (Fleming et al. 1997). They may also be helpful in motivating patients with alcohol dependence to seek specialized alcohol treatment.

In a brief intervention, the health care provider basically follows three steps (NIAAA 1995):

- State the medical concern. This is typically done by providing direct feedback, such as, "As your physician, I am concerned about how much you drink and how it is affecting your health."

- Advise the patient to abstain from alcohol use (if alcohol dependent) or to cut down (if not).

- Agree on a plan of action. This may be done by making an informal "contract" or agreement with the patient that sets specific goals, such as a certain number of drinks per week.

A health care provider who employs a brief intervention can also offer patients techniques to help them modify their behavior. This might consist of having patients make a list of situations in which they typically lose control of their drinking, then helping them to devise ways to avoid those situations. The health care provider may also suggest self-help material for the patient to read.

Effectiveness of Brief Intervention

A substantial body of research indicates that brief interventions are a valuable resource for reducing patients' problems with alcohol (Bien et al. 1993; Kahan et al. 1995; Wilk et al. 1997). One study (Bien et al. 1993) analyzed 32 trials of brief interventions and found that most of these efforts had positive results, reducing alcohol use by up to 30 percent. Another analysis of 12 controlled trials (Wilk et al. 1997) found that drinkers who received brief interventions were almost twice as likely as those not receiving an intervention to reduce or moderate their drinking in the subsequent 6 to 12 months. This effect was consistent among both men and women and in various clinical settings. The intervention procedures used in these studies differed, but most involved an initial counseling session lasting 5 to 20 minutes and one or more follow-up sessions.

Researchers have studied brief interventions in hospitals (Chick et al. 1988), in primary care clinics (Fleming et al. 1997; Israel et al. 1996; Wallace et al. 1988), on college campuses (Marlatt et al. 1995, 1998), in clinical research settings (Miller and Sovereign 1989), and in urgent care settings (Gentilello et al. 1995, 1999). The studies described here are notable for clarifying the role of brief interventions in the prevention and treatment of alcohol use disorders.

Brief Intervention in Family Practice Settings

Findings from three large, randomized, controlled clinical trials support the use of brief interventions in the family medicine setting. In the first study, conducted in the United Kingdom, researchers randomly assigned 909 patients to the control group or to the intervention group, which received two 5- to 10-minute visits with a general practitioner and two 5-minute follow-up telephone calls by nurses (Wallace et al. 1988). During the visits, patients were given written materials and advised to reduce their alcohol use. One year later, the intervention group had significantly reduced their drinking levels compared with the control group. In addition, men receiving the intervention showed improved health through lower levels of the liver enzyme GGT and reduced blood pressure.

The second trial, Project TrEAT (Trial for Early Alcohol Treatment), was designed to replicate the British study and to test the hypothesis that physicians can be trained to effectively deliver a brief intervention protocol within the constraints of a health maintenance organization-based health care system (Fleming et al. 1997). Sixty-four physicians (family physicians or general internists) from 17 clinics participated in the study, attended training sessions, and delivered brief interventions to patients who had scored positive for problem drinking on a screening survey. The interventions included two 10- to 15-minute physician visits as well as two 5-minute follow-up calls from nurses, and involved offering feedback, comparing each individual's drinking habits with drinking norms, contracting with the patients, and reviewing a patient-centered workbook.

The researchers were able to retain 93 percent of the 774 patients in Project TrEAT to the end of the 12-month follow-up. Both the intervention and the control groups showed significant reductions in drinking over time, but subjects in the intervention group showed a greater reduction in their alcohol use at 12 months than did those in the control group. In the intervention group, binge drinking within the previous 30 days was decreased by 35 percent (33 percent for men and 37 percent for women), and drinking excessively

within the previous 7 days was reduced by 63 percent (60 percent for men and 66 percent for women).

A third trial examined the effect of brief counseling interventions, delivered as part of routine primary care by physicians and nurse practitioners, in reducing alcohol consumption by high-risk drinkers (Ockene et al. 1999). The researchers randomly assigned 46 physicians and nurse practitioners at primary care practice sites to provide either a brief intervention or usual care. The intervention providers were trained in a brief (5- to 10-minute) patient-centered counseling intervention and in the use of an office support system that screened patients, cued the providers to intervene, and offered patient education materials. The usual care providers were encouraged to identify and intervene with their alcohol-using patients in any way they thought appropriate; their patients received a booklet on general health issues (the same booklet was given to the intervention patients) and were told that they could discuss any questions they might have with their providers. The researchers enrolled 530 high-risk drinkers in this study and retained 91 percent of them across the 6-month follow-up period.

Results showed that weekly alcohol consumption dropped in both the usual care and the intervention group, but that the intervention group had a significantly larger reduction, averaging 5.8 fewer drinks per week compared with 3.4 fewer drinks per week for the usual care group. This trial provides evidence that screening, very brief advice (5 to 10 minutes), and counseling delivered by a physician or nurse practitioner as part of routine primary care can significantly reduce alcohol consumption by high-risk drinkers.

Brief Intervention in Emergency Care Settings

The efficacy of brief intervention in emergency care settings, such as hospital emergency departments and trauma centers, is a relatively new area of research. One recent study—a randomized, prospective, controlled trial—examined alcohol intake in 762 patients who had been admitted to a trauma unit for treatment of injuries (Gentilello et al. 1999). The patients had screened positive for alcohol problems by measurement of blood alcohol concentrations and serum GGT and by administration of the S-MAST. They were then randomly assigned to a control group or a group receiving a single motivational interview with a psychologist trained in the use of brief interventions. Patients were given personalized feedback about their drinking patterns compared with national norms, their level of intoxication at admission, and the negative consequences of drinking. Emphasis was placed on the patient's assumption of personal responsibility for reducing drinking in order to decrease his or her risk level. A number of strategies were then offered to assist the patient's attempts to change his or her drinking behavior, and follow-up sessions were conducted 6 and 12 months later.

Among the 304 patients for whom the intervention was completed, alcohol consumption was decreased significantly at 12 months compared with the control group. At 6 months, patients in the intervention group had 47 percent fewer new injuries than control patients and had decreased their alcohol consumption by 22 standard drinks per week. In contrast, the control group had decreased their drinking by only about 7 drinks per week. The difference in alcohol intake was most pronounced in patients with drinking problems in the mild-to-moderate range as determined by the S-MAST; no benefit was seen in patients with very high S-MAST scores. Perhaps the most notable result of this study was that, at 12 months, the intervention group had continued to decrease their alcohol intake, whereas the control group had returned to the level at which they had been drinking at the start of the study.

A second recent study evaluated the use of a brief motivational intervention to reduce alcohol-related consequences and use among adolescents treated in an emergency room following an alcohol-related event (Barnett et al. in press; Monti et al. 1999). The researchers randomly assigned 94 patients aged 18 or 19 years to receive either the intervention or standard care. In the emergency room, an assessment and the intervention (a 30-minute session delivered by

a project staff member) were conducted during or after the patient's medical treatment. Follow-up assessments at 6 months showed that both the intervention and the standard care groups had reduced their levels of consumption, but that the patients who received the brief intervention also had significantly lower rates of other alcohol-related problems (such as drinking and driving, traffic violations, and alcohol-related injuries) than did patients who received standard care.

Another study, Project ASSERT (an acronym for "improving Alcohol and Substance abuse Services and Educating providers to Refer patients to Treatment"), tested the feasibility of using the emergency room visit as an opportunity to facilitate access to substance abuse treatment for patients with alcohol and other drug problems (Bernstein et al. 1997). In this case, the brief intervention was not the treatment itself, but instead a means of linking patients to more traditional substance abuse treatment. Emergency department staff screened patients for problems related to alcohol and other drug use. They then directed those who screened positive to trained "health promotion advocates" who assessed the problem severity, evaluated the patients' readiness to change, presented options for substance abuse treatment, and provided referrals to support services and treatment. A follow-up interview was conducted at 60 days. Although there was no control group, the 245 patients who returned a scheduled follow-up visit demonstrated a 56-percent reduction in alcohol use and a 64-percent reduction in heavy drinking (defined in the study as having six or more drinks on one occasion). This program demonstrates an innovative approach with great potential for identifying and referring patients seen in emergency departments.

Comparison With More Lengthy Counseling

Yet to be determined are the optimal length of an intervention and the optimal number of contacts with the patient for the intervention to be effective. Two studies provide some information in this area. The first studied drinking patterns in eight countries (WHO 1996); the second took place in primary care practices in a small community outside Toronto, Canada (Israel et al. 1996). The international study, conducted by the WHO Brief Intervention Study Group, found no difference between a group receiving "simple advice" and a second group receiving "brief counseling" with more extensive intervention (WHO 1996). In contrast, results of the Canadian study suggest that multiple counseling sessions have a stronger treatment effect than a single visit for brief advice (Israel et al. 1996).

In the WHO study, nurses, physicians, psychologists, and other professionals provided the interventions, in which 1,260 men and 299 women were randomly assigned to one of the two intervention groups or a control group. Eligibility criteria included having more than five drinks (for men) or more than three drinks (for women) per occasion. Persons with a history of serious mental illness, liver damage, or previous alcohol treatment were among those excluded from the study.

In the core design of the WHO study, the control group simply received a 20-minute health interview. Within the two intervention groups, those in the simple advice group received the same interview plus 5 minutes of advice and a pamphlet, and those in the brief counseling group received the interview plus 15 minutes of counseling and the same pamphlet, which referred to a 30-page manual. Five of the eight participating centers also offered extended counseling (up to three follow-up sessions) for the brief counseling group. Follow-up averaged 9 months, and the overall dropout rate was 25 percent.

The WHO study found that the average amount of alcohol consumed daily was 17 percent lower for men in the intervention groups than for those in the control groups (WHO 1996). Among women, there were no such differences between the intervention and the control groups, although both intervention and control groups showed significant reductions in drinking over time.

In the smaller Canadian study, which retained 72 of 105 original patients for the 12-month follow-up, researchers sought to determine

whether a single brief-advice message was as effective as six counseling sessions delivered over the course of 1 year (Israel et al. 1996). In the group receiving brief advice, a nurse recommended reduced alcohol consumption, provided a pamphlet with guidelines for achieving abstinence or acceptable drinking, and gave feedback about the patient's GGT level. In the counseling group, a nurse provided the same pamphlet as that given to the brief-advice group and augmented it with as many as six 30-minute counseling sessions. Although the absence of a "no advice" group is a potential limitation of the study, the researchers found that the counseling group did significantly better than the brief-advice group in terms of alcohol use and illness. At the 1-year follow-up, the brief-advice group reported a 46-percent reduction in their alcohol use (from 139 to 75 drinks per 4 weeks), while the counseling group reported a 70-percent reduction (from 152 to 46 drinks per 4 weeks).

Brief Intervention in Special Populations

Several U.S. trials have tested the efficacy of brief interventions in special populations, including college students, pregnant women, Mexican Americans, and older adults.

Two studies of college students have found that brief interventions can reduce alcohol use and alcohol-related problems over the long term. In the first study, the researchers randomly assigned 348 heavily drinking students to a control group or to a brief intervention group (Marlatt et al. 1995). The intervention included a 1-hour counseling session with personalized feedback and a discussion of drinking risks and norms. The researchers followed the students for 24 months, retaining 88 percent of them until the end of the study. The results were modest but statistically significant for both reduced alcohol use and less frequent binge drinking. The reduction was greatest for alcohol-related problems as opposed to alcohol use itself. The participants most resistant to change were fraternity members and men with a history of conduct disorders.

A more recent study differed in that, instead of using students already on campus, the researchers recruited students prior to the freshman year by sending a questionnaire to high school seniors who had been accepted to a State university (Marlatt et al. 1998). From a group of 2,041 students who responded to the questionnaire, 366 high-risk drinkers were randomly assigned to receive a brief intervention in the winter term of their freshman year, a time of both high risk and potentially high receptiveness to prevention messages. Another 115 students, randomly selected from the original group of 2,041 and representing drinkers at all risk levels, were assigned to a comparison group that provided a "natural history" with which drinking changes in the intervention group could be compared over time. The intervention in this study consisted of individual motivational interviews and personalized reports in which students were provided with feedback about their drinking patterns, risks, and beliefs about alcohol's effects. Overall, the high-risk students in both the intervention and the comparison groups drank less and reported fewer alcohol-related problems over the 2 years of the study. Reductions were greater, however, among the intervention group than among the comparison group at all assessment points (6 months, 1 year, and 2 years) (Marlatt et al. 1998).

In the first brief intervention trial for pregnant women (Chang et al. 1999), a control group received a 2-hour assessment only, and an experimental group received a 2-hour assessment plus an intervention delivered by a physician. Pregnant women in their second trimester were eligible to participate in this study if they had a positive score on the T-ACE. Despite this requirement, by the time they were randomly chosen for the control or the experimental group, more than half (57 percent) of the participants were abstaining from alcohol. The results showed that both groups significantly reduced their alcohol use, and the difference between the intervention and control groups was minimal. Overall, the 107 women who were drinking at the time random selection took place reduced their alcohol use by 67 percent (from an average of 1.8 drinks per drinking day to 0.6) between assessment and delivery. It is possible that the

intervention had no significant effect in this study because the 2-hour assessment period already accomplished the intended effect. Other possible explanations for the lack of treatment effect are the fairly high rate of abstinence among the women at the time of random assignment, as well as the tendency of many women to reduce drinking during pregnancy (Chang et al. 1998).

In a trial at a family medicine teaching clinic in Texas, participants included 175 Mexican Americans who screened positive for alcohol abuse or dependence (Burge et al. 1997). Researchers randomly assigned patients to groups that received counselor-led patient education, physician intervention, both of these interventions, or neither. More than three-fourths of the participants completed an 18-month follow-up session in which researchers evaluated changes in alcohol use, alcohol-related problems, and GGT levels. In this study, all of the groups demonstrated significant improvement over time, with little difference between the intervention and control groups. As with the study just mentioned (Chang et al. 1998), the results suggested that for the control group, the assessment procedure itself may have served as a brief intervention.

Project GOAL (Guiding Older Adult Lifestyles) was the first clinical trial to use a brief intervention with older adults who were problem drinkers (Fleming et al. 1999). The project, which included 153 patients aged 65 and older, tested the efficacy of a brief intervention provided by 43 physicians in 24 community-based practices in Wisconsin. The physician's intervention consisted of two 10- to 15-minute counseling visits using a scripted workbook that included advice, education, and contracting information. The researchers randomly assigned 105 men and 53 women to intervention or control groups and followed their progress for 12 months, retaining 146 (92.4 percent) for the full year of follow-up. Compared with the control group, the patients who received the physician intervention showed significant reductions in alcohol use in the past week, episodes of binge drinking, and frequency of excessive drinking at 3, 6, and 12 months after the intervention. This study provides the first direct evidence that brief physician advice can decrease alcohol use by older adults in community-based primary care practices.

Areas for Future Research

The preponderance of the available evidence indicates that brief interventions delivered in primary care settings can decrease alcohol use for at least 1 year in persons who drink above recommended limits. Nevertheless, more research is needed to increase understanding of important related issues. Some of the remaining questions include identifying the essential components of a brief intervention in terms of its content, length, number of sessions, and the role of the health professional delivering it. Further studies are also needed on whether brief interventions have a role in treating alcohol-dependent patients, and whether they should be used routinely in hospital emergency departments and trauma centers as well as in primary care settings. Finally, questions remain as to whether brief interventions reduce morbidity, mortality, use of health services, and costs in the community as a whole.

Essential Components of Brief Intervention

The essential elements of brief intervention protocols, as well as the terms used to describe brief interventions, vary by trial. The protocols used in the large community-based trials to date are primarily physician centered, providing information and advice rather than patient-centered counseling (Fleming et al. 1997; Kristenson et al. 1983; Wallace et al. 1988; WHO Brief Intervention Study Group 1996). Although the WHO trial (WHO 1996) suggests that simple advice may be as effective as brief counseling, the relative importance of patient-centered techniques (such as motivational interviewing and cognitive-behavioral treatment) compared with physician-centered advice is not yet clear. In addition, other aspects of brief intervention that need to be defined are the length of the intervention, the number of contacts, and the importance of continuity of care in terms of the involvement of personal

physicians versus additional involvement by nurses, psychologists, and other health care personnel.

Brief Intervention in Alcohol-Dependent Patients

At this time, evidence is not sufficient to support the replacement of traditional outpatient counseling for alcohol-dependent patients with brief intervention in a primary care setting. Of interest for future research, however, is the question of whether brief interventions could be used as part of a stepped-care approach for alcohol-dependent patients (Drummond 1997). In such an approach, the level of intensity of an intervention would be tailored according to each patient's needs.

Effects of Brief Intervention on Community Health

Two studies (Fleming et al. 1997; Kristenson et al. 1983) have shown that brief interventions can decrease the overall use of health services in communities. Information is limited in this area, however, as well as on the cost-effectiveness of alcohol screening and brief intervention (see the section"Cost Research on Alcoholism Treatment" in the chapter on economic and health services perspectives). Especially in the current managed health care environment, knowledge of the cost-effectiveness of screening and brief intervention would be particularly valuable.

Improving Physicians' Use of Brief Intervention

Research devoted to finding ways to encourage physicians to use brief interventions more widely indicates that routine educational approaches may not be effective. In a systematic review of continuing medical education strategies, programs using peer discussion and sessions for practicing skills were more effective than formal courses with lectures and handouts, which had limited effect (Davis et al. 1995). In that review, several group education strategies were found to be effective: (1) conducting on-site educational programs at the clinic or hospital; (2) using specific, step-by-step, evidence-based clinical protocols; (3) skills-based role playing; (4) holding peer group discussions; and (5) using a credible expert trainer or educator. Brevity, repetition, and reinforcement of recommended practices have been identified as key program elements (Soumerai and Avorn 1990). For guidance, physicians may also consult NIAAA's *Physicians' Guide* (NIAAA 1995) and *A Medical Education Model for the Prevention and Treatment of Alcohol Use Disorders* (Fleming and Murray 1998).

Research suggests that health care organizations might consider peer review feedback, such as confidential performance reviews based on audits of medical records or written feedback by quality assurance committees, as one way of improving physician performance. In a relevant study, 31 providers (faculty, residents, and advanced nurse practitioners) underwent training in brief-advice counseling for patients with alcohol use disorders (Ockene et al. 1997). The researchers found significant increases in skills, attitudes, and knowledge on the part of the clinicians after they had participated in a 90-minute training workshop and a 30-minute, one-on-one feedback session 2 to 6 weeks later.

Another strategy for increasing the use of both screening and brief interventions is to develop and evaluate clinic-level systems, which take into account the complexity of implementing new clinical activities into a busy practice and the need to make them a systematic part of routine care. A clinic-based system requires active participation of all members of the clinic staff, not just the individual clinician. Components of a comprehensive clinic-based program might include, for example:

- A pencil-and-paper questionnaire, perhaps with alcohol questions embedded in a general health survey, provided by a nurse or receptionist.
- A readily available assessment tool, such as the AUDIT, S-MAST, or SADD.
- A computerized reminder system, maintained by clerical staff, to remind the physician to

screen or follow up on a previous treatment recommendation.

- Documentation of clinical protocols for brief intervention.

- A current list of local alcohol specialists, Alcoholics Anonymous or Al-Anon meetings, and community support agencies.

In Closing

The U.S. health care system offers a great opportunity to identify and treat the majority of people in our Nation who are adversely affected by alcohol use disorders. A number of screening tests can help to identify at-risk drinkers, and research suggests that brief advice and counseling can reduce their levels of drinking and health care utilization. The challenge, however, is to incorporate alcohol screening and brief intervention practices in the context of other clinical activities and prevention programs in these systems of care. For example, screening for immunization status, breast cancer, colon cancer, prostate cancer, cholesterol levels, and smoking status have become high priorities in many managed care systems. Alcohol screening and intervention will need to fit in with these other procedures and compete with other priorities. Changing systems of health care is a complex endeavor, similar to changing patient alcohol use —education is a critical first step, but the next, and far more difficult step, is taking action.

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Treatment of Alcohol Dependence With Psychological Approaches

A broad range of psychological therapies and philosophies currently are used to treat alcoholism, as noted in a recent review (Miller et al. 1995) that cited 25 approaches, including social skills training, motivational enhancement, behavior contracting, cognitive therapy, marital and family therapy, aversion therapy, and relaxation training. As might be expected, these varied approaches have different levels of scientific support for their ability to produce positive outcomes. The task for the scientific community is to evaluate the various approaches and determine which offer the best chances of successful outcome, with the understanding that some types of treatment may have better results for certain types of clients.

Recent progress toward the overall goal of evaluating psychological therapies has been greatest in four areas, which are consequently the principal topics of the section to follow. These are:

- Client-treatment matching, or the use of a client's individual characteristics (such as gender, anger level, social functioning, and severity of alcohol dependence) to select an appropriate treatment therapy.
- The effectiveness of professional treatments modeled on the 12 steps of Alcoholics Anonymous (AA).
- The value of supportive ancillary counseling for life problems that often cooccur with alcoholism (such as difficult family relationships, employment problems, and psychiatric disorders).
- The effects of variations in treatment intensity (the frequency and duration of therapy) on treatment outcomes.

This section focuses on these topics, but progress has been made in other related areas as well. Advances in our knowledge of the effectiveness of "brief intervention," in which health care providers offer brief sessions of advice, are described in the previous section of this chapter, "Screening and Brief Intervention for Alcohol Problems." In addition, social and family interventions continue to find support in research reviews for their use with alcohol and other substance abusers (Baucom et al. 1998; Edwards and Steinglass 1995; Stanton and Shadish 1997). Recent studies of social and family interventions, however, have largely been long-term follow-ups or reanalyses of studies cited in the *Ninth Special Report to the U.S. Congress on Alcohol and Health* (National Institute on Alcohol Abuse and Alcoholism 1997) and, as such, will not be discussed here.

Client-Treatment Matching

No single psychological treatment approach has been found clearly superior in promoting long-term recovery from alcoholism (Donovan and Mattson 1994). Instead, many different treatment approaches appear to be equally effective. However, it may be the case that an overall similarity of outcomes hides certain relationships whereby one type of treatment might produce better results for certain patients. For example, patients with long-term, stable marriages might be expected to benefit more from marital and family counseling approaches than would patients in shorter term or unstable relationships. Researchers have hypothesized that if they could identify important client characteristics and the treatments that work best for them, clients could be "matched" to the treatment from which they would benefit most. Prior to 1997, several studies had examined potential client-treatment matches, but these early studies were small in

scale and limited in scope (see Mattson et al. 1994 for a review).

A project called Matching Alcohol Treatments To Client Heterogeneity (Project MATCH) has provided the most careful and extensive test to date of the contributions of client-treatment matching to treatment outcome (Project MATCH Research Group 1997*a,b,* 1998*a,b*). In this multisite clinical trial, 1,726 clients were assigned randomly to either a cognitive-behavioral, a motivational enhancement, or a 12-step facilitation treatment. While the study showed that the three treatments produced comparable outcomes, the study's primary goal was not to evaluate which treatment produced the best outcomes per se, but to evaluate whether treatments that were appropriately matched to the client's needs produced better outcomes than did treatments that were not matched. The study investigated many client characteristics, among them gender, alcohol involvement, cognitive impairment, meaning seeking (spirituality), motivation, sociopathy, social network support for drinking, alcohol dependence, level of anger, interpersonal dependency, prior AA involvement, self-efficacy, social functioning, antisocial personality disorder, type and severity of psychiatric disorder, religiosity, alcoholism type, and readiness to change. Each of the characteristics was evaluated to see whether clients who had different variations of the characteristic benefited differently from the various treatments provided.

Participants in the study were divided into two general treatment groups: 952 received only outpatient treatment, and 774 received outpatient aftercare following a more intense course of inpatient treatment (hereafter labeled the aftercare group). The study's results were reported separately for these two groups. Outcomes were measured at 1 year following treatment for both groups as well as at the 3-year mark for the outpatient group.

The results of Project MATCH yielded minimum support for matching the patient characteristics studied to the treatment types. Patients with only 4 of the 21 potential matching characteristics had different responses depending on the treatment received. These characteristics were:

- Alcohol Dependence: In the aftercare group, individuals with high levels of alcohol dependence benefited more from 12-step treatment than from cognitive-behavioral treatment, whereas the reverse was true for patients low in dependence.
- Psychopathology: In the outpatient group, those without psychopathology were found to benefit more from 12-step facilitation than from cognitive-behavioral therapy.
- Anger: Also in the outpatient arm of the trial, patients high in anger had more successful outcomes with the motivational enhancement approach than with the other two approaches.
- Social Network Support for Abstinence: Patients whose social networks offered less support for abstinence had better outcomes in 12-step facilitation than in motivational enhancement therapy.

In sum, Project MATCH's findings challenged the notion that patient-treatment matching is a prerequisite for optimal alcoholism treatment. Other than the four relationships described above, the findings did not show that matches between patient characteristics and treatments produced substantially better outcomes. The paucity of matching findings might be seen in the context of the finding that the three treatments studied in Project MATCH were approximately equal in their efficacy. Any one of the treatments, therefore, would be expected to achieve results similar to the others. Moreover, Project MATCH showed that reductions in drinking observed at the 1-year mark were sustained over the 3-year follow-up period (Project MATCH 1998*a*).

Professional Treatment Modeled on the 12 Steps of Alcoholics Anonymous

Participation in AA or professional treatment programs based on the 12 steps of AA is the dominant approach to alcoholism treatment in the United States. Higher levels of AA attendance

during and following professional treatment are consistently associated with better outcomes, but AA affiliation without professional treatment has not routinely resulted in improvement (Emrick et al. 1993). Two recent studies have made significant progress in confirming the effectiveness of professional treatment based on 12-step principles. One of these studies was based on further analysis of the Project MATCH trial just discussed (Project MATCH 1998*b*). Although the trial had not been designed to test which of the three treatments (cognitive-behavioral, motivational enhancement, or 12-step facilitation) offered the best outcomes, one of the findings to emerge was that each produced approximately equal results according to the study's principal outcome measures—the percentage of abstinent days and the number of drinks per drinking day. In the outpatient group, however, the 12-step treatment had more favorable results according to several other measures, including (1) continuous abstinence from alcohol during the first posttreatment year, (2) length of time before first relapse (with longer times indicating better outcomes), (3) percentage of clients not drinking at 1-year follow-up, and (4) percentage of clients not drinking at 3-year follow-up. Thus, by all of the measures studied, 12-step clients achieved outcomes at least as pronounced and durable as those of clients in other therapies, and by some measures, 12-step clients achieved better outcomes.

The other recent study on the topic of professional treatment modeled on the 12-step approach was an analysis of 15 treatment programs offered through the U.S. Department of Veterans Affairs (Ouimette et al. 1997). Programs were classified as 12-step, cognitive-behavioral, or a combination of the two on the basis of the primary treatment philosophy employed. The researchers followed 3,018 clients for 1 year. Patients were not randomized to different treatment conditions in this study, as they had been in the Project MATCH trial. Results at 1-year follow-up indicated that patients in 12-step programs were more likely to be abstinent than were patients from cognitive-behavioral or mixed programs (25 percent vs. 18 and 20 percent, respectively). Most of the other variables studied—mean alcohol consumption, alcohol dependence symptoms, use of other drugs, depression, anxiety, and arrests—revealed no significant differences between patients treated by different approaches.

How 12-step approaches function to produce positive treatment outcomes is another important topic of study. Findings from the Project MATCH trial indicated that for clients who had social networks that supported drinking, 12-step facilitation therapy was more effective than motivational enhancement therapy at the 3-year follow-up (Longabaugh et al. 1998). Involvement in AA was a partial mediator of this effect. Among those clients who had social networks that were supportive of drinking and who were assigned to 12-step facilitation treatments, those involved in AA had better 3-year outcomes.

Another study on this topic followed 100 clients (not randomly assigned to treatment) for 6 months after treatment and found that five patient characteristics were related to both stronger affiliation with AA and better treatment outcome (Morganstern et al. 1997). The five characteristics were self-efficacy, commitment to abstinence, cognitive coping, behavioral coping, and primary appraisal of harm due to drinking. These results suggest that these five characteristics should be considered in future studies that seek to define the underlying mechanisms of effectiveness for 12-step-based treatments.

Supportive Ancillary Services

Typically, clients entering treatment arrive with a number of other problems in addition to alcoholism. Problems that often appear along with alcoholism include other drug abuse, mental health disorders (particularly depression), unemployment, domestic violence, and legal problems. Two consequences flow from this "bundling" of alcoholism and related problems. First, measures of treatment success often must be concerned with a wide number of outcomes

Psychological Treatment Outcomes: A Broad Perspective

How effective are psychological interventions for persons experiencing alcohol abuse and alcoholism? At first glance, this question appears to be relatively straightforward. However, attempts to provide simple answers to this question may overlook a number of important considerations. Experts in alcohol research urge moving away from global statements about the effectiveness of alcohol treatments and adopting a broader, more complex perspective on the outcomes of psychological interventions. Among the factors for consideration are the following:

- Patient Diversity: Persons who receive treatment for alcohol abuse and alcoholism are a remarkably diverse group. For example, the nature and severity of alcohol problems vary considerably, from severe forms of alcohol dependence to occasional problems with drinking. The major implication here is that judgments about outcomes must take into account individual patient characteristics.
- Context for Treatment: Alcohol treatment itself is a complex phenomenon. Specific psychological interventions are part of a larger context that includes expectancies of clinicians and clients as well as different settings, therapist characteristics, treatment intensity, treatment goals, and methods of payment. Thus, treatment actually represents a mix of these factors and attributes.
- Outcomes Other Than Changes in Drinking Behavior: Treatment outcome is a multidimensional event. The usual standard for judging the effectiveness of alcohol treatments is change in drinking behavior. While this measure is critical, there are other equally important outcomes that deserve consideration. For example, it is important to understand how alcohol treatment affects patients' rates of illness and death, the nature of psychological disorders that accompany alcohol problems, and the use and costs of medical services triggered by alcohol misuse.
- Changes in Outcomes Over Time: In addition to expanding the scope of outcome measures, it is important to consider that relatively few patients remain in the same outcome status over a span of years. At any given time, many factors other than the treatment itself can contribute to positive or less-than-positive results. For example, the extent to which a patient's posttreatment social environment supports the changes resulting from treatment has an enormous effect on long-term outcomes. Thus, it is critical to consider the timing of evaluations of patient outcomes, to distinguish short-term efficacy from the much broader phenomenon of long-term treatment effectiveness, and to examine the factors that hinder or support effectiveness at different stages.

where improvement is sought (see the box, above). Second, treatment for the alcoholism per se may have a greater chance of success if the other problems are being successfully addressed by appropriate services. Some recent research has focused on the impact of these supportive ancillary services.

In one study, researchers randomly assigned 94 clients of employee assistance programs to one of two treatments: standard alcoholism counseling or standard alcoholism counseling plus adjunctive professional treatment sessions in areas that may result from, or contribute to, alcohol abuse (McLellan et al. 1997). At 6 months following treatment, patients in both groups had similar rates of abstinence. However, the adjunctive counseling group was more likely to be working 20 or more hours per week and less likely to be having family conflicts or to have been readmitted for alcohol or drug abuse treatment, arrested, or charged with a crime. In addition, clients assigned to adjunctive counseling stayed in treatment longer and were more likely to complete treatment. These results suggest that treatment programs can improve a broad range of outcomes by giving attention to multiple problem areas as a part of alcohol counseling.

In another recent study of ancillary services (Longabaugh et al. 1995), treatment staff devoted different amounts of time (eight, four, or zero sessions) to relationship enhancement therapy. Sessions included one or more members of the client's social network (family or friends) and were aimed at increasing social support for the client's

abstinence and strengthening the client's investment in his or her social support network. Follow-up results after 18 months were mixed. Eight-session counseling was beneficial when there was either a deficit in the social network's ability to support the client's abstinence or a deficit in the client's investment in the social network. However, four counseling sessions, or none at all, seemed more effective than eight sessions when there were no such deficits in the client's social network.

Intensity of Services

Along with managed care has come pressure to reduce treatment costs and eliminate unnecessary services. This makes more urgent the task of determining what the optimal intensity (or duration and amount) of treatment services for alcoholism should be. Earlier research had noted that there were few differences in long-term outcomes between inpatient and outpatient alcoholism treatment (Finney et al. 1996). Fewer studies have compared the relative effectiveness of more versus less intensive forms of outpatient treatment. Emerging findings, however, suggest that while intensity may not predict long-term outcomes, it may affect the speed at which an individual achieves some control over his or her drinking during treatment.

Project MATCH (although, again, not originally designed to answer the question of optimal treatment intensity) has provided some useful findings on this question. In the Project MATCH trial, the motivational enhancement treatment was less intensive than either the cognitive-behavioral treatment or 12-step facilitation treatment. The motivational enhancement treatment consisted of four individual therapy sessions (administered during weeks 1, 2, 6, and 12 of the trial), whereas both of the other treatments consisted of 12 weekly individual sessions.

In the outpatient group, the three treatments showed similar long-term outcomes at the 1-year and 3-year follow-up stages in terms of the number of abstinent days and drinks consumed per drinking day. Earlier in the study, however, the short-term outcomes differed: at the end of the 12 weeks of treatment, only 28 percent of the outpatient clients in the lower intensity, motivational enhancement therapy were either abstinent or drinking moderately without problematic consequences, compared with 41 percent of those in both the 12-step facilitation treatment and the cognitive-behavioral treatment. These findings may suggest that lower intensity treatment is slower at helping patients to achieve control over their drinking than is higher intensity treatment. However, among the aftercare group, long-term and short-term outcomes were similar for both the more and less intensive therapies. Additional research on treatment intensity from a cost-effectiveness perspective can be found in the chapter on economic and health services perspectives.

In Closing

Treatment outcome studies have repeatedly found large and sustained reductions in drinking among persons seeking help for alcoholism. Still, many individuals continue to suffer problems with alcohol following treatment. Researchers are trying to improve treatment by undertaking further investigations of the factors and conditions that might improve psychological treatment outcomes (as well as ways to supplement psychological treatments with medications—see the next section in this chapter, "Treatment of Alcohol Dependence With Medications"). Recent findings on psychological therapies have suggested that:

- Matching broad categories of client characteristics to treatment modality does not substantially improve overall treatment outcomes.
- Professional treatments based on 12-step approaches can be as effective as other therapeutic approaches and may actually achieve more sustained abstinence.
- Supportive ancillary services can be effective in remediating common problems that cooccur with alcoholism.

- Higher intensity outpatient treatment (12 weekly sessions) may help a client gain control over drinking more quickly.

As this research progresses, it promises to yield further knowledge about the effectiveness of various psychological treatment approaches, the "active ingredients" of those approaches, the proper array of ancillary services that can be offered, and the amount or dosage of treatment that produces the best results.

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Treatment of Alcohol Dependence With Medications

In recent years, the development of new medications to treat alcohol dependence, representing the combined efforts of neuroscientists and clinical researchers, has begun a new era in alcoholism treatment. Until 1995, the only medical treatment approved for use in the United States (disulfiram) simply provoked intense physical symptoms such as vomiting upon the ingestion of alcohol. In contrast, newer drugs for alcoholism treatment operate at the molecular level of the brain processes that promote and maintain addiction. The targeted actions of these newer drugs offer the possibility of more effective treatment options for the millions of alcohol-dependent persons in our Nation.

Over the past decade, advances in knowledge of the biology underlying drinking behavior have laid the groundwork for new pharmacologic treatments for alcohol dependence. For example, it is now known that multiple chemical messenger systems in the brain, called neurotransmitter systems, are involved in problem drinking. Several medications that affect different neurotransmitter systems have been tested in humans.

In particular, one area of research has focused on a class of medications called "opiate antagonists." These medications interfere with neurotransmitter systems that produce pleasurable effects, such as feelings of euphoria, upon the use of alcohol and other drugs. If patients resume drinking while taking opiate antagonists, they are not rewarded with the expected "high" from the alcohol. Two of these drugs, naltrexone and nalmefene, have shown promising results for treating alcohol dependence. In 1995 naltrexone (ReVia) was approved by the U.S. Food and Drug Administration (FDA) for treating alcohol dependence, while nalmefene is in the testing phase of development.

In addition, researchers are evaluating medications that target different neurotransmitter systems involved in maintaining dependence on alcohol. One such medication, acamprosate, holds promise in reducing the return to drinking, following a brief period of abstinence, that typifies alcohol dependence. Moreover, investigators are examining the possibility that combining a medication that reduces the risk of relapse (such as acamprosate) with one that reduces the risk of heavy drinking should relapse occur (such as an opiate antagonist) may increase treatment effectiveness.

Pharmacology research has focused not only on drugs to treat alcoholism itself, but also on medications for coexisting conditions that can threaten recovery. Current research continues to show that antidepressants, both old and new, are powerful agents for helping persons with alcohol dependence who also suffer from depression to gain and maintain abstinence from alcohol. Patients with untreated depression often relapse to drinking, whereas those who take antidepressants generally participate more in treatment programs and respond better. Recent studies in this area have strengthened the findings of previous research by using larger, more diverse patient samples and new types of antidepressants.

Medications hold great promise but at present cannot replace psychological treatments for people with alcohol dependence. These two classes of treatment strategies are complementary rather than competitive, in that studies suggest that pharmacologic agents may be combined effectively with skilled counseling to improve treatment outcomes (O'Malley et al. 1992, 1996). This section focuses on recent advances in pharmacotherapy research in two main areas: (1) medications specifically used to treat alcohol dependence, and (2) medications to treat some patients who suffer not only from alcohol dependence but also from psychiatric disorders, primarily depression. (For an update on research on psychological treatments, see the previous section "Treatment of Alcohol Dependence With Psychological Approaches" in this chapter.)

Medications for Alcohol Dependence

In 1992, alcohol researchers proposed the attributes of a "perfect medication" for treating alcohol dependence (Volpicelli et al. 1992). The drug they were seeking would reduce the craving for alcohol so that an individual would be less motivated to drink. The ideal drug also would block the reinforcing effects of alcohol so that if the individual resumed drinking, pleasant effects would not be felt. In addition, the medication would have few, if any, side effects. With these goals in mind, researchers have made significant progress in recent years.

Blocking the Reward: Opiate Antagonists

The treatment of alcohol dependence has benefited from decades of research that have led to an understanding of the mechanics of addiction and of the way in which certain medications can counter the effects of addictive drugs. Substances like heroin and morphine, called opiates, act like chemicals the brain produces naturally, called endogenous opioids, which stimulate pleasurable feelings and suppress pain. Medications known as opiate antagonists bind with the brain's receptors for endogenous opioids, thus blocking the desired effects of heroin and similar drugs while having no effect themselves.

Alcohol is not an opiate-like substance, and researchers do not know the exact mechanism by which opiate antagonists affect drinking. Animal studies suggest, however, that these medications block some of alcohol's rewarding effects. When researchers administered an opiate antagonist (naltrexone) to rats that were later given alcohol, the medication decreased the amount of alcohol-induced dopamine, a neurotransmitter involved in motivation and reinforcement that is available in a reward center in the brain (Benjamin et al. 1993). Moreover, rats given larger doses of naltrexone showed even greater decreases in dopamine. This "dose-dependent" effect demonstrated that the opioid system is an important target for medications to control alcohol consumption and reward. Recent studies on two opiate antagonists, naltrexone and nalmefene, are summarized below.

Naltrexone. Studies in humans also support the hypothesis that opiate antagonists reduce the pleasurable effects associated with alcohol's stimulation of the endogenous opioid system and related reward systems. Patients given naltrexone described less euphoria, or "high," from drinking than did patients taking a placebo (Volpicelli et al. 1995*b*). Similarly, social drinkers given naltrexone in a laboratory told researchers they felt fewer stimulant effects of alcohol and more of its sluggish, sedative effects (Swift 1995; Swift et al. 1994). Thus, by reducing the positive reinforcement of drinking and increasing unpleasant effects, naltrexone may help abstinent individuals who relapse to refrain from heavy drinking.

In another study, social drinkers who were pretreated with naltrexone waited longer to have both their first and their second drinks (Davidson et al. 1996*b*). This finding suggests that opiate antagonists block both the chemical changes in the brain elicited by environmental cues before drinking and the "priming" effects of alcohol during drinking—phenomena associated with the urge to drink and loss of control over drinking. Researchers who reexamined data (O'Malley et al. 1995) from two previous clinical trials of naltrexone (O'Malley et al. 1992; Volpicelli et al. 1992) found that patients with alcoholism who took naltrexone and who ultimately returned to drinking refrained a longer time until their first drink and their first episode of heavy drinking than did patients who took a placebo. Among the patients in the study who drank, those using naltrexone drank less frequently and on a significantly smaller percentage of days than did placebo-treated patients, and they were less likely to relapse to heavy drinking.

Persons with alcoholism share two core symptoms: the tendency to drink more than they intend to and drinking at levels that lead to medical, psychological, or social problems, such as missing work and failing to fulfill family responsibilities. Naltrexone appears to have a significant effect on both of these symptoms of alcohol dependence. In two early studies, the researchers gave naltrexone to recently detoxified outpatient

volunteers who came from diverse racial/ethnic and economic backgrounds and who had received different types and intensities of behavioral treatments for alcoholism (O'Malley et al. 1992; Volpicelli et al. 1992). Regardless of differences in demographic traits and behavioral treatments, patients given naltrexone had similar outcomes across all groups: they drank less frequently, and when they drank, they consumed less alcohol.

No medication can be fully effective unless it is used as directed, that is, taken as scheduled and for the full course of treatment. The degree to which patients are compliant in taking medication as directed is a key measure of efficacy in all drug studies. Reasons for noncompliance include unpleasant side effects, expense, and complicated dosing schedules. Recent research suggests that patients' compliance with naltrexone is excellent in a treatment research setting. When naltrexone use was verified by urine testing, it was found that 92 percent of naltrexone-treated patients were compliant, compared with 78 percent of placebo-treated patients (O'Malley et al. 1992). Other investigators noted that naltrexone was especially effective in preventing relapse to heavy drinking among patients who took the medication regularly and who completed the 12-week treatment course (Volpicelli et al. 1997). Patients who took more of their naltrexone pills correctly had lower percentages of drinking days then did patients who did not take all of them correctly.

Investigators have developed an effective new method for monitoring naltrexone and its major metabolite, 6-beta-naltrexol, in human plasma (Davidson et al. 1996*a*; Huang et al. 1997). The new blood test, analyzed by high-performance liquid chromatography with electrochemical detection, may help researchers to refine naltrexone dosing to improve its efficacy. Some patient groups, such as women and the elderly, often respond much better to medications at lower dosages, whereas other groups require relatively high levels.

Several investigators have examined the side effects of naltrexone. A study of 570 patients with alcoholism found no serious adverse events associated with naltrexone treatment (Croop et al. 1995). Although no systematic studies have ascertained the range of doses that might be used to treat alcoholism, the typical dose is 50 milligrams per day (mg/day). At a much higher dose—300 mg/day—naltrexone is associated with adverse liver effects (hepatotoxicity). The drug label notes that this medication is not appropriate for patients with acute hepatitis or liver failure.

Follow-up studies of patients who have used a medication can yield important information about its long-term effects as well as the potential for drug "rebound," which could lead to relapse, when the medication is discontinued. Six months after treating patients for 12 weeks with naltrexone, researchers (O'Malley et al. 1996) interviewed a subset of participants from their earlier study (O'Malley et al. 1992). They found that two-thirds of the patients originally treated with a placebo, but only one-third of naltrexone-treated patients, had resumed drinking to the point that they again met criteria for alcohol abuse or dependence. Naltrexone-treated patients also were less likely to relapse during the first month after they stopped using the medication and less likely to drink heavily during the first 4 months after treatment.

As mentioned, however, the study did find that one-third of the patients relapsed after the 12-week treatment period, suggesting that naltrexone should be continued beyond 12 weeks for some people. At the 6-month follow-up interview, patients were more likely to be abstinent from alcohol if they had been able to sustain abstinence during the initial 12 weeks of treatment with naltrexone (O'Malley et al. 1996). Because establishing abstinence is linked with better treatment outcomes, use of naltrexone beyond the 12-week period may be particularly helpful to patients who have difficulty with abstinence during initial treatment.

In addition, some patients may have no trouble achieving abstinence during initial naltrexone treatment, but they may anticipate periods of

relapse risk, such as an upcoming vacation, or experience sudden stressful events, such as the death of a friend. These patients may benefit by using naltrexone again for short periods until they feel more secure about their coping skills in avoiding relapse. Longer term studies of maintenance treatment with naltrexone are under way to determine the appropriate duration of treatment for different groups of patients.

Determining which patients are likely to benefit from this treatment is prudent because naltrexone is moderately expensive: the standard daily 50-mg tablet for an alcohol-dependent person retails at almost $5. Additionally, as with any new medication, naltrexone must be used more widely before firm conclusions are drawn about risks and benefits. Early trials suggest that the patients who may derive the greatest benefit from naltrexone are those who experience an intense urge to drink and who have physical symptoms, such as chronic pain or discomfort, coupled with poor cognitive functioning, such as impaired learning skills and memory (Jaffe et al. 1996; Volpicelli et al. 1995*a*).

A large cooperative study is now under way at 15 U.S. Department of Veterans Affairs medical centers to examine alcoholism treatment with naltrexone for up to 1 year. The 600 veterans assigned to naltrexone or a placebo also will receive a standardized behavioral intervention, the Alcoholics Anonymous-based 12-step facilitation treatment designed for the project Matching Alcohol Treatments To Client Heterogeneity (Project MATCH) (see also the previous section in this chapter, "Treatment of Alcohol Dependence With Psychological Approaches"). The study will also evaluate the cost-effectiveness of naltrexone.

Nalmefene. Nalmefene, a newer opiate antagonist that is not yet approved by the FDA for treatment of alcoholism, is structurally similar to naltrexone but has potential advantages for treating alcohol dependence. Unlike naltrexone, for example, nalmefene has shown no dose-dependent liver toxicity (Mason et al. 1999). In addition, nalmefene is considered a "universal" opiate antagonist, in that it binds more readily with the three subtypes of opioid receptors that are thought to reinforce alcohol consumption (Charness et al. 1983; Culpepper-Morgan et al. 1995; Emmerson et al. 1994; Michel et al. 1985; Tabakoff and Hoffman 1983), whereas naltrexone specifically binds to just one receptor subtype and may affect the other two only at high doses (Sawynok et al. 1975).

This new study reinforced findings from a small pilot study on nalmefene that showed that alcohol-dependent patients taking 40 mg/day had significantly lower rates of relapse in preliminary studies than did either patients on the placebo or those on 10 mg/day of nalmefene (Mason et al. 1994).

In a recent study of 105 patients, those who were randomly assigned to nalmefene (20 or 80 mg/day) were 2.4 times less likely to relapse to heavy drinking during the 12 weeks of treatment than those who received a placebo. Although one-third of the patients treated with nalmefene did relapse to heavy drinking at least once during the trial, they had fewer subsequent heavy-drinking episodes than did those taking the placebo. The researchers found no significant differences between 20-mg and 80-mg doses of nalmefene, and the patients taking either dose of nalmefene had high rates of compliance and showed no evidence of medically serious side effects (Mason et al. 1999).

Replicating the results of naltrexone studies with this structurally similar compound supports the importance of further research on opiate antagonists to treat alcohol dependence. Nalmefene may be an option for patients who experience adverse side effects from naltrexone or who do not respond to that drug.

Reducing Rates of Relapse: Acamprosate

The medication acamprosate interacts with different biochemical pathways in the brain than those affected by opioid antagonists. Although the precise mechanism of action is still under investigation, acamprosate is known to affect two neurotransmitter systems involved in maintaining alcohol dependence: the glutamate system and

the gamma-aminobutyric acid system. While chronic alcohol exposure disrupts both systems, causing changes that may persist for many months following withdrawal, acamprosate may act by restoring normal activity in these systems (al Qatari and Littleton 1995).

Having been available by prescription in France since 1989, and more recently in more than 30 countries around the world, acamprosate has been used to treat more than 1 million alcohol-dependent people. In the United States, the FDA has granted acamprosate the status of an investigational new drug. A 6-month clinical trial was designed to evaluate the safety and efficacy of acamprosate in the United States across 21 different treatment settings, including psychiatry, internal medicine, and alcoholism treatment programs (Mason and Goodman 1997). This study has recently been completed, and the data are now being analyzed.

Studies of acamprosate in animals and humans have demonstrated many potential benefits. For example, it decreases voluntary alcohol intake with no effects on food and water consumption, no potential for abuse, and no pharmacologic effects other than those involved in reducing alcohol dependence (Soyka 1996). In addition, there is no evidence that acamprosate interacts pharmacologically with alcohol or with other medications prescribed for alcoholism, such as disulfiram, or for depression, anxiety, psychoses, or insomnia (Durbin et al. 1996). Moreover, unlike naltrexone, acamprosate is not metabolized to a meaningful extent in the liver; therefore, patients with liver dysfunction can gain the same therapeutic effects as other patients (Wilde and Wagstaff 1997).

In 11 clinical trials in Europe, which included a total of 3,338 patients from many treatment centers, researchers compared the effectiveness of acamprosate with that of a placebo. In 10 of the studies, patients on acamprosate experienced higher abstinence rates and, for those who did resume drinking, a significantly longer period of abstinence until their first drink than did patients on the placebo (Geerlings et al. 1997; Lhuintre et al. 1990; Paille et al. 1995; Pelc et al. 1997; Sass et al. 1996; Soyka 1996; Whitworth et al. 1996). Acamprosate produced better outcomes than the placebo in studies in which the drug was administered for as long as 1 year, as well as in follow-up studies in which subjects were reinterviewed 6 to 12 months after stopping the acamprosate treatment (Geerlings et al. 1997; Sass et al. 1996). The single European trial with negative results differed from the other 10 trials in that treatment that is normally initiated immediately after detoxification was delayed up to 2 months. By the time that study began, one-third of the subjects had relapsed (Soyka 1996).

Although some of the 10 positive European trials had stronger results than others, the outcomes consistently favored acamprosate over the placebo in rate and duration of abstinence and other measures. When researchers analyzed pooled data from all 11 trials, the patients on acamprosate were found to have significantly higher rates of abstinence and treatment attendance than those on the placebo, as well as longer alcohol-free periods (Mann et al. 1995). The effects of acamprosate were evident during the first 30 to 90 days of treatment (Ladewig et al. 1993; Sass et al. 1996), the interval in which the risk of drinking is the highest and pharmacologic support may be most effectively implemented (Meyer 1989). In these trials, any additional effect of behavioral therapy could not be evaluated because none of the trials included standardized behavioral therapy; instead, each treatment center provided whatever behavioral therapy it routinely offered (Mann et al. 1995).

Comparing and Combining Acamprosate With Naltrexone

No single study has directly compared acamprosate with naltrexone. However, researchers have compared each medication with a placebo in separate studies that yielded quite similar results. At the end of the 12-week course of medication, 51 percent of the acamprosate-treated patients (Pelc et al. 1997) and 54 percent of the naltrexone-treated patients (O'Malley et al. 1995)

had stopped drinking. The rates for placebo were 26 percent and 31 percent, respectively. Although the abstinence rates achieved by both acamprosate and naltrexone were notably better than the rates with placebo, nearly one-half of the subjects remained at risk for drinking during the treatment study.

Because several neurotransmitter systems are involved in maintaining alcohol dependence, the effect of any single medication on alcohol intake may be modest. Both acamprosate and naltrexone are well tolerated by patients, and the medications' affinities for different neurotransmitter receptors may lead to different effects on drinking outcomes (such as preventing relapse to heavy drinking or prolonging abstinence). Thus, the National Institute on Alcohol Abuse and Alcoholism is currently funding a cooperative, multicenter study that will test acamprosate and naltrexone, both alone and in combination, and evaluate their use (vs. a placebo) in conjunction with behavioral interventions of either moderate or minimum intensity.

Evaluating Serotonergic Agents for Treatment of Alcohol Dependence

The neurotransmitter serotonin affects multiple actions in the brain, including the regulation of mood states, appetite, and sleep. The exact nature of the relationship between serotonin and alcoholism is unknown. One theory suggests that individuals with alcohol dependence are naturally deficient in brain serotonin. According to this view, alcoholism may represent an attempt to increase brain serotonin levels. Another theory suggests that serotonin either directly influences the reinforcing effects of alcohol and other drugs or exerts an indirect influence through an effect on the neurotransmitter dopamine. A third suggestion is that low levels of serotonin lead to impulsive behavior, including an inability to modulate alcohol intake. Abnormalities in the brain's serotonin system may contribute to anxiety, potentially leading to "self-medication" of anxiety symptoms with alcohol. Finally, serotonin may affect general appetite behaviors.

Researchers have examined whether alcohol intake could be reduced by medications that increase the amount of serotonin available for binding with receptors on nerve cells in the brain. Among the "serotonergic" agents that have been evaluated for alcoholism treatment are sertraline (Zoloft), fluoxetine (Prozac), and several other "selective serotonin reuptake inhibitors" (SSRI's), a class of drugs developed in the 1980's to treat depressive disorders. These drugs act at the molecular level where nerve cell endings release serotonin, which then binds to specialized receptors—of which at least 14 different subtypes have been identified—on adjacent nerve cells (Fuller 1996). Normally, the nerve cells that release serotonin also reabsorb some of it, but SSRI's inhibit that reuptake so that more serotonin is available to bind with receptors on other nerve cells.

In addition to medications that inhibit reuptake of serotonin, other agents take advantage of different mechanisms in the serotonin system. For example, a "serotonin receptor antagonist" that blocks a specific receptor subtype (called 5-HT_3) has been shown to reduce one of the reinforcing effects of alcohol, the release of the neurotransmitter dopamine in the brain (Campbell and McBride 1995; Yoshimoto et al. 1991).

Thus far, studies on the effectiveness of serotonergic agents in reducing alcohol intake have shown only a mild and transient effect in moderate drinkers and no effect in alcohol-dependent patients (for a review of these studies, see Litten et al. 1996). In one multicenter study involving 423 alcohol-dependent patients, researchers examined ritanserin, a drug that blocks a serotonin receptor called 5-HT_2, and found it no more effective than a placebo in controlling alcohol craving and consumption (Johnson et al. 1996). Because patients on higher doses of ritanserin had abnormalities in their electrocardiograms, no further study of this drug was undertaken.

Similarly, when researchers gave fluoxetine, a widely used SSRI, to 28 male inpatients with

severe alcohol dependence, they found it to be no better than a placebo in reducing relapse rates (Kabel and Petty 1996). These findings confirmed those of an earlier study of 101 patients in which fluoxetine was not any more effective than a placebo in reducing alcohol consumption (Kranzler et al. 1995).

Although serotonergic agents have not fulfilled the promise they once seemed to offer in treating alcoholism, a recent study in animals suggests this as an area for further research. The researchers gave rats a combination of fluoxetine and a serotonin receptor antagonist called WAY 100635, which is still in development (Zhou et al. 1998). This combination of medications reduced the rats' alcohol consumption more than either compound alone. The authors speculated that combining these drugs increased the available serotonin to a level not achievable by fluoxetine alone.

Overall, however, clinical findings to date suggest that the serotonergic agents studied thus far are not effective for treating alcohol dependence itself, but rather, as described next, for the treatment of cooccurring psychiatric conditions such as depression.

Medications for Patients With Both Alcoholism and Depression

People with alcohol dependence often experience symptoms of depression when they stop drinking. For most individuals, these symptoms disappear or wane during the first 1 or 2 weeks of abstinence. However, studies have shown that patients who continue to report serious depressed feelings after the 1st week of abstinence are likely to have a depressive disorder that coexists with their alcohol dependence. These patients are often referred to as having "comorbid depression" or a "dual diagnosis." If the depression is left untreated, many will relapse to drinking. Thus, accurate diagnosis of depression and its swift treatment are critical in the care of alcohol-dependent patients.

Investigators have examined different types of antidepressant agents for dually diagnosed patients, including the older tricyclic antidepressants such as imipramine and desipramine, which have been available since the 1960's, and the newer SSRI's such as sertraline and fluoxetine. The availability of SSRI's has allowed more aggressive treatment of depression in alcohol-dependent patients because these medications have few side effects and can be taken safely by individuals who continue to drink, unlike tricyclic and other antidepressants that interact significantly with alcohol (Schottenfeld et al. 1989).

As described below, studies show that regardless of the type of antidepressant used, depressed alcohol-dependent patients who take antidepressants have better outcomes in terms of their drinking than do those who take a placebo. Clinical trials of antidepressants for dually diagnosed patients tend to have small sample sizes, which limits the extent to which the findings can be generalized to larger and more diverse patient groups. However, the scientific methods used in these small studies are generally rigorous, and, taken as a whole, the findings suggest significant progress in refining treatment for this subgroup of persons with alcohol dependence who are at increased risk for illness and death because of their dual disorders.

Recent studies of imipramine (McGrath et al. 1996) and fluoxetine (Cornelius et al. 1997) confirm previous work showing that depressed people with alcoholism who are given antidepressants experience greater decreases in depression and alcohol consumption than do those given a placebo (Kranzler et al. 1995; Mason and Kocsis 1991; Mason et al. 1996; Nunes et al. 1993). Some participants in these antidepressant trials continued to drink even though their depression lifted, which demonstrates the need for additional interventions specific to drinking.

In making decisions about diagnosis and treatment of alcohol-dependent patients, some clinicians distinguish between primary depression, which occurs before the onset of alcoholism, and secondary depression, which occurs afterwards.

Studies of both types of depressed patients with alcoholism have shown essentially the same findings: antidepressant medications improve mood and reduce drinking whether the patients' depression is primary (McGrath et al. 1996; Nunes et al. 1993) or secondary (Mason et al. 1996).

Finding the optimal dosage of antidepressants for dually diagnosed patients has also been an area of investigation, because ineffective treatment of depression may lead to relapse during the early stages of abstinence. Many patients with a long-term history of alcoholism have liver dysfunction, which may alter their metabolism of certain medications so that they require higher or lower dosages. A 6-month study examining the metabolism of antidepressants by patients with and without current alcoholism found that alcoholic patients without cirrhosis may benefit from higher dosages of antidepressants, because changes in their liver functioning during early abstinence speed up their metabolism of these drugs (Mason 1996).

In Closing

Alcohol's precise effects on the reward centers of the brain are still not fully understood, but laboratory studies and clinical trials continue to increase our knowledge of new medications to augment behavioral therapies for alcohol dependence. In recent years, these studies have shown that: (1) naltrexone and a similar compound, nalmefene, help reduce the chance of heavy drinking when abstinent individuals relapse; (2) acamprosate can prevent relapse by making it easier to maintain abstinence; (3) SSRI's are not useful in treating alcohol dependence itself; and (4) not only SSRI's, but also other antidepressants, are successful in treating coexisting depression that may lead patients with alcohol dependence to relapse if the depression is left untreated.

Currently, clinical trials are under way to search for new and more effective pharmaceutical agents to treat alcohol-dependent individuals. Among these are trials designed to explore whether combining acamprosate and naltrexone, two highly tolerable and effective drugs, can enhance treatment outcomes when they are provided along with behavioral therapies; to test the safety and efficacy of different dosages of acamprosate; and to study sertraline as a representative of the safe and tolerable SSRI's for treating depression that coexists with alcoholism.

Studies will also be needed to identify the most appropriate medications for different subgroups. Current research has confirmed that alcohol is metabolized differently by women (see review by Romach and Sellers 1998) and by older adults (see review by Ownby et al. 1996) than it is by younger men, who have constituted the majority of subjects in studies of the pharmacotherapy of alcoholism. Future research will need to examine data from women, older adults, and other subgroups to determine the medications that are most effective and acceptable, with the fewest adverse side effects, for different groups of patients.

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