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important determinant of alcoholism in some individuals. What then is the contribution of environmental influences to the expression of alcoholism in other individuals? Do these influences affect severity of the disorder in the genetically susceptible individual?

In other words, are subtypes of alcoholism and alcohol abuse each affected to different extents by genetic and environmental variables? To study these questions, researchers from Washington University in St. Louis and from Sweden collaborated to analyze further the population of adoptees studied by Bohman (1978). This research team first examined adopted men with alcohol abuse problems (Cloninger et al. 1981). Out of 1,125 adopted men in the Stockholm adoption study reported by Bohman, 862 subjects were selected whose paternity was known and who were adopted before the age of 3 by nonrelatives.

These adoptees were first divided into groups according to severity of alcohol abuse. Mild abuse was defined as one registration for abuse (by the excise board) without treatment. Moderate abusers had two or three registrations without treatment, whereas severe abusers had at least four registrations and compulsory treatment or psychiatric hospitalization for alcoholism. The characteristics of the biological parents (e.g., severity of alcohol abuse, occupational status) and of postnatal environment (e.g., occupational status of adoptive father, age at adoptive placement) were analyzed to find which factors would best distinguish one group from another. The discriminant characteristics of each group were then applied to the total population to measure the extent to which these characteristics contributed to the number of individuals with alcohol problems.

As a result of these statistical analyses, two heritable subtypes of alcoholism were identified, which the authors named Type I (or milieu-limited) and Type II (or male-limited). Type I alcohol abuse occurred in 13 percent of the adopted men. Both their biological fathers and mothers typically exhibited mild alcohol abuse requiring no treatment, and postnatal environment determined both the frequency and the severity of alcohol abuse in the susceptible sons. The sons' alcohol abuse was usually mild or isolated, but could be severe, depending upon the nature of the environmental provocation. With such provocation, the relative risk of developing alcohol abuse in congenitally predisposed individuals was increased twofold; without it, the risk was the same as that in the general population.

Type II alcohol abuse occurred in 4 percent of the adopted men. It represented, therefore, about 25 percent of the alcohol abusers in the study. Their biological fathers, but not their mothers, had severe alcoholism requiring extensive treatment. Postnatal environment had no effect on the expected numbers of abusers but may have influenced severity. Alcohol abuse in the susceptible sons was usually recurrent and moderate, although sometimes it was severe. An estimated ninefold increase in risk of developing alcohol abuse or alcoholism was evident in the affected individuals, regardless of postnatal environment. The characteristics of this type of alcohol abuse/alcoholism are similar to those described in the Danish adoption studies (Goodwin et al. 1973).

It is notable that an average of 60 percent of the men in all three categories of alcohol abuse had no family history of abuse. Their alcohol abuse may have been caused by other disorders, such as psychiatric or behavioral. Alternatively, they could represent, in part, a group whose parents were genetically susceptible to alcohol abuse but lacked the necessary environmental provocation to become abusers. This issue remains unresolved.

Bohman et al. (1981) studied adopted women, using a similar statistical analysis. From the 1,199 adoptees originally reported by Bohman (1978), 913 satisfied the entry criteria. Because only 31 women (3.3 percent) out of this sample were alcohol abusers, they were not grouped by severity of abuse. A fourfold increase in alcohol abuse occurred in the adopted women if their biological mothers were alcohol abusers. A relationship between alcohol abuse in the biological father and that in the daughter was less clear-cut. It appeared, therefore, that in daughters maternal alcohol abuse was a more significant predictor of abuse than was paternal alcohol abuse or alcoholism. Both biological parents of alcohol-abusing female adoptees were mild alcohol abusers who usually did not require extensive treatment. When young, the alcohol-abusing female adoptees were frequently placed in rural homes in which adoptive fathers had low occupational status; the women generally had had contact with their biological mothers before final placement. Alcohol abuse in the adoptive home did not modify the risk of alcohol abuse in the daughters. As with the study on male adoptees, many women came from families with no history of alcohol abuse.

The most remarkable finding of this study was the strong component of mother-and-

daughter transmission in the adoptee daughters. But the influence may not be purely genetic, since alcohol abuse by the pregnant mother may have affected the growing fetus (the latter would, of course, be true for mother-daughter or mother-son transmission). In the adopted women, both the severity of alcohol abuse and the characteristics of their biological parents resembled those of the Type I male alcohol abusers. The influence of postnatal environment on frequency and severity of abuse could not be conclusively established, however, because of the limitations of the sample population or the failure to identify the relevant variables. Both of these unresolved issues will require further investigation. Nevertheless, the study demonstrated for the first time the existence of a genetic or congenital determinant for alcohol abuse in women.

The demonstration that sociocultural influences are critically important in the majority of genetically predisposed individuals suggests that changes in behavior and social attitudes by and toward individuals at high risk can alter both the course and the prevalence of alcohol abuse and alcoholism. Potential alcohol abusers could be identified through sensitive and accurate physiological, biochemical, and behavioral predictors of alcoholic vulnerability. These recent discoveries are significant for future treatment and prevention strategies as well as for future research on this important health problem. To this end, prospective and longitudinal studies with children of alcoholics, several of which are in progress, offer a promising approach (Schuckit 1980; Gabrielli et al. 1982; Elmasian et al. 1982).

Genetic Factors in Physiological Responses to Alcohol

A number of biological responses to alcohol potentially have pathophysiological significance for alcohol abuse, including

- alcohol craving or alcohol-seeking behavior
- sensitivity of the central nervous system (CNS) to alcohol
- sensitivity of other body systems (systemic sensitivity) to alcohol
- rate of alcohol metabolism or elimination

- rate of acquisition of tolerance to alcohol
- rate of development and severity of physical dependence on alcohol
- susceptibility to the medical complications of chronic alcohol consumption.

Studies in humans and in experimental animals have shown a tremendous degree of individual variation in their biological responses to alcohol. A considerable body of evidence now shows that much of this variation is genetic in origin (McClearn and Erwin 1982). The findings in humans and in experimental animals will be described separately as they use different experimental approaches and design.

Human Studies

Because genes cannot be manipulated in humans, studies have been limited to the comparison of fraternal and identical twins and of different ethnic groups. Identical twins have identical sets of genes, whereas fraternal twins do not. By comparing variability or, conversely, similarity in the expression of a trait within sets of identical and fraternal twins, researchers can determine the heritability or the importance of genes in the expression of that trait. Twin studies are not perfect, however, since the environment of identical twins tends to be more similar than that of fraternal twins. Hence, the extent to which genetic factors affect that trait cannot be established with absolute certainty. A similar limitation pertains to the comparison of different ethnic populations: They differ socioculturally. Accordingly, all candidate genetic traits predisposing to alcohol abuse should be studied in experimental animals so that environmental influences can be experimentally controlled.

Several twin studies have been performed on drinking behavior (Kaij 1960; Partanen et al. 1966; Jonsson and Nilsson 1968; Loehlin 1972; Kaprio et al. 1978). General agreement prevails that genetic factors influence the quantity and frequency of drinking as well as such symptoms of heavy drinking as hangovers and loss of control. Identical twins are more alike than fraternal twins in their drinking behavior, but the environment may play a considerable role.

Twin studies have also been used to demonstrate that neurophysiological sensitivity to alcohol and alcohol elimination rate are genetically controlled. Propping (1977) showed

that alcohol's effects on brain-wave function are nearly identical in identical twins, whereas they are disparate in fraternal twins. Alcohol elimination rate varies by a factor of 2 to 3 among individuals, even after adjustment for body weight (Bennion and Li 1976). Several studies have compared identical and fraternal twins to determine how much genetic factors contribute to this variation (Vesell et al. 1971; Kopun and Propping 1977). Genetic factors account for about 40-50 percent of the variation in alcohol elimination rate. Daily alcohol intake, smoking, diet, and drug use are some of the environmental factors that account for the remainder.

A potential biochemical explanation for genetic variation in human alcohol elimination rate has recently been discovered. Alcohol is eliminated from the body primarily through metabolism. The enzymes or protein catalysts responsible for this process are alcohol dehydrogenase and aldehyde dehydrogenase. The first enzyme oxidizes alcohol to acetaldehyde and the second enzyme oxidizes acetaldehyde to acetate. Acetate then enters the general metabolic pathway for sugars and fats and is oxidized further to carbon dioxide and water (Li 1977). The amount and properties of alcohol dehydrogenase in the liver determine the rate of alcohol metabolism--and there are many genetically disparate forms of this enzyme in human livers, varying among individuals. The individual molecular forms of human liver alcohol dehydrogenase have now been isolated, and many of them differ markedly in their catalytic properties (Bosron and Li 1981). Since the combination of forms is determined genetically, the variation in elimination rate among individuals can be readily accounted for by the large differences in the genetically determined properties of the different enzyme forms. No experiments have yet tried to correlate the specific enzyme makeup of individuals with their alcohol metabolism rates. However, it has been reported that Chinese and Japanese individuals, on the average, metabolize alcohol 30 percent faster than Caucasians do (Hanna 1978). More than 90 percent of Orientals possess the so-called atypical alcohol dehydrogenase genetic trait (Bosron and Li 1981). The atypical alcohol dehydrogenase enzyme forms are much more active than the forms present in Caucasians.

Some individuals, particularly Orientals, respond to alcohol with an "alcohol flush," a systemic reaction consisting of facial flushing and rapid heart rate and, in severe cases, nausea, vomiting, and low blood pressure. For

example, approximately half of the Japanese population exhibit the reaction, which has been linked to elevated blood acetaldehyde levels after alcohol intake (Mizoi et al. 1979). Alcohol flush was once thought to be the consequence of an overproduction of acetaldehyde (Stamatoyannopoulos et al. 1975). More recent research, however, indicates that the reaction may result from the absence of a particular form of aldehyde dehydrogenase, thereby affecting the oxidation of acetaldehyde (Inoue et al. 1980; Agarwal et al. 1981; Teng 1981). Indirect evidence suggests that acetaldehyde can cause the release of histamine and perhaps other substances affecting blood vessels; hence, the flush reaction.

Finally, studies of twins have shown that some individuals may be genetically susceptible to certain medical complications of prolonged alcohol abuse, namely liver cirrhosis and psychosis (Hrubec and Omenn 1981). Also, some people may be susceptible to developing the Wernicke-Korsakoff syndrome due to an inherited metabolic defect involving one of the thiamine (vitamin B₁)-requiring enzymes (Blass and Gibson 1977). Studies to confirm these important observations are clearly needed.

Animal Studies

Animals, like humans, vary in their responses to alcohol. Genetic factors are responsible for some of the differences, including such responses to alcohol as the acquisition of tolerance and physical dependence. An important feature of animal experimentation, impossible with humans, is the ability to manipulate the genetic background of the animals through inbreeding, selective breeding, and other measures. It has been possible to develop lines or strains of animals with high or low responsiveness to the various actions of alcohol. Such animals can then be used to study the biochemical and physiological mechanisms underlying genetic variability and to discern how these developed traits and mechanisms affect alcohol-drinking behavior. Conversely, breeders can develop animals that prefer or disdain alcohol, and researchers can test their responsiveness to the various actions of alcohol. Such animal studies can suggest hypotheses and experimental approaches in human research to learn what predisposes individuals genetically to aberrant drinking behavior. Research with animal models thus provides a cornerstone of future biological knowledge

about the nature of genetic susceptibility to alcoholism.

Inbred strains of mice differ in their preference for alcohol consumption when food, water, and alcohol are made freely available to them (McClearn and Rodgers 1959). Inbred mouse strains also differ in "sleep time," that is, the time required to recover from the hypnotic effects of alcohol (Kakihana et al. 1966), and in alcohol metabolic rate (Sheppard et al. 1970). Inbred strains are developed by mating successive generations of close relatives. After about 20 generations of sibling matings, the animals within each inbred strain are almost genetically uniform and show the trait readily. The strains constitute *prima facie* evidence of genetic influence on that trait.

A genetic influence on alcohol-drinking behavior, CNS sensitivity to alcohol, and alcohol metabolic rate has also been demonstrated in selectively bred lines of rats and mice. Selective breeding is the process by which animals showing a chosen characteristic are mated in successive generations in order to segregate the genes responsible for that trait into one line of animals. Thus, if a quantitative trait is under genetic control, separate strains can be bred, one in the high and the other in the low direction. Rats that differ in alcohol metabolic rate have also been raised through selective breeding (Thurman 1980). Lines of rats have now been bred selectively to differ in voluntary alcohol consumption: the alcohol-preferring AA and P lines and the alcohol-nonpreferring ANA and NP lines (Eriksson 1968; Li et al. 1979). Lines of mice and rats that differ in CNS sensitivity to the sedative-hypnotic effects of alcohol have also been developed: the long-sleep (LS) and short-sleep (SS) mouse lines (McClearn and Kakihana 1973) and the most-affected (MA) and least-affected (LA) lines of rats (Riley et al. 1977). Such selectively bred animals are particularly useful for studying the underlying mechanisms that contribute to these genetic differences. For example, the difference in sleep time between the LS and SS mice is related to a genetically determined difference in the brain that is both region-specific and drug-specific (Sorensen et al. 1981). New and exciting findings are likely to emerge from further studies with these animals that will improve researchers' understanding of the differential CNS sensitivity to alcohol in humans.

Various inbred strains of mice as well as the selectively bred LS and SS lines of mice differ in how rapidly they develop tolerance after

the chronic administration of alcohol (Grieve et al. 1979; Tabakoff et al. 1980). Inbred mouse strains also differ in the severity of withdrawal symptoms after physical dependence has been established. Goldstein (1973) and Goldstein and Kakihana (1974) bred mouse lines with those reactions. Thus, both the rate of tolerance development and the severity of physical dependence caused by chronic alcohol ingestion are genetically determined in mice and possibly in humans.

Potential Mechanisms of Genetic Influence

Alcoholism and alcohol abuse lie at one extreme of a continuum of drinking behavior whose opposite end represents abstinence. Drinking behavior as a trait, therefore, is a continuous variable, as are height and weight. Such traits are usually determined by many sets of genes that sometimes tend to appear together or to be correlated. When different traits can be influenced by common sets of genes, a phenomenon called pleiotropy, true genetic correlation has occurred. The association may come about because one trait influences the expression of the other. For example, preliminary reports from Japan indicate that, compared with the normal population, alcoholic populations contain fewer individuals with deficiencies in the mitochondrial enzyme aldehyde dehydrogenase that oxidizes acetaldehyde (Harada et al. 1982; Yoshihara et al. 1982). When this enzyme is absent, alcohol consumption leads to high blood acetaldehyde levels and the unpleasant alcohol flush reaction. Thus, an individual with the enzyme deficiency is likely to avoid alcohol and the unpleasant reaction it brings.

Animal studies have revealed other potential mechanisms of genetic influence. Mice that consume large amounts of alcohol voluntarily are more likely than others to acquire tolerance rapidly (Erwin et al. 1980). Alcohol-preferring lines of rats recover more rapidly from the sedative-hypnotic effects of alcohol than do alcohol-nonpreferring ones (Lumeng et al. 1982). These studies suggest an experimentally verifiable hypothesis: An ability to adapt quickly to alcohol (tolerance) may predispose individuals to patterns of heavy drinking.

Other mechanisms of alcohol preference are likely to be discovered, each of which may contribute in some way to the trait of high voluntary alcohol consumption. Animal exper-

iments can reveal such mechanisms of alcohol consumption (NIAAA 1981). This research approach may ultimately lead to an understanding of the nature of genetic heterogeneity of alcohol abuse and alcoholism in humans, the physiological and biochemical mechanisms underlying this problem behavior, and how environmental factors interact with these inherited pathways.

Summary

Great strides have been made in recent years in researchers' knowledge and understanding of the genetic factors contributing to alcohol abuse and alcoholism. It has been firmly established that heredity plays a role in determining individual differences in susceptibility to the disorder. Genetic influence is identifiable in at least 35 to 40 percent of alcoholics and alcohol abusers, and it affects both men and women. People with family histories involving parental alcohol abuse face increased risk. Furthermore, many types of alcohol abuse may exist, each with its own genetic predisposition interacting with a particular environment.

Genetic factors also affect individual differences in response to alcohol, such as drinking behavior, sensitivity of the brain and other body systems to alcohol, alcohol elimination rate, the acquisition of tolerance, and the development of physical dependencies. Much of this knowledge has been obtained from experiments in laboratory animals specifically developed for the purpose of alcoholism-related research.

Collectively, the gains in research in the past decade predict an exciting era of new discoveries in the next. Future research should focus on improving methodology for detecting subtypes of alcohol abuse and on developing behavioral, physiological, and biochemical predictors of genetic vulnerability. In this regard, ongoing and future work in experimental animals can provide invaluable clues for human investigation. Existing animal models and those yet to be developed can be used not only to identify genetic correlates of alcohol-seeking behavior, but also to elucidate the biological nature of the process. When this stage of knowledge is reached, the genetic subtypes of alcohol abuse and alcoholism will be precisely defined as pharmacogenetic disorders of behavior by the nature of their underlying pathology.

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Chapter III

Psychobiological Effects of Alcohol

Alcohol acts on virtually every cell of the body, but the central nervous system is the target most affected. Alcohol's influence is profound—from the personality disarray created by chronic drinking to the distorted judgment of the drunken driver. Current research is converging on explanations for some of these effects and their underlying biological mechanisms, but a comprehensive understanding of an individual's response to alcohol is still elusive.

Because no unitary explanation of alcohol's effect on human behavior seems adequate, researchers continue to explore all levels of brain function and behavior. Accordingly, this chapter presents selected research findings at four broad levels—cognition and neuropsychological effects, neuropathological illness, electrophysiology, and neural and biochemical effects. Finally, a brief overview of theories that may explain the appeal of alcohol and the causes of alcohol addiction are discussed.

Cognitive and Neurophysiological Effects

Driving-Related Cognitive Skills

Our society has acknowledged the profound and often harmful behavioral effects of alcohol, especially as it involves drinking and driving. Driving is a complex task requiring such skills as psychomotor coordination, reaction time, memory, perception, judgment, information processing, and conscious control of behavior. Not surprisingly, many researchers have chosen to investigate alcohol's cognitive effects by measuring how it impairs various driving-related skills. Such studies can yield practical applications while also revealing more basic psychological mechanisms.

Clayton (1980) found that driving skills are impaired at blood alcohol concentrations (.04-.05 percent) one might observe after drinking

only two to three alcoholic beverages on an empty stomach. In addition, he found that the same blood alcohol level decreased a driver's ability to divide his attention among several stimuli while maintaining acceptable performance. Clayton suggested that the resulting diminished performance could be caused by a decreased ability to process information.

Driving a car is a learned skill that requires good judgment based on experience and practice. McNamee et al. (1980) examined how alcohol affects experience and judgment in estimating the velocity of a moving object—an essential task for drivers. Initially, with low doses of alcohol, the subjects actually improved their estimates. But after continuing to drink (resulting in a blood alcohol concentration above .10 percent), their performance declined dramatically. This biphasic phenomenon, of initial stimulation or excitation of the central nervous system with low doses followed by depression as the dose is increased, will be encountered again later in this chapter.

In a study closely related to velocity estimates, Collins and Chiles (1980) investigated how alcohol affects tracking skills in airline pilots. The results confirmed McNamee's study and showed, in addition, that the pilot's errors were greatest and most frequent during evening hours. Thus, it appears that biological rhythms may influence alcohol's effects on judgment. The researchers also found that many hours of abstinence are required to eliminate all such alcohol-induced errors.

Many people believe they can override or control alcohol's negative effects on behavior. Young and Pihl (1980) evaluated the degree to which volunteer subjects could control their speech and behavior and prevent visible symptoms of intoxication. Although the subjects varied greatly in their suppression of symptoms, none was completely successful.

Fatigue impairs cognitive performance in much the same way that alcohol does, leading some researchers to examine the relationship between the two. Ryder et al. (NHTSA 1981)

reported that alcohol increased the cognitive impairments produced by fatigue as determined by driving performance. Caffeine is thought by many to counteract the effects of both alcohol and fatigue. Moskowitz and Burns (1981), using a driving simulator, evaluated caffeine as a possible antidote to alcohol in tracking, searching, and information processing. They found that caffeine could partially counteract the behavioral effects of alcohol. However, since the effects were marginal, these findings should discourage the folk belief that coffee is an effective antidote to alcohol, especially when driving. In a study of another often-used combination, Tong et al. (1980) found that both tobacco and alcohol individually diminished auditory vigilance (ability to detect sound stimuli); taken together, they led to even greater impairments.

Using an animal research design that is likely to reflect human reactions, Moody et al. (1980) demonstrated that alcohol significantly slowed monkeys' reaction time to sound signals. Recordings of electrical activity in the brain's auditory pathways showed that alcohol had not impeded the signal from the ear to the brain. Rather, the impairment seemed to be caused by slow information processing in the brain's "higher" centers.

Cognitive Functioning in Social Drinkers

Since this topic was reviewed in previous reports to Congress (USDHHS 1981; Parsons and Leber 1982), MacVane et al. (1982) have also found that performance on some neuropsychological tests correlates with social drinking patterns. Five studies have found some statistical relationships between alcohol use and decreased cognitive performance in social drinkers (Parker 1982). However, as Parsons and Fabian (1982) have pointed out, such relationships were not consistent for the same cognitive tests in each of these studies. Furthermore, in the MacVane study, although the 58 heavy social drinkers drank three times as often and twice as much as did the 48 light-moderate drinkers, the performance of the two groups on the cognitive tests was not significantly different.

Methodologic issues may partially explain the lack of a dose-response relationship between consumption and cognitive ability (Parker 1982). However, variables other than alcohol use, as yet unknown, may also be involved (Parsons and Fabian 1982). Individuals with poor cognitive function, for example,

may drink more than those with high functioning; the former, due to poor verbal skills, may provide less valid drinking histories. Heavy drinkers may be more anxious and depressed perhaps due to underlying problems or the recency of drinking. Finally, individuals may have to consume a minimal amount of alcohol (threshold) before it has detrimental effects.

As more sensitive techniques for assessing neuropsychological functioning have been applied to individuals with differing social drinking patterns and socioeconomic circumstances, it has become increasingly clear that many questions must be answered. Specifically, what are the limits of normal functioning? At what point should an individual be considered impaired due to alcohol use? Is alcohol use a causative or an exacerbating factor, a complication of or simply coincidental to such measured impairments? The social use of alcohol is sufficiently widespread in our culture, and the degree of behavioral impairment attributed to social drinking is difficult to measure. Therefore, long-term studies of many individuals with varied drinking patterns will be needed to clarify the cognitive consequences of social drinking.

Alcohol and Aging

On average, older persons perform less well on standard psychological tests than younger ones with equivalent patterns of alcohol consumption (Carlen et al. 1981b). However, people of the same chronologic age may age quite differently physiologically.

Because young alcoholics resemble old people in their performance on neuropsychological tests, some researchers have hypothesized that alcohol consumption may accelerate the normal process of aging (Ryan 1982). However, electrophysiologic data, particularly brain evoked potentials (electrical activity in response to sensory stimulation), suggest that the organic brain disease of alcoholics is caused by an underlying mechanism different from premature aging (Porjesz and Begleiter 1982).

Whether or not the two processes share a common cause, alcohol consumption may interact with aging in several ways (Freund and Butters 1982). Changes in their ability to metabolize alcohol and in their central nervous system function may make the elderly increasingly vulnerable to the deleterious effect of alcohol (Wood and Armbricht 1982). In addition, alcohol may interfere with normal

regenerative processes of the central nervous system (West et al. 1982).

Alcoholics Versus Nonalcoholics

All of the previously discussed human studies examined alcohol's effects on the behavior of individuals from the population at large. But the population includes both alcoholics and nonalcoholics, who may respond to alcohol differently. Recent research has attempted to measure alcohol's cognitive and neuropsychologic effects on alcoholics compared with nonalcoholics. Further, it has examined both the effects of acute (short-term) doses of alcohol and the impact of chronic drinking.

Cognitive Effects of Alcoholism

O'Leary et al. (1980) found that alcoholics performed significantly worse than did nonalcoholics when tested for their ability to note and distinguish slight differences between closely related objects. In a study that could explain the results obtained by O'Leary and his associates, Rubin (1980) found that, compared with nonalcoholics, alcoholics exhibit various autonomic nervous system difficulties, including poor physiological regulation of eye pupil size and the rate at which pupils respond to visual stimuli. Such poor regulation could hamper alcoholics in distinguishing between closely related objects.

Several studies have suggested that while alcoholism does impair cognitive skills, alcoholics regain such skills quite rapidly after they stop drinking. Chaney et al. (1980) confirmed the earlier studies, adding that younger alcoholics regain their verbal skills after detoxification more rapidly than do older alcoholics.

Ryan (1980) found that, at the beginning of a testing session, alcoholics and nonalcoholics performed equally well in a short-term memory test. But, when asked to recall words after a 3-hour interval, the alcoholics remembered significantly fewer words than did the nonalcoholics, possibly as a result of more mental fatigue.

Neuropsychological Performance in Alcoholics

Brain abnormalities underlie cognitive impairment in alcoholics (Wilkinson 1982). In the

largest long-term study of computer-assisted tomography (brain scan) changes in alcoholics, all brain scan measurements differed significantly between alcoholics and controls. None of the alcoholics had clinically overt signs of brain damage, but all showed the syndrome of alcohol dependence (Ron et al. 1982).

Alcoholics over 43 years of age differed from their controls more markedly than did the younger alcoholics. Brain scan measurements were significantly correlated with age, but not with such measures of alcoholism as length of drinking history, measures of amount consumed, or scores on a "social decline scale."

In the older subjects, abnormalities seen by brain scans were least severe in those who had abstained longest before scanning. In addition, it was noted that recovery proceeded at a faster rate in younger alcoholics compared with older alcoholics. In followup tests, from 30 weeks to 3 years after initial examination, the largely abstinent patients showed significant improvement over time in brain scans, while the continuing drinkers showed little change. The length of abstinence was correlated with the degree of improvement.

The work of Ron and his colleagues (1982) suggests that neuropsychologic deficits may be reversible. However, Adams et al. (1980) were unable to demonstrate improved neuropsychological performance in patients in their late thirties from an alcoholism treatment program tested 3 weeks after their last drink and again 1 year later. Posttreatment alcohol consumption by 63 percent of these patients may have influenced this study, however, as Eckardt et al. (1980) noted that abstainers perform better than those who resume alcohol consumption. These results emphasize that total abstinence is desirable if alcohol-related cognitive deficits are to be reversed. Reviews of existing literature noted, however, that many studies fail to assess alcohol intake accurately during so-called periods of abstinence (Orrego et al. 1979; Parsons and Leber 1982).

Nutrition and Alcoholism

Because alcohol is a concentrated source of energy (about 200 calories per ounce), alcoholics often find their caloric needs largely satisfied by the alcohol they consume but develop deficiencies of vital nutritional elements. Indeed, most medical textbooks recommend restoration of a proper diet with vitamin supplementation as a first-order treatment of alcoholism. In particular, thia-

mine (vitamin B₁) deficiency may result in the damage to brain cells (Blass 1980), and alcohol itself may interfere with thiamine's absorption from the gastrointestinal tract (Hoyumpa 1980).

A genetic enzyme abnormality may largely determine which individuals are most likely to become thiamine deficient during periods of poor nutrition (Leigh et al. 1981). Shaw and his associates (1981) reported impaired learning in thiamine-deficient rats, but not in rats fed a balanced diet or an alcohol-containing liquid diet. Thus, it appeared that thiamine deficiency alone can cause neuropsychological damage.

Other evidence (Walker et al. 1981), however, suggests that, despite adequate diet, chronic alcohol consumption is in itself neurotoxic and causes learning deficits as well as long-lasting brain damage. Clearly, both nutrition and alcohol contribute to neurotoxicity, and their relative roles in alcoholic brain injury remain to be resolved.

Neuropathologic Illnesses

Chronic Organic Brain Syndromes

Chronic consumption of harmful quantities of alcohol may lead to two clinically and neuropathologically distinguishable chronic organic brain syndromes: alcoholic dementia and alcohol amnesic (memory loss) syndrome (also called Korsakoff's psychosis) (Wilkinson and Carlen 1981; Lishman 1981).

Chronic organic brain syndromes due to alcoholism are the second most common of the known causes of dementia in adults (approximately 10 percent) next to Alzheimer's disease (40-60 percent) (Wells 1979). Despite emerging technological advances, a large proportion of dementing illnesses can be diagnosed with certainty only by examining the microscopic structure of the brain at autopsy. For example, alcoholic dementia is characterized pathologically by destruction of cerebral cortical neurons, particularly those in the frontal lobes.

The clinical picture of alcoholic dementia may be indistinguishable from that of Alzheimer's disease. Global intellectual decline, seen in both, is characterized by deficits in abstracting ability and problem solving, dysphasia (deficit in verbal expression), and apraxia (diminished skill in motor tasks).

Electroencephalographic (EEG) abnormalities, cerebral and cerebellar tissue loss, and the enlargement of the fluid spaces in the interior of the brain are also similar in the two disorders. But the overall course of the diseases is potentially different. In alcoholic dementia, cognitive impairment is reversible to some degree with abstinence, although cognitive decline usually occurs with continued drinking (Cutting 1978). Potential reversibility clearly differentiates alcoholic dementia from Alzheimer's disease, which is invariably progressive. Gottfries (1980) suggests that alcoholic dementia may be differentiable from Alzheimer's disease on the basis of abnormal acetylcholine neurotransmission in the latter. This may be difficult to demonstrate, however, due to the many areas of neurochemical overlap among Alzheimer's disease, alcoholic dementia, and aging.

Patients with Korsakoff's psychosis (see USDHHS 1981; Butters 1982), unlike those with alcoholic dementia, suffer severe and often persistent memory impairment while other intellectual functions remain relatively intact. There are marked deficits in acquiring new learning and amnesia for more recent events. Unlike early-stage Alzheimer patients with superficially similar memory deficits, Korsakoff patients can recall rules for organizing information and can recall previously acquired knowledge (Weingartner et al. 1983). At autopsy, Korsakoff patients have characteristic lesions that resemble those described in patients who have died from acute thiamine deficiency (Wernicke's encephalopathy). Those lesions, whose precise relationship to the Korsakoff memory deficits is still controversial (Butters 1982), are near brain pathways that in animal studies have been implicated in learning, memory, drive, and reward. Mair et al. (1982) have found reductions in neurotransmitters, which are correlated with the performance of Korsakoff patients on learning tasks. However, it is unclear whether such neurochemical changes are significantly different from those seen in age-matched healthy controls or in individuals with dementia due to other causes.

Harper (1979) diagnosed 51 cases with the pathological findings of Wernicke's encephalopathy (thiamine-related degeneration of neurons in the brain) or approximately 2 percent of the brains examined from diseased alcoholics at autopsy in a 4-year study. These findings were not appreciably different from those of similar prior studies (Cravioto et al. 1961; Victor et al. 1971). In only 7 of Harper's

51 cases had the clinical diagnosis of Wernicke's encephalopathy or Korsakoff's psychosis been considered during life. The majority of affected patients were known alcoholics; 10 had died suddenly and unexpectedly, apparently as a result of hemorrhages in the part of the brain that controls the heart rate and respiration.

It is disturbing that Wernicke's encephalopathy is so greatly underdiagnosed because it is treatable and preventable with adequate thiamine supplementation. Harper (1979) and Lishman (1981) suggest that the present clinical appearance of Wernicke encephalopathy and Korsakoff syndrome may have changed somewhat from classical descriptions because many alcoholics may now routinely receive thiamine treatment before the clinical signs are obvious. Such treatment, while insufficient to prevent the disease, masks the classical syndrome, thereby making a traditional diagnosis difficult. Thus, clinical symptoms may develop after repeated episodes of barely detectable brain degeneration in which the usual signs of mental confusion, ataxia (loss of body coordination), ophthalmoplegia (eye paralysis), nystagmus (abnormal eye movements), and memory loss are absent or not readily recognized (Kearsley and Musso 1980).

In alcoholics, Alling and Bostrom (1980) have found damage to myelin, the covering sheaths that enhance electrical conduction in some nerve cells. The damage occurred in a part of the brain almost always affected in classical Korsakoff's psychosis. These randomly selected alcoholics never had Wernicke encephalopathy or Korsakoff syndrome in life and did not show the typical pathologic changes of this disorder under microscopic examination at autopsy.

Alcoholic dementia and Korsakoff's psychosis probably represent ends of a continuum, with the majority of patients seen in clinical practice falling somewhere in between and having some characteristics of both (Parsons and Leber 1982; Butters 1982; Harper 1982). It is not uncommon to find the symptoms of alcoholic dementia (cortical atrophy, enlarged fluid space in the interior of the brain, and moderate intellectual decline) in patients with Korsakoff's psychosis. Conversely, those with alcoholic dementia probably have some memory loss and frequently have microscopic findings that are characteristic of Korsakoff's psychosis. Both nutritional deficits and alcohol neurotoxicity may contribute to either chronic organic brain syndrome.

Relationship Between Alcohol Abuse and Psychiatric Illnesses

Drinking in sufficient amounts to cause serious medical, social, domestic, vocational, or legal problems may reflect, occur together with, or lead to various psychiatric illnesses (Martin 1981). Alcohol use itself may produce various forms of psychopathology as a direct result of its pharmacologic actions (Behar and Winokur 1979), through psychosocial consequences of its chronic use (Goodwin and Guze 1979), or by alteration of psychological equilibrium during alcohol withdrawal (Hamm et al. 1979). Depression, anxiety, hysteria, sociopathy, drug abuse, anorexia nervosa, and childhood hyperactivity are more common in alcoholics and in their family members than in the general population (Morrison and Stewart 1971; Overall et al. 1973; Goodwin et al. 1975; Tarter et al. 1977; Andreasen and Winokur 1979; Eckert et al. 1979; Goodwin and Guze 1979; Munjack and Moss 1981; Wood et al. 1983).

Whether psychopathology is the result of, or the cause of, alcoholism is sometimes difficult to determine. There are, however, definite clinical implications for each alternative (Andreasen and Winokur 1979; Hamm et al. 1979; Weissman and Myers 1980; Linnoila and Martin 1983). For example, if alcoholism predates psychiatric symptoms, abstinence from alcohol is indicated before beginning other treatments (Schuckit 1982). If the alcoholism follows psychiatric disease, it is important to diagnose the psychiatric illness accurately so that treatment may be tailored to the patient's needs (Linnoila and Martin 1983).

The considerable overlap between alcoholism and the affective disorders (mania and depression) has become an important area of research. Alcoholism and depression are the two behavior-associated illnesses with the highest rates of suicide (Tsuang 1977). Recent evidence suggests possible common abnormalities in metabolism of the neurotransmitter serotonin in alcoholism, aggression, suicide, and depression (Ballenger et al. 1979; Rosenthal et al. 1980; Brown et al. 1982). Such neurochemical similarities between alcoholism and depression suggest that there may be a common underlying mechanism. Tricyclic antidepressants and lithium—medications for depression and mania—may offer significant therapeutic benefit to alcoholics who are depressed (Coppin 1980).

Indirect Alcohol-Induced Neuropathology

Liver disease associated with alcoholism may result in behavioral deficits ranging from subtle neuropsychologic abnormalities (Smith and Smith 1977; Rehnstrom et al. 1977) to serious brain degeneration, delirium, and coma (Schenker et al. 1980). In addition, head trauma and inadequate oxygen supply to the brain, frequently sustained during intoxication, can become a recurrent theme in the life of an alcoholic, with cumulative and adverse neurologic effects (McLeod 1982).

Alcohol inhibits the respiratory center of the brain and renders the individual more susceptible to obstructive sleep apnea (inability to breathe normally during sleep), an increasingly recognized condition that causes hypoxemia (reduced blood oxygen content) during sleep (Guilleminault et al. 1978). Even mild hypoxemia may adversely affect brain function and lead to dementia, particularly in individuals who have chronic obstructive lung disease, as is often the case in alcoholics (Blass 1980).

Hillbom and Kaste (1982) have reported that both occasional alcohol intoxication and regular heavy drinking carry an increased risk of stroke due to subarachnoid hemorrhage, but the mechanism for this is not yet clear. In addition, alcohol withdrawal may be accompanied by serious metabolic disturbances that can impair cerebral function (Linnoila and Martin 1983).

The common use of other psychoactive drugs by alcoholics may also contribute to behavioral deficits (Linnoila and Martin 1983). Depression, which frequently accompanies harmful alcohol use (Schuckit 1982), can also impair cognition considerably (Weingartner et al. 1981). Cognitive impairment may often precede alcoholism, however. The high prevalence of attention disorders in young male alcoholics (Wood et al. 1983), for example, suggests that part of the cognitive impairment attributed to alcohol-related brain damage was probably present before the use of alcohol (Parsons and Leber 1982).

Electrophysiology

Increasingly over the past half century, electrophysiological recordings have been expanding researchers' knowledge of the nervous system. Until about 25 years ago, such recordings were limited to macroelectrodes, large

probes that recorded only gross brain activities of thousands or even millions of nerve cells. The recordings, called electroencephalograms (EEGs), could indicate the results of either spontaneous brain activity or the brain's responses to a stimulus such as a light flash (evoked potentials). More recent technological advances allow microrecordings from single nerve cells. In today's research, both macro- and microrecordings of alcohol's effects augment one another to contribute to an understanding that neither alone can provide.

In general, the electrophysiological effects of alcohol are complex and vary at different sites within the brain. Most alcohol research with these techniques has attempted to determine functional central nervous system differences between alcoholics and nonalcoholics and, sometimes, to quantify the acute effects of alcohol.

EEG Studies

Recent studies have compared EEGs accompanying the loss of consciousness resulting from alcohol ingestion, normal sleep, and barbiturates (Zornetzer et al. 1982). Although the loss of consciousness caused by most barbiturates and by alcohol superficially resembles normal sleep, the conditions are quite different electrophysiologically.

Surprisingly little detailed information exists on how acute doses of alcohol affect the EEG. Several recent studies have investigated the relation between alcohol's effects on the cortical (outer brain layer) EEG and its effects on EEGs from deep brain structures. Grupp (1981) reported that alcohol altered the electrical activity of both the hippocampus (a deep brain structure associated with memory and emotion) and the cerebral cortex (involved in high-level information processing). Partly on the basis of such studies, Klemm and Sherry (1981) proposed a brain model of intoxication. They theorized that alcohol "scrambles" brain messages, thus disrupting normal communication within the central nervous system. Because Klemm and Sherry rely largely on supporting evidence recorded from the cerebellum (a part of the brain associated with posture, movement, and balance), their model may not account for the pervasive effects of intoxication on other brain structures.

Evoked Response Studies

Electrophysiological responses to sensory stimuli reveal a great deal about the brain.

Because responses to individual stimuli are often lost in a sea of electrical "noise," however, researchers often resort to a technique called the average evoked response (AER). In essence, a readable AER depends on a computer's averaging a large number of the brain's electrical responses to repetitive sensory stimuli. Individual responses that would be imperceptible without computer assistance become magnified and visible when averaged together.

Recently, several researchers have turned to the AER to investigate the brain's response to sensory stimuli under various conditions of alcohol use. Studies showed that alcohol disrupted (1) the normal AERs to visual stimuli (Hetzler et al. 1980); (2) the normal patterns of attention to visual stimuli (NHTSA 1980); and (3) the normal AERs to auditory stimuli (Pfefferbaum et al. 1980), which were correlated with slowed reaction times to sound signals. Such disrupted electrophysiological responses to perceptual stimuli could explain alcohol's adverse effects on driving.

Many investigators have attempted to detect whether AERs in alcoholics differ from those in nonalcoholics. A frequently cited study demonstrated that, compared with non-alcoholics, alcoholics produce higher amplitude AERs when presented with light flashes of low intensity, even though these alcoholics had been abstinent from alcohol for 1 week or more (Buchsbaum and Ludwig 1980). When the flash intensity was increased, alcoholics' responses increased more than those of normal subjects. Thus, the alcoholics' AERs were somewhat greater than normals' at low intensities, but much greater at high intensities. Buchsbaum and Ludwig (1980) noted that alcoholics, in increasing their AERs at higher light intensities, are more sensitive to higher level stimuli. They speculated that alcoholics may be neurophysiologically vulnerable to intense sensory inputs either by predisposition or as a result of the toxic effects of alcohol, and that perhaps they use alcohol to diminish their augmented sensitivity.

One provocative question is whether differences seen in the AER are consequent to, or predispose for, alcoholism. Recent research indicates that there may be inherited differences in the brain's electrical activity. Elmasian et al. (1982) observed that AERs from groups of individuals with and without a family history of alcoholism were markedly different. These differences were apparent whether or not the individuals had consumed alcohol. Electrophysiological methods may, therefore,

prove to be valuable in future research, especially in identifying specific indicators or markers of alcohol susceptibility.

Neural and Biochemical Effects

Behavior and thought, learning and memory, sensations and movements, all of which are affected by drinking alcohol, find their biological basis in the nervous system. The individual units of this system are neurons (nerve cells).

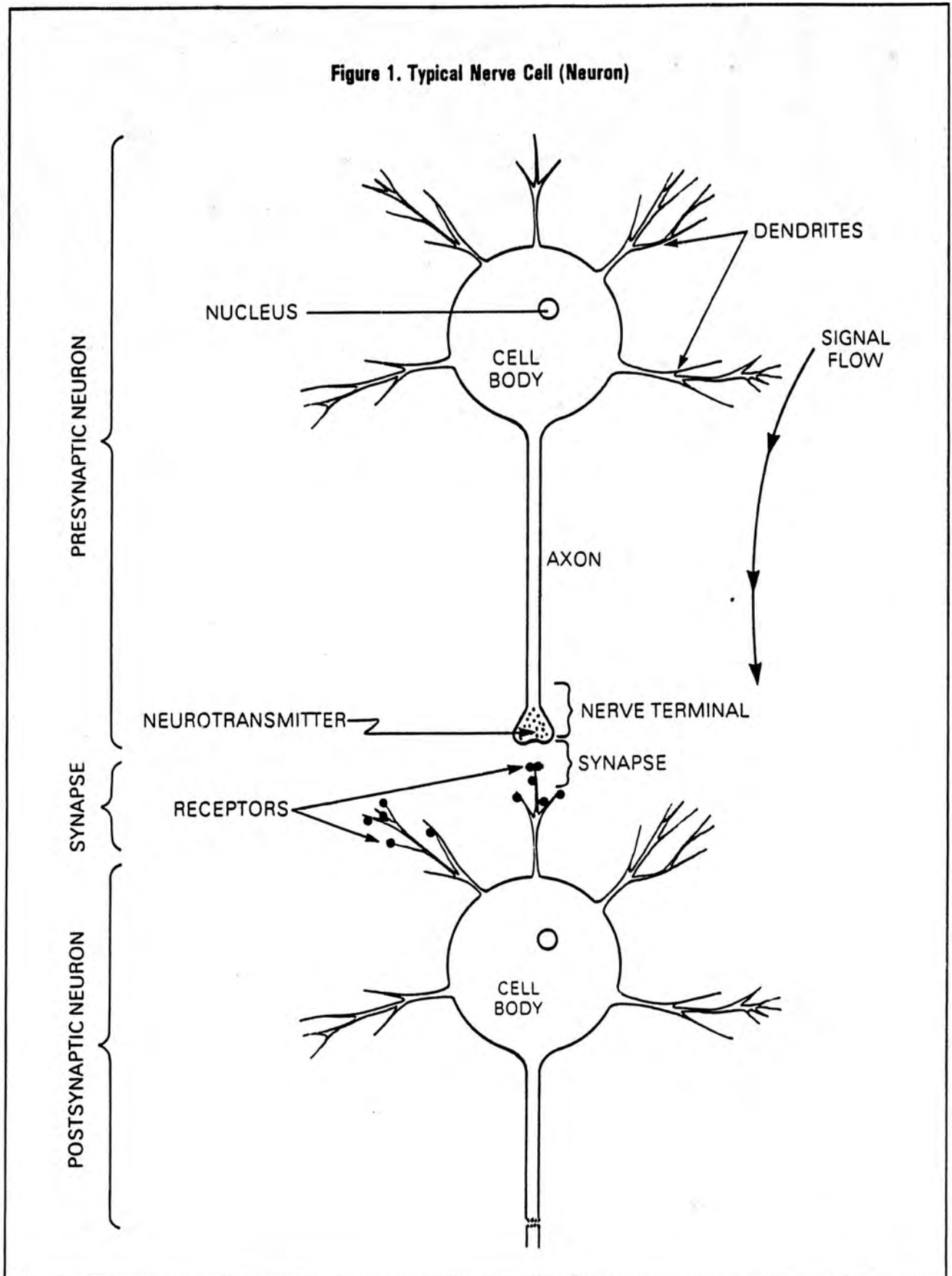
Neurons are now known to be extraordinarily subtle electrochemical processors. New knowledge of neurons, accompanied by new measurement techniques, has encouraged some optimism that a deeper examination of alcohol's effects on neurons could reveal how alcohol affects the nervous system and, in turn, how the nervous system affects behavior. Before discussing alcohol's effects on neurons, it is necessary to understand what a neuron is and how it works.

Neurons are, in computer parlance, logic elements. They conduct information and, based on a combination of electrical and chemical signals, communicate with other neurons, with muscles, and with the body's endocrine system hormones.

A typical neuron (shown highly simplified in figure 1) usually receives chemical inputs, through its dendrites, from other neurons. It changes the chemical signal into an electrical signal, which travels to the other end of the neuron (the nerve terminal or output end) where neurotransmitter chemicals, which continue to carry the signal, are released across a space called the synapse to adjacent neurons. The process is usually repeated many times to create signal paths throughout the nervous system. Essentially, the transmission between neurons is chemical, while the transmission within neurons is electrical.

If we probe into the nature of the electrical signal that is carried along the neuron, we find that it is formed by the movement of sodium and potassium ions (charged particles) flowing across the thin semipermeable membrane enclosing each nerve cell and crossing back again. When the flow of these ions reaches threshold conditions, an impulse is propagated down the neuron to its destination, the nerve terminal. Instruments can detect these short electrical pulses as the electrical signal travels through each neuron. Alcohol could affect the propagation of electrical pulses by making the membrane more or less permeable

Figure 1. Typical Nerve Cell (Neuron)



to the charged particles. After a pulse is propagated, the neuron must be recharged before it can carry another electrical impulse. This process is regulated by an enzyme that moves ions that entered the neuron back outside. Alcohol may also interfere with this ion "pump" mechanism, which maintains the electrical stability of each neuron.

When the electrical impulses reach the nerve terminal, calcium ions, acting as gatekeepers of the synaptic membrane, enter the neuron and allow tiny packets of neurotransmitter chemicals to be released across the synapse. On the adjacent neuron, receptors exquisitely matched to the neurotransmitter chemical characteristics will recognize the chemical message and unlock the membrane of the receiving neuron to allow the signal to continue. Continuation of the signal, inside the receiving neuron, depends on increased flow of sodium and potassium ions to reach the threshold conditions for generating an electrical impulse and allowing the whole process to repeat. (Depending on the neurotransmitter chemical, however, the receiving neuron may be inhibited from firing, rather than being fired. In this manner, the nervous system can turn off, as well as turn on, the flow of information.) This activity can occur hundreds of times a second and in billions of neurons in the brain. The result is thoughts, feelings, learning, or the link between a red light and muscles flexing to step on the brake. Any interference with the neurotransmission process could affect that link.

Electrical Conduction

In the late 1940s, it was found that sodium and potassium ions were responsible for the electrical conduction in the neuron. Researchers interested in alcohol's effect on the brain hypothesized that alcohol could impede the movement of ions necessary to produce and conduct the electrical impulse. Early studies on the squid's giant axon confirmed the hypothesis, but only at alcohol levels four to five times the lethal concentration (Gallego 1948). Therefore, many researchers concluded that alcohol's ionic effects could not explain why or how drinking alcohol could affect the nervous system. The hypothesis seemed to lead to a dead end. With time, new technology and instrumentation have allowed a more detailed view of the brain and individual neurons. After examining and recording the electrochemical activity of neurons throughout the brains of various mammals, it was found that a neuron

is not simply a standard element repeated billions of times in the brain. Rather, a wide diversity exists among neurons—in speed of conduction, size, number of inputs, and chemical makeup; therefore, the case for alcohol's effect on neurons' electrical activity was reopened. It was realized that a differential sensitivity to alcohol might result because of differences between neurons.

Recently, researchers (Carlen et al. 1982; Shefner et al. 1982) have demonstrated that alcohol diminishes electrical activity in parts of the brain of mice and rats. In particular, neurons in the hippocampus and locus ceruleus, deep inside the brain, are affected by alcohol concentrations below those that might be expected in a person after several cocktails.

The differential sensitivity of various brain areas to alcohol seems to be genetically influenced. In a line of mice (LS) bred for sensitivity to the effects of alcohol, the hippocampus was less sensitive than another brain area, the cerebellum. These two brain areas were equally sensitive, however, to the effects of alcohol in another line of mice (SS), bred for resistance to alcohol's effects (Sorenson et al. 1981; Basile et al. 1982). Comparisons between strains also clearly demonstrated a genetically influenced differential response to alcohol. Neurons in the cerebellum of the mice resistant to the disruptive effect of alcohol were less affected electrophysiologically by alcohol (Sorenson et al. 1980, 1981; Basile et al. 1982) than were those from the sensitive mice.

The nature of the effects of alcohol on electrical activity led Carlen and his coworkers (1982) to postulate that alcohol altered, in a complex way, the movement of potassium ions across the neuronal membrane.

Another neuronal component related to the electrical activity of the cells is the enzyme sodium-potassium-ATPase. This enzyme, the ion "pump," is responsible for maintaining the proper concentrations of sodium and potassium ions on either side of the neuronal membrane. Alcohol alone in nonlethal amounts does not affect the enzyme activity. When combined with the neurotransmitter chemical norepinephrine, however, brain alcohol concentrations that could be achieved by beverage consumption can inhibit the enzyme. Such inhibition would be expected to affect the conduction of electrical impulses (Rangaraj and Kalant 1979). Thus, alcohol's effects on the locus ceruleus, which has norepinephrine-containing neurons, could be related to inhibition of the enzyme.

As mice and rats become more tolerant to the sedative effect of alcohol, the sodium-potassium-ATPase becomes more resistant to alcohol's inhibitory effects (Levental and Tabakoff 1980; Rangaraj and Kalant 1982). Such a change suggests that alcohol tolerance may, in part, be based on neurochemical changes in the brain. Clearly, more information is required to establish unequivocally the link between alcohol, electrical activity in the brain, and behavioral responses to alcohol.

Neurotransmission

Chemical messages carried across the synapses—the tiny spaces between adjacent neurons—are critical to brain function. Any interference with the release of neurotransmitters, their recognition by receptors, or the development of the new signal in the adjacent neuron will affect the flow of information in the brain. Without chemical transmission, brain function stops. Therefore, various researchers have examined the chemical flow at the synapse to determine the potential effects of alcohol on neuronal activity. Measurement of neurotransmitter release and metabolism represents an alternative to direct measurement of electrical activity, since the rate of neurotransmitter release and synthesis usually reflects the electrical activity of neurons.

The release and recognition of chemical neurotransmitters between neurons propagates messages through the brain. Neurochemicals are allowed to pass through the nerve cell membrane by a mechanism that is dependent on the movement of calcium ions into the neuron. Could alcohol interfere with this process? Friedman et al. (1980) found that alcohol stimulated the initial rate of calcium accumulation in a special preparation of neuronal membranes deprived of calcium. In another study on mice (Harris and Hood 1980), alcohol inhibited the flow of calcium into a neuronal membrane preparation that was enriched with calcium. Furthermore, this latter effect was detectable only under conditions that mimic the electrical signals' arrival at the synapse. In effect, when there was a message and no calcium ions, alcohol quickly mobilized a new calcium cadre. With an excess of calcium ions, however, alcohol inhibited the calcium stimulated release of neurotransmitter.

Recent studies (Stokes and Harris 1982) have found that the inhibitory effects of alcohol on calcium uptake depend on the part of the brain that is examined. Samples from rat

striatum and cerebellum (both associated with movement) were more sensitive to alcohol's effects than were samples from the cortex and brain stem. These results confirm again that, even at the chemical level, different brain areas seem to respond according to their own programs.

Perhaps more important, neuronal preparations from mice chronically fed alcohol resisted alcohol's effects on calcium uptake, regardless of what the initial alcohol effects were. This evidence suggests a possible direct link between behavioral tolerance of alcohol and the microenvironment of the neuron.

The aforementioned studies measured alcohol's effects on the uptake of calcium—that is, the movement of calcium ions into the neuron. Calcium is also stored within cells near the membrane in a kind of chemically adhesive process called binding, which is also affected by alcohol. Low levels of alcohol increased the binding of calcium, whereas higher levels were not as effective (Michaelis and Myers 1979). As with calcium uptake, alcohol had little effect on calcium binding when added to neuronal preparations from rats fed a chronic diet containing alcohol. Thus, this study also indicates a link between behavioral and biochemical tolerance. It is, however, premature to conclude that behavioral tolerance is the direct result of alcohol's effects on calcium—whether related to calcium uptake or binding.

Evidence linking neurotransmitters to behavior led alcohol researchers to investigate three neurotransmitter systems: norepinephrine, dopamine, and GABA (gamma-aminobutyric acid). They found that alcohol affects the release of the neurotransmitters as well as their recognition by receptors at the post-synaptic membrane (Bacoupoulos et al. 1978; Ticku and Burch 1980; Rabin et al. 1980).

When alcohol is acutely given to an animal, the amount of norepinephrine released depends on the level of alcohol in the brain. Moreover, the process is biphasic: It reverses with larger amounts of alcohol (Hunt and Majchrowicz 1974). That is, a small amount of alcohol leads to an increased release of norepinephrine, while higher doses actually depress the release of norepinephrine. Since release of a neurotransmitter reflects nerve activity, this suggests that low doses of alcohol have an excitant or disinhibiting effect, while high doses have an inhibiting effect on neurons containing norepinephrine. These effects on norepinephrine release may, in turn, be related to the behavioral changes produced by alcohol. Sim-

ilar results were obtained when the effects of alcohol on dopamine were examined in rats (Hunt 1981). In mice, however, the reaction is reversed (Kilianmaa and Tabakoff 1983). Low doses of alcohol lead to low release of dopamine, whereas higher doses lead to greater release. The causes of these different reactions to acute infusions of alcohol in closely related species are not yet understood; they may, however, be related to different organization of the nervous system of these species. In both species, the effect of chronic doses of alcohol is consistent, leading to increased release of norepinephrine and decreased release of dopamine (Hunt and Majchrowicz 1974; Pohorecky 1974).

Over the years, laboratory animals have been bred with specific characteristics in mind. One strain of mice has been developed for its relatively high resistance to the behavioral effects of alcohol. These mice are also more resistant to the effects of alcohol on dopamine release (Kilianmaa and Tabakoff 1983). This finding suggests that some animals may be genetically more tolerant of alcohol than others, and that differences in behavior may be related to differences in biochemistry.

The preceding research collectively shows that alcohol's effects on norepinephrine and dopamine release, as well as on movement of calcium ions, vary with dosage, species, genetic strain, and brain area.

The discussion thus far has focused on the neurotransmitters at the transmitting neuron. Across the synapse, the receiving neuron with its receptors must recognize the neurotransmitters. Much of the research at the receptor end has been devoted to GABA, a neurotransmitter that inhibits firing in neurons and is of particular interest to alcohol researchers. By inhibiting electrical impulses, it controls the tendency to convulsions, which are caused by uncontrolled electrochemical activity in the brain. Because the symptoms of alcohol withdrawal include convulsions, GABA is a prime suspect as a cause of these symptoms.

In fact, research strongly implicates GABA receptors in alcohol withdrawal symptoms. In mice, an acute dose of alcohol results in an increase in the number of GABA receptor sites (Ticku and Burch 1980), suggesting lessened neural activity. This finding is consistent with alcohol's depressive effects. Chronic administration of alcohol results, conversely, in a decrease in the number of GABA receptor sites—a finding that could explain convulsions in withdrawals. Indeed, in rats, the decreased number of receptor sites was most pronounced

at the time of the most severe withdrawal symptoms.

Clinical results demonstrate that benzodiazepines such as diazepam (Valium[®]) and chlordiazepoxide (Librium[®]) control the major symptoms (especially convulsions) of alcohol withdrawal. Specific receptors in the nervous system for the benzodiazepines are related to GABA receptors. Part of this relationship appears to be a common effect on the flow of chloride ions across the nerve membrane. It appears that alcohol disturbs the natural linkage between GABA and diazepam. The strongest evidence for this effect comes from studies in which the receptors were removed from their normal membrane environment (Ticku and Burch 1980).

Recent studies have demonstrated that chronic feeding of alcohol to animals affects the receptors for other neurochemical messengers, including the endogenous opiates (Hoffman et al. 1982), acetylcholine (Tabakoff et al. 1979), norepinephrine (Rabin et al. 1980), and dopamine (Barbaccia et al. 1982).

After the receptors have recognized the neurotransmitter message, a new signal is generated within the receiving neuron. A chemical (cyclic adenosinemonophosphate or cAMP) sometimes called the second messenger carries the message from the receptors to the interior of the receiving neuron. Recent research indicates that after withdrawal of animals from chronic alcohol treatment, the release of the second messenger is inhibited (Tabakoff and Hoffman 1979; Luthin et al. 1983).

As the number of identified neurotransmitters increases (some researchers expect it to go from the current 40 to as many as 200 or even more), and with growth in understanding how they work, neurotransmission is likely to help explain the nature of alcohol's biological effects on the central nervous system.

The Membrane

The transmission of information between nerve cells is dependent upon the function of receptors, enzymes, and ion gates. All of these components are proteins located in and on the neuronal membrane. Changes in the physical state of these membranes could have adverse effects on the ability of the specialized proteins to function normally. A number of researchers are studying this problem and in particular are examining the lipids in membranes, which are the biochemically important elements in maintaining the structural integ-

ity of the membrane. Results have clearly shown that membrane viscosity is decreased by acute treatment with levels of alcohol that can be attained through consumption of alcoholic beverages (Chin and Goldstein 1977). After chronic treatment of mice with alcohol, however, it was found that subsequent acute doses of alcohol would no longer change the viscosity of neuronal membranes (Chin and Goldstein 1977). This suggests that behavioral tolerance to alcohol may, in part, be associated with a tolerance of membrane lipids to alcohol-induced decrease in viscosity.

Goldstein et al. (1982) compared alcohol's effects on neuronal membranes from two different genetic strains of mice: LS mice (long sleep, with greater sensitivity to alcohol) and SS mice (short sleep, with less sensitivity to alcohol). They found that neuronal membranes taken from LS mice were more sensitive to alcohol than were membranes taken from SS mice. Another study (Lyon et al. 1981) showed that alcohol's well-known sedative effect is correlated with its effects on neuronal membranes. In turn, these membrane effects would be expected to influence the function of the specialized proteins that reside in the membrane and are critical for proper neuronal transmission.

Tolerance and Dependence

Alcohol produces tolerance in chronic drinkers—that is, the subjective effects of alcohol decrease with continued exposure. It may take a chronic drinker a pint of whisky to obtain the same effect that an occasional drinker gets with a cocktail or two. Physical dependence—the need to continue to drink alcohol to prevent withdrawal symptoms—may be related to tolerance, as it develops only after chronic ingestion of alcohol.

At one time, it was thought that tolerance and dependence would develop only after relatively long periods of exposure. A recent study (Gallagher et al. 1982), however, found that tolerance to alcohol's ataxic effects (loss of muscular coordination) developed after only 2 days. The fairly straightforward behavioral effects of tolerance and dependence have yet to be described fully; biological mechanisms underlying these phenomena are currently even more obscure.

Recent studies suggest that learning may play an important role in developing tolerance, and several investigators have proposed a Pavlovian model of alcohol tolerance (Crowell et al. 1981; Melchior and Tabakoff 1981). Ac-

cording to this model, animals learn to associate environmental cues with the pharmacological effect of alcohol, much as Pavlov's famous dog associated a bell with food. In the presence of those cues, an animal may develop a response designed to counteract the effect of alcohol. In essence, the Pavlovian model suggests that animals learn to reduce their response to alcohol in a particular context, which provides the cues for their response. Tolerance is reduced or absent, however, when the animal is subsequently tested in a different environment. Thus, in some cases, the mere exposure of an animal to alcohol is not sufficient to cause tolerance development; the initial environmental cues must be repeated (Crowell et al. 1981).

Neurochemical studies have also suggested that the presence of alcohol, while necessary, is not a sufficient condition for the development of tolerance; neurons containing the neurotransmitters norepinephrine and serotonin seem to play a role in developing tolerance. When those neurons were destroyed, animals tended to retain their initial responses to alcohol (Tabakoff and Ritzmann 1977; Le et al. 1981) or to develop tolerance more slowly. Thus, the activity of specific neuronal systems, in conjunction with alcohol, seems to be quite important for tolerance development. In addition to neurotransmitter systems, certain hormonal systems appear to affect the development of tolerance. Vasopressin (sometimes called antidiuretic hormone) can maintain an already developed tolerance, even in the absence of continued exposure of the organism to alcohol (Hoffman et al. 1978). Vasopressin's ability to maintain tolerance depends on the presence of intact norepinephrine—and/or serotonin-containing neuronal pathways (Le et al. 1982; Hoffman et al. in press). Whether vasopressin plays a role in developing alcohol tolerance under normal conditions is not clear, but in at least one study, a strain of rats lacking this hormone could not develop alcohol tolerance (Pittman et al. 1982).

Changes in neuronal membranes could account for tolerance and physical dependence. Alcohol initially increases membrane fluidity, but membranes from alcohol-tolerant animals are less sensitive to this effect. Also, enzymes in the membrane demonstrate a biochemical tolerance to alcohol (Levental and Tabakoff 1980; Rangaraj and Kalant 1982). Membrane fluidity could affect sodium-potassium-ATPase activity and therefore, indirectly, electrical conduction in the brain. The mem-

brane's biochemical adaptation could be related to behavioral tolerance.

Physical dependence, like tolerance, may result from an adaptation of neuronal membranes during chronic alcohol exposure. This adaptation might be expected to produce inappropriate neuronal activity in the absence of alcohol. If so, when alcohol is withdrawn, the membranes of physically dependent animals might be more viscous than normal. Although initial studies did not reveal such changes in animals' brain cell membranes following chronic alcohol consumption (Chin and Goldstein 1977), more recent studies have confirmed the expectations (Lyon and Goldstein 1983). Another study (Ingram 1982) also cataloged a number of changes in lipid (fat) content of brain cell membranes derived from chronically alcohol-fed animals, which could contribute to changes in fluidity. These adaptive changes could well be responsible for some aspects of physical dependence and tolerance.

Tolerance and dependence are complex phenomena, however, and may result from different but interacting biochemical mechanisms. As tolerance and dependence are studied in more detail, it becomes increasingly clear that they are influenced by various neuronal and hormonal systems.

Theories of Alcohol's Effects

Alcohol as Reinforcer

Since the publication of the Fourth Special Report (USDHHS 1981), a new hypothesis has emerged to explain the mechanism behind alcohol's reinforcing activity. Most earlier studies focused on specific neurochemical and behavioral correlates of alcohol's depressive effects. Although the stimulant effects had been noted in the past (USDHEW 1974, 1978; Hunt and Overstreet 1977; USDHHS 1981), most earlier studies lacked the theoretical focus that has emerged in recent years. Now much of alcohol's appeal is thought to be directly related to its excitatory effects, and many current studies are attempting to verify the relationship (Taberner 1980; Lindman 1982).

Essentially all studies of alcohol as a drug of abuse are based on the premise that humans and animals consume alcohol because of its reinforcing (or rewarding) effects. Recent years have seen considerable interest in the

similarities between alcohol's reinforcing properties and those of other drugs of abuse. But how does reinforcement work? Many researchers have noted the similarity between the reinforcing properties of alcohol and those of opiate drugs (Altshuler 1982; Amit and Brown 1982). They have reasoned, therefore, that drugs (opiate antagonists) that nullify the brain's reaction to opiates may well block similar reactions to alcohol. The research results have been somewhat difficult to interpret. In some cases, the opiate antagonist blocked a specific effect of alcohol, while in others the opiate antagonist was ineffective.

Striking similarities have been reported between the electrophysiological effects of alcohol and opiates, especially opiate peptides naturally occurring in mammals (Siggins and Bloom 1980; Siggins et al. 1982; Hoffman et al. 1982). Furthermore, in rats and mice, chronic alcohol doses caused significant changes in the characteristics of opiate receptors (Hoffman et al. 1982). All of these reports confirm the link between alcohol and the opiate system in the central nervous system. In general, it appears that, while opiate antagonists do not affect alcohol's depressive properties, they can alter some of its stimulant or excitatory properties.

Such findings suggest a possible relationship between alcohol's excitatory effects and the phenomenon known as reinforcement. Drinking studies conducted with almost every laboratory species have provided many demonstrations that alcohol is a reinforcer in animals as it is in humans.

Some researchers contend that the most appropriate way to study alcohol reinforcement in laboratory animals is to study their voluntary oral alcohol consumption. Yet the usefulness of oral alcohol consumption studies in animals for measuring alcohol preference or reinforcement has been a persistent source of disagreement among researchers. Advocates contend that since humans consume alcohol by drinking it, oral studies are most likely to provide meaningful results. Opponents argue that when drugs, including alcohol, are taken orally, animals will choose them based on flavor rather than for their reinforcing effects. The problem of estimating or controlling how flavor affects oral intake studies has plagued researchers for many years, but a recent study (Crawford and Baker 1982) suggests a method to distinguish between the reinforcing effects of flavor and alcohol.

Because drinking studies in animals are often difficult to conduct, a technique called

self-administration was developed to substitute for oral consumption. The technique allows animals to work for alcohol by pressing a lever to obtain intravenous (directly into a vein) or intragastric (into the stomach) alcohol infusions through surgically implanted cannulae (tubes). Early studies (Deneau et al. 1969) demonstrated unequivocally that monkeys would self-administer alcohol intravenously. Altshuler (1982) showed that monkeys would also self-administer alcohol intragastrically for extended time periods. Both investigations showed that many animals would work for alcohol over time periods sufficiently long to develop tolerance, physical dependence, and eventually, alcohol-related toxicity.

Another less direct technique to measure alcohol's reinforcing effects is the intracranial self-stimulation (ICSS) model. Stimulating electrodes are placed in parts of the brain where electrical stimulation presumably produces pleasurable sensations. The animals, usually rats, are able to press a lever to activate the stimulating electrode in their brains. Most animals will press the lever frequently to obtain the apparently pleasurable sensation that follows. This ICSS phenomenon is thought to be associated with many different reinforcers, perhaps through a common pathway or center of reinforcement. Indeed, most addictive drugs seem to affect ICSS. Because alcohol (and other reinforcing drugs) changes the rate at which animals will press the lever during ICSS, a number of researchers (Wise 1980; Amit and Brown 1982) have concluded that the drugs were acting as reinforcers.

A controversy has emerged over the neurochemical mechanism responsible for alcohol's reinforcing properties in the ICSS model. Most researchers agree that alcohol is a reinforcer and that reinforcement is controlled by the brain's reward system (Wise 1980; Amit and Brown 1982). Wise (1980) hypothesized that alcohol affects dopamine's role in information transfer within the reward system. Amit and Brown (1982) suggested that norepinephrine rather than dopamine is affected. In either event, alcohol reinforcement is probably associated with a specific cluster of neurons that may also be the site of the reinforcement produced by several drugs and ICSS. The experimental evidence implicates several neurotransmitters, including dopamine, norepinephrine, and opiate peptides, as the neurochemicals responsible for the reinforcing properties of alcohol.

Alcohol Metabolism and TIQs

Another theory about alcohol and its actions is based on the hypothesis that biologically active chemicals called tetrahydroisoquinolines (TIQs) may be formed during alcohol metabolism (Davis and Walsh 1970). Interest arose in these compounds because some of the TIQs are structurally related to morphine (an opiate) and, therefore, could involve a common addictive mechanism.

About 6 years ago, Myers and Melchior (1977) proposed a provocative hypothesis relating TIQs and alcoholism. The hypothesis was based on the observation that infusions of a TIQ, tetrahydropapaveroline (THP), into a brain cavity changed an animal's drinking behavior from rejecting alcohol to choosing moderate doses. It was speculated that excessive drinking by human alcoholics could be caused by metabolic abnormalities that result in the formation of TIQs. They reasoned that because drinking creates TIQs, and TIQs stimulate drinking, the positive feedback loop could explain uncontrolled drinking by alcoholics. That conjecture generated both support and disagreement, which continue unabated to this day. Several research groups (Sinclair et al. 1982; Tuomisto et al. 1982) attempted to replicate the initial studies with, at best, only mixed results. Myers et al. (1982), however, reported recently that TIQ infusions produced outcomes in monkeys identical to those in rats, and that THP infusions produced increased alcohol drinking by monkeys. However, these infusion studies use TIQ that is synthesized in the laboratory. While it is theoretically possible that TIQ is formed in the brain, a great deal of controversy remains as to whether TIQs are in fact formed in the brain, or if the concentrations of these chemical compounds are increased following alcohol ingestion. A number of investigators have searched for these compounds using increasingly sophisticated and sensitive techniques, with only limited success (Bloom et al. 1982).

A less controversial hypothesis relates endogenous (naturally produced in the brain) opiate mechanisms to alcohol's behavioral effects. These studies have investigated possible pharmacological relationships between TIQs, endogenous opiate compounds, and the reinforcing properties of alcohol. Most have reported that the reinforcing properties of alcohol and opiates could be related to TIQ mechanisms.

In future studies, many researchers will probably turn their attention to the biphasic effects of alcohol and may reexamine many assumptions about its effects on behavior. Additional research about alcohol reinforcement, preference, and voluntary consumption is likely to illuminate the role of the TIQs, opiate mechanisms, and alcohol-induced stimulation. These data may provide an understanding of the underlying biological mechanisms that contribute to alcohol abuse.

Summary

Alcohol affects every level of the nervous system—from the neurochemicals within single cells to the macrofunctions governing thought processes and behavior. Research on cognition and brain responses to various stimuli continues to expand the inventory of alcohol's effects on humans. Driving-related studies have shown that alcohol impairs judgment, attention, information processing, and reaction time. Alcohol also alters the brain's responses to visual and auditory stimuli. Chronic drinking affects memory and the ability to detect small differences and creates such autonomic difficulties as lack of proper eye pupil control. Abstinence can reverse alcohol's cognitive effects more easily in young drinkers than in older ones.

Social drinking appears to result in some cognitive impairment, but methodologic issues cloud the picture. Alcoholism, on the other hand, definitely impairs cognitive performance. Late stages of alcoholism may also result in organic brain damage—alcoholic de-

mentia and Korsakoff's psychosis.

Alcohol may be the indirect cause of other neuropathology. Liver damage, head trauma, malnutrition, and breathing impairment during sleep, resulting from alcoholism, can lead to a range of adverse effects from behavioral deficits to serious brain damage.

In an effort to understand the neuropsychological effects of alcohol, researchers have examined the effects of alcohol on structures and neurochemicals in various regions of the brain. Chronic drinking seems to cause several biochemical adaptations in nerve cells that could partially explain why alcoholics become tolerant to alcohol and why they suffer withdrawal symptoms after sudden abstinence.

In a search to explain why people drink alcohol to excess, researchers have proposed several theories. One theory suggests that alcohol's appeal stems from its initial excitatory effects. Animal research tends to support the theory, as animals will work to receive infusions of alcohol—thus meeting one criterion of reinforcement.

Another provocative preliminary hypothesis is that tetrahydroisoquinolines, or TIQs, may play a role in habitual heavy drinking. TIQs are formed when alcohol is metabolized. In some animal experiments, when these chemicals are injected into the brains of previously abstinent animals preference for alcohol is increased.

Empirical and theoretical progress over the past decade offers encouragement that research will continue to acquire fundamental knowledge essential to understanding how humans react to alcohol and what makes them drink excessively.

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Chapter IV

Medical Consequences of Alcohol

For most of us, alcohol conjures up pleasant social occasions--wine with a good meal, beer at a ball game, or cocktails during a party of friends. Rarely do we consider the harmful effects of alcohol. Even many experienced drinkers who know every vineyard, vintage year, distillery, and brewery are relatively unaware of the basic medical and biological consequences of drinking.

This chapter follows the trail of adverse effects of alcohol throughout the body and its impact on various organ systems.

Alcohol and the Digestive System

The Mouth

The application of dilute alcohol and a number of alcoholic beverages to the tongue and mucous membranes of the cheek stimulates the flow of saliva (Martin and Pangborn 1971). However, after a short time, the secretion rate of saliva is inhibited for 60 to 90 minutes before returning to normal (Winsor and Strongin 1933). Enlargement of the parotid (a specific salivary gland) is common in alcoholics (approximately 12 percent), but it is uncertain whether it occurs as a result of alcohol use or is due to the protein deficiency frequently seen in alcoholics (Bode 1981).

Inflammation of lips and soft tissue of the mouth, common in alcohol abusers, is thought to occur as a result of nutritional deficiency, particularly of the various B vitamins and iron (Larato 1972).

Cancers of the mouth, tongue, pharynx, and esophagus occur more often in alcoholics than in nonalcoholics. Wynder (1975) has suggested that a synergistic effect between alcohol and tobacco may be responsible. Other factors that may contribute to such carcinogenesis include deficiencies of vitamin A, vitamin B, and zinc that may occur in the alcoholic (Wynder and Chan 1970). Sporn et al. (1976) found that vitamin A deficient animals are

more susceptible to cancers of the skin, mouth, and esophagus than are nondeficient animals.

The Esophagus

The occurrence of nonmalignant esophageal disease such as esophagitis has been associated with chronic alcohol abuse (Shirazi and Platz 1978). In normal human volunteers, alcohol has been shown to interfere with acid clearing mechanisms and to irritate the mucous membranes (Mayer et al. 1978). Mucosal tissue tends to be abnormal in alcoholics (Zeus 1970). Moreover, there is an increased risk of Barrett's esophagitis (a premalignant lesion) in alcoholics when compared with nonalcoholics (Martini and Wienbeck 1974). Esophageal varicose veins, which can develop in cirrhotic patients, can be eroded, resulting in bleeding into the gastrointestinal tract (Chaput et al. 1974).

The Stomach

The effect of alcohol on gastric emptying largely depends on the concentration of alcohol in the stomach (Cooke 1972). Gastric emptying is slowed when alcohol concentrations are greater than 6 percent (Pirola and Davis 1970).

While it has no effect on the muscle that empties the stomach, alcohol has been shown to produce a diminution in the sphincter muscle response to acidity in the duodenum (Phosawasdi et al. 1979).

Chronic consumption of alcohol causes a diminution of gastric acid secretion in humans (Cooke 1972). Furthermore, alcohol increases the formation of prostaglandins, which are known to inhibit acid secretion (Main and Whittle 1976). Such an increase may account for the reduced stomach acid observed in individuals who have abused alcohol for 5 or

more years. Acute administration of alcohol into the mouth, stomach, or blood, however, stimulates secretion of gastric juice. The secretion appears to be maximal at alcohol concentrations between 8 and 16 percent, approximately the concentration found in wine (Elwin 1969).

Acid often injures the mucous membranes of the stomach (Gottfried et al. 1976). Thus, drinking can produce gastric hemorrhage. While alcohol alone does not cause gastric bleeding in normal subjects, it significantly increases blood loss in persons with aspirin-derived mucous membranes injury (DeSchepper et al. 1978). Therefore, the aspirin commonly taken by alcohol abusers to alleviate discomfort may aggravate further stomach injury (Robert et al. 1980).

Alcohol abuse as a cause of gastric ulcer disease, however, remains controversial. Although the incidence of peptic ulcer has been reported to be as high as 20.6 percent in patients with alcoholic liver disease, an association between the two disease conditions has never been proven (Bode 1981).

There is conflicting evidence concerning the role of alcohol in stomach cancer, with most studies showing no clear association. However, a limited number of studies have shown a positive correlation between alcohol use and the development of gastric cancer (Bode 1981). Whether alcohol-induced gastritis is a premalignant lesion, particularly if it occurs repeatedly, is an important question for which sufficient evidence is not yet available (Bode 1981).

The Intestine

The intestine is an important site for the absorption of nutrients into the blood stream. The major focus of research in this area has been on the small intestine. This site is exposed to higher concentrations of alcohol than any other organ in the body except the stomach. After either acute or chronic alcohol consumption, the small intestine may demonstrate structural injury.

In humans, a single small dose (1 gm/kg body weight) of alcohol can produce lesions in the duodenum, a part of the small intestine (Gottfried et al. 1976). Additional studies with human volunteers found that the structural changes that occurred upon consumption of alcohol disappeared once alcohol consumption ceased (Rubin et al. 1972). Similarly, in rats,

intestinal lesions occur within 10 minutes of alcohol ingestion, are well developed within an hour, and disappear after 4 to 16 hours (Baraona et al. 1974). This same study found that animals that chronically consumed alcohol did not respond with such lesions.

Decreases in intestinal enzymes, including those that act on milk, are common in experimental animals and man after alcohol ingestion. Thus, milk intolerance may be exaggerated in alcohol abusers (Perlow et al. 1975).

When applied directly to small intestinal membranes, alcohol decreases the sodium-potassium-ATPase activity from 94 percent to 17 percent of control values (Hoyumpa et al. 1977). As a result of this effect, alcohol in excess of 2 percent can inhibit the transport of electrolytes, amino acids, and glucose across the small intestine (Kuo and Shanbour 1978). Thus, both in animals and in humans, alcohol inhibits the transport of essential amino acids (Israel et al. 1968). Although tissue damage resulting from large amounts of alcohol can inhibit amino acid transport, the fact that it is rapidly reversible suggests that a physiochemical change rather than a toxic injury is responsible (Israel et al. 1968).

Vitamin absorption is adversely affected by alcohol. Alcoholics have shown a significant reduction in the absorption of folic acid (a vitamin) into the jejunum, another part of the small bowel (Halsted et al. 1973). However, after 2 weeks of nutritional supplementation, the folic acid absorption of alcoholics improves despite continued use of alcohol. This suggests that, in alcoholics, impaired folic acid absorption may be primarily a result of poor nutrition rather than a direct toxic effect of alcohol. In support of this contention, studies of acute alcohol administration to normal subjects have shown a decreased folic acid absorption in only 20 percent of the subjects studied (Halsted et al. 1967). However, folic acid deficiency is the most common nutritional deficiency present in alcoholics (Leevy et al. 1965). There also is evidence to suggest that liver tissue is less able to take up folic acid from blood after acute alcohol administration to either normal or alcoholic individuals (Lane et al. 1976).

Thiamine (vitamin B₁) is absorbed much like folic acid. The active absorption of thiamine by cells lining the small intestine is not affected by alcohol (Hoyumpa et al. 1974). However, thiamine movement out of the intestinal cell is impaired by alcohol (Hoyumpa et al. 1975). Both human and animal studies suggest that alcohol inhibits the mechanism

for absorption of thiamine at normal levels of the vitamin (Thomson et al. 1970), but has no effect on the diffusion mechanism that comes into play at high thiamine concentrations (Hoyumpa et al. 1974).

Alcohol's effect on iron absorption is unclear. In one human study (Charlton et al. 1964), a single dose of alcohol increased absorption of a dietary form of iron, ferrous chloride, while others have found no effect of either acute or chronic alcohol administration on iron absorption (Murray and Stein 1965). Adding further confusion to this issue are the studies that showed that ferrous iron absorption is inhibited rather than enhanced by alcohol (Tapper et al. 1968).

Although high levels of zinc are commonly found in the urine of alcoholics, it has not been established that alcohol consumption produces zinc deficiency by increased urinary zinc losses (Sullivan 1962). While alcohol is metabolized by a zinc-containing enzyme, zinc deficiency is not known to decrease alcohol metabolism (Wang and Pierson 1975).

The mechanism involved in calcium transport by the small intestine has not been elucidated. An animal study showed that alcohol inhibits calcium absorption (Krawitt 1975), but the mechanism of such inhibition is not entirely clear. In contrast to animal studies, one study of nonalcoholics given short-term alcohol showed no adverse effect on calcium absorption (Verdy and Caron 1973). Others, however, have reported a doubling of fecal calcium in human volunteers after drinking, suggesting a reduced calcium absorption (Krawitt 1975).

Alcohol has multiple effects on lipid metabolism within the small intestine. In general, alcohol increases triglyceride synthesis in intestines and in mucous membranes (Baraona et al. 1975). It also causes a decrease in fatty acid oxidation.

After exposure to alcohol, the intestinal lymph glands produce more cholesterol and triglyceride, an effect seen only when alcohol is present within the intestine (Middleton et al. 1971). In addition, cholesterol is redistributed among the various intestinal lymph lipoproteins. If alcohol is injected rather than drunk, the redistribution does not occur. This suggests that alcohol acts on the small intestine mucosal enzymes in altering the synthesis and transport of cholesterol. Interestingly, chronic alcohol feeding to animals abolishes or inhibits these acute effects of alcohol on intestinal lipid transport (Baraona et al. 1975; Rodgers and O'Brien 1975). Thus,

the relationship of these findings to the clinical condition of alcohol-induced hyperlipidemia (excess lipids in the blood) remains unclear (Baraona et al. 1975).

The effect of alcohol on the motility of different small intestine segments is variable, but the net effect is to shorten the transit time through the intestine. Initially, when intravenous alcohol is given to volunteers, motility increases, particularly in the second portion of the duodenum (Pirola and Davis 1970). This increased motility is characterized by an increase in intestinal pressure and in the number of contractile waves generated. Later, there is a decrease in duodenal activity with a gradual return toward normal. Moreover, alcohol depresses nonpropulsive motility of the colon in both dogs and humans. It should be noted that these changes in small and large intestinal motor activity may contribute, at least in part, to the diarrhea commonly seen following excessive drinking (Martin et al. 1980).

The Pancreas

Excessive alcohol use can cause chronic pancreatitis, in which lesions and functional impairment persist even in the absence of alcohol (Sarles 1974). This contrasts with gallstone-induced acute pancreatitis in which the pancreas returns to normal after each episode.

More than 75 percent of the cases of chronic pancreatitis in the United States occur in alcoholics. Moreover, pathologic changes or alterations in pancreatic function can be detected in half the alcoholics without pancreatitis symptoms (Reber 1978). Steady alcohol consumption over about 6 to 12 years is necessary before pancreatic symptoms occur.

Acute pancreatitis usually does not occur in the nonalcoholic who occasionally drinks excessively (Strum and Spiro 1971). On the other hand, alcoholics develop symptoms of acute pancreatitis, but only after functional and histologic (tissue) changes of chronic pancreatitis are well established. Progressive destruction of the pancreas continues even after the individual stops drinking.

Surprisingly, chronic alcohol administration to dogs stimulates pancreatic secretion, whereas alcohol's acute effect is inhibitory (Brooks and Thomas 1953). This excitatory effect can be abolished by atropine (a drug that blocks some nervous system activities) and does not occur in previously vagotomized (cutting the nerves connecting the brain to the stomach) dogs. Again, the neurochemical

mechanism acting on alcoholic animals is opposite to that seen in nonalcoholic animals. The reason why chronic alcoholism reverses this acute effect of alcohol on the pancreas is not known.

Regardless of the specific mechanism involved, chronic alcohol consumption results in the secretion of a juice more concentrated in protein. Protein precipitates are rich in calcium carbonate and are identical to the small pancreatic stones found in humans with chronic pancreatitis (Nakamura et al. 1972). In both dogs and humans, these "plugs" of precipitated protein obstruct the ducts, blocking secretion. Acetaldehyde is a highly labile and reactive substance that readily forms adducts with proteins. If sufficient amounts of acetaldehyde are present in the pancreas, it may contribute to the formation of pancreatic stones which obstruct the ducts.

The fine structural changes that occur in the pancreas after alcohol ingestion are similar to those found in liver cells (Darlie et al. 1970), and the changes in early human chronic pancreatitis appear to be similar to those observed in animals chronically treated with the hormones gastrin or cholecystokinin.

A relatively recent finding is that a specific genetically controlled cell surface antigen (a substance that activates the immune system) has an increased prevalence in individuals with chronic pancreatitis due to alcoholism. This suggests a possible genetic mechanism predisposing alcoholics to pancreatitis (Fauchet et al. 1979).

An association between alcoholism and cancer of the pancreas has been hypothesized. Burch and Ansari (1968) were the first to make such a suggestion, based on a retrospective study in which 75 percent of the patients with pancreatic cancer also had a history of moderate to heavy alcohol intake. Additional support for this thesis was provided by the report that the risk of pancreatic cancer was twice as great in males who consumed alcohol daily as it was in nondrinkers (Lieber 1977).

Alcohol and the Liver

Until recently, it was unclear whether liver disease associated with alcohol consumption was a direct effect of the alcohol or of the malnutrition that often accompanies alcoholism. The landmark work, primarily of Lieber (1981) and his colleagues, has now established that alcohol is directly toxic to the liver.

Metabolism of Alcohol

Alcohol is not effectively stored in tissues, and little less than 10 percent of an ingested dose can be eliminated through the kidneys, lungs, and skin. For practical purposes, one can assume that the body rids itself of alcohol only by oxidizing it in the liver, the organ containing the bulk of the enzymes required for alcohol oxidation. The liver's complexity and unique role in alcohol oxidation contribute to the many deleterious effects of alcohol within the liver. Unlike other major sources of calories, alcohol cannot be stored either in the liver or in other tissues; it must therefore be metabolized immediately in preference to all other fuels.

Three liver enzyme systems have been shown to promote the oxidation of alcohol to acetaldehyde. They are, in descending order of importance: alcohol dehydrogenase (ADH), microsomal ethanol-oxidizing system (MEOS), and catalase. The acetaldehyde produced is itself toxic, so a second step is subsequently required to convert it to a final nontoxic substance, acetate.

The major pathway for alcohol metabolism involves ADH. Although an increase in ADH activity above that seen normally may not necessarily increase the rate of alcohol oxidation, reductions in ADH activity do diminish alcohol metabolism (Bosron and Li 1980). Thus, low protein diets, which reduce ADH levels, slow the metabolism of alcohol both in rats and in humans (Pekkanen et al. 1978). Consistent with this observation, prolonged fasting reduces the metabolism of alcohol (Bode and Thiele 1975). Moreover, the sex steroid testosterone inhibits ADH activity while estradiol, an estrogen, enhances it (Rachamin et al. 1980).

As noted above, other systems in addition to ADH can oxidize alcohol. Thus, in animal experiments, as much as 30 percent of the total chronically administered alcohol may be oxidized by a non-ADH enzyme pathway in which MEOS plays the major role (Matsuzaki et al. 1981). However, the contribution of this system to alcohol elimination in humans has not been quantitated. The issue in humans is complicated by the presence of many forms of ADH, including one form, the π ADH, which has an activity profile similar to MEOS (Bosron et al. 1979). Nonetheless, following chronic alcohol consumption, the MEOS system is significantly increased in activity (Lieber and DeCarli 1968).

In humans, alcohol consumption accelerates blood alcohol clearance, particularly at high alcohol concentrations. This observation is consistent with the metabolic activity of MEOS (Salaspuro and Lieber 1978) but is also consistent with the activity of α -ADH. MEOS activity generates only heat, while ADH oxidation can produce storable forms of energy. This may account for the observation that alcohol produces a greater increase in oxygen consumption in alcoholics than in normal individuals, and also for the lesser growth in animals that are fed alcohol as compared to their controls (Pirola and Lieber 1972). Such energy wasting could explain, at least in part, the weight loss experienced when alcohol calories are substituted for a balanced diet (Lieber et al. 1965).

Alcohol oxidation always produces acetaldehyde which, in turn, is metabolized to acetate. It is generally accepted that more than 90 percent of the acetaldehyde formed as a consequence of alcohol oxidation is oxidized by aldehyde dehydrogenase (ALDH) to acetate immediately within the liver.

The principal cellular site of acetaldehyde metabolism lies within the mitochondria, which are found in the cytoplasm of cells. Moreover, the major portion of acetaldehyde oxidation within the mitochondria occurs where ALDH is located.

Acetaldehyde, like its precursor alcohol, adversely affects many tissues. It appears to interfere with vitamin B₆ metabolism and promotes the vitamin's degradation (Veitch et al. 1975). Acetaldehyde has been shown to impair the synthesis of proteins in the heart and can inhibit protein secretion by liver cells (Schreiber et al. 1972, 1974; Sorrell et al. 1983). Finally, acetaldehyde can depress the capacity of the liver to oxidize fatty acids (Cederbaum et al. 1975). The alcoholic may therefore be a victim of a vicious cycle; high acetaldehyde levels and chronic alcohol consumption impair the liver's mitochondrial function, which decreases acetaldehyde metabolism, which accelerates the accumulation of acetaldehyde, all leading to liver damage.

Amino Acid and Protein Metabolism

Alcohol disrupts amino acid (the building blocks of proteins) metabolism in the liver, which leads to their excessive accumulation (Krebs et al. 1973). Amino acid abnormalities in the blood appear in patients with alcoholic hepatitis, cirrhosis, and liver insufficiency (Rosen et al. 1977). In an isolated rat liver,

relatively high concentrations of alcohol inhibit the uptake of amino acids (Krebs et al. 1973).

Patients with cirrhosis frequently have an increased plasma level of aromatic amino acids (Ono et al. 1978). These amino acids convert to amines within the gastrointestinal tract and can adversely affect the central nervous system by acting as false neurotransmitters. In this regard, Faraj and co-workers (1976, 1979) found a statistically significant correlation between the level of plasma tyramine (an amino acid product) and the degree of hepatic encephalopathy (liver-caused brain damage).

The level of alpha amino N-butyric acid (AANB) in the blood is increased after chronic alcohol consumption, which has led to suggestions that it may be of use as a biochemical marker or indicator of alcoholism (Shaw et al. 1976). However, the plasma level of AANB may reflect at least two different factors present in chronic alcoholic individuals: Chronic alcohol consumption tends to increase the level of AANB, while dietary protein deficiency tends to decrease it. It is therefore necessary to control for nutritional factors if one is to use the level of AANB in plasma as a biochemical marker of chronic alcohol consumption (Shaw and Lieber 1978).

Alcoholics with cirrhosis and malnutrition have depressed hepatic levels of carnitine, an amino acid needed for oxidation of fatty acids (Rudman et al. 1977). Possibly this is due to an impaired ability of such patients to synthesize it. The blood level of free proline (an amino acid) is higher in some patients with cirrhosis compared with controls (Rojkind and DeLeon 1970) and appears to be proportional to the collagen (the structural protein that accumulates in cirrhosis) content of the livers of such individuals (Kershenobich et al. 1970).

Increased levels of acetaldehyde have been noted in patients with alcohol-induced liver disease, and acetaldehyde, but not alcohol, has been shown to interfere with protein synthesis (Schreiber et al. 1972, 1974; Sorrell et al. 1983). Consistent with this finding is the observation that alcohol does not inhibit protein synthesis by those liver cells that do not oxidize alcohol to form acetaldehyde (Morland et al. 1979). A similar lack of an inhibitory effect occurs in a variety of nonhepatic tissues in which the ADH activity is absent or less than that present in the liver (Perin and Sessa 1975). Thus, the inhibitory effects of alcohol on protein synthesis are dependent, at least in part, on alcohol metabolism to acetaldehyde.

Fatty Acid Metabolism

Fatty infiltration of the liver after alcohol consumption is the most common hepatic abnormality associated with alcohol abuse. The infiltration is due to an increased accumulation of triglycerides in response to alcohol. The origin of the triglycerides depends upon the pattern of alcohol consumption (dose and duration) and the lipid content of the diet. With acute ingestion of a large dose of alcohol, the excess hepatic triglycerides are derived from peripheral fat stores, while after chronic alcohol ingestion, the excess of triglycerides is the result of fat synthesis by the liver itself.

The replacement of dietary triglycerides containing long chain fatty acids with fat consisting of medium chain triglycerides reduces the propensity of alcohol to induce a fatty liver (Lieber and DeCarli 1966). Apparently the greater propensity of medium chain triglycerides to undergo oxidation accounts for this phenomenon (Lieber 1967). Protein deficiency may also contribute to an alcohol-induced fatty liver in some circumstances; however, even with adequate protein in the diet, alcohol may cause the development of fatty liver. It would appear that the main factors leading to the development of alcoholic fatty liver are as follows: Alcohol replaces fatty acids as the preferred fuel for mitochondria. The metabolic consequence is that more lipid (fatty acid) is synthesized and less is burned. In addition, alcohol at high concentrations inhibits the transport of newly synthesized lipids out of the liver cell. The net effect is accumulation of fatty acids.

A consequence of the hepatic accumulation of fatty acid is the excess formation of ketones (Lefevre et al. 1970). This results in alcoholic ketoacidosis (increased levels of ketones and acids in the blood), which is usually associated with a mild hyperglycemia (elevated blood sugar). Susceptibility to alcoholic ketoacidosis varies among individuals. The basis for alcoholic ketoacidosis is still unclear; however, its development may not be related to the amount of alcohol ingested nor to the levels of alcohol in the blood. It is possible that disrupted hormone levels are involved. Blood insulin levels are low during the ketoacidosis episode, while those of growth hormone, epinephrine, glucagon, and cortisol are high. Such a hormone pattern could act to mobilize free fatty acids from peripheral adipose (fat) tissue to enhance fatty acid metabolism

by the liver and contribute to the mild hyperglycemia.

Other Metabolic Effects

Chronic alcohol ingestion leads to proliferation of liver microsomes, fine intracellular structures that are responsible for detoxifying many drugs. Therefore, it is not surprising that an enhanced metabolism of drugs is common in alcoholics. For example, the metabolism of meprobamate, pentobarbital, antipyrine, tolbutamide, warfarin, and diphenylhydantoin is enhanced after heavy alcohol intake and can persist for up to 3 weeks after alcohol intake has been discontinued (Mezey 1979).

Chronic drinking is associated with a raised metabolic rate, which is characterized by increased oxygen consumption, inefficient use of calories, increased heat output, and weight loss (Pirola and Lieber 1972). This hypermetabolic state has been hypothesized to result, at least in part, from increased enzyme activity within the liver (Israel et al. 1973). The increased rate of oxygen consumption can be markedly depressed by surgically removing the thyroid and can be abolished by treatment with propylthiouracil (PTU), a thyroid inhibitor (Orrego et al. 1979). These observations suggest that PTU may be of potential therapeutic value in alcoholic patients with liver disease. Indeed, in a recent study, PTU was reported to exert a beneficial short-term effect on both the magnitude and the rate of improvement in patients with alcoholic hepatitis (Orrego et al. 1979). Moreover, the therapeutic value of PTU was found to be greatest in those patients with the most severe liver disease. There are, however, some conflicting reports. For example, Halle et al. (1982) performed a double-blind controlled trial in patients with severe acute alcoholic hepatitis. No beneficial effects of PTU therapy were observed. The question of the therapeutic usefulness of PTU therefore remains to be answered.

Pathology

There are three specific subtypes of hepatic pathology associated with alcohol use: alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis. In its early stages, alcoholic liver disease is characterized by accumulation of excess fat in the liver as a result of the mechanisms already described above. Alcoholic hepatitis is characterized by the death and inflammation of individual liver cells. This

more severe form of alcohol-associated hepatic injury may cause death in 10 to 30 percent of the afflicted individuals. Eventually the entire structural and functional capacity of the liver is impaired, resulting in cirrhosis, the most severe and presumably irreversible form of alcohol-induced liver disease.

Most patients with alcoholic fatty liver are virtually asymptomatic; the various laboratory tests appear nearly normal. Importantly, alcoholic fatty liver is a completely reversible lesion that does not necessarily progress to a more severe disease.

The study of patients with alcoholic hepatitis may lead to an understanding of the natural evolution of alcoholic liver disease culminating as cirrhosis. In some populations, particularly in Europe and Japan, cirrhosis develops in alcoholics without an apparent intermediate stage of alcoholic hepatitis (Karasawa et al. 1980). This observation raises the question as to whether alcohol can promote the development of cirrhosis without being preceded by a stage of alcoholic hepatitis. It now appears from both human and animal studies that alcoholic hepatitis may not be necessary for the development of alcoholic cirrhosis (Popper and Lieber 1980).

According to a new theory, the balloon-like swelling characteristic of alcoholic hepatitis develops as a result of the accumulation within the cell of lipid and protein, which normally would have been secreted into the blood. The retention of such proteins presumably results from degenerative effects of alcohol on subcellular structures (microtubules) that are important for the secretory activity of the liver (Matsuda et al. 1979). Thus, the effect of alcohol may be similar to that of drugs which bind to the cellular proteins and produce lesions similar to those seen in human liver cells with prolonged alcohol use (Denk et al. 1979).

The severity of the various alcohol-associated pathologies of the liver correlates poorly with either the duration of drinking or the amount of alcohol consumed.

Not all patients with alcoholic hepatitis develop cirrhosis, and alcoholic hepatitis appears to occur in 29 percent of male and 47 percent of female alcoholics (Wilkinson et al. 1969; Morgan and Sherlock 1977; Gavalier 1982). Since specific histocompatibility antigens (HLA) are more prevalent in patients with cirrhosis than in controls, these genetic factors might determine an alcoholic's susceptibility to develop cirrhosis (Goodwin 1971; Bell and Nordhagen 1980).

Alcohol and Muscle Systems

Heart Muscle

An association between alcoholism and heart disease has been recognized for more than 100 years. Until recently, however, heart disease was thought to result from malnutrition, particularly thiamine deficiency, and not alcohol itself. Now that thiamine deficiency has been eliminated as an important contributing factor, heart disease has been directly linked to alcoholism.

Specifically, cardiomyopathy, a primary disorder of heart muscle, is often found in chronic heavy drinkers. It generally appears in patients with a long history of alcohol consumption, usually somewhat greater than 10 years in duration. The major symptoms of alcohol cardiomyopathy are chronic shortness of breath and signs of congestive failure such as edema, chest pain, fatigue, palpitations, and blood-stained sputum.

Alcoholic cardiomyopathy does not occur suddenly (Demakis et al. 1974). It gradually progresses from a subclinical condition characterized by minimal cardiac findings and nonspecific electrocardiographic abnormalities to overt congestive heart failure. The severity of the illness appears to be related directly to the duration of alcohol abuse. The prospect for recovery is reasonably good, if the individual ceases to drink, but recovery is slow and may require 5 to 6 years (Fuster et al. 1981).

It is generally believed that damage to the cell mitochondria of the heart muscle is the major mechanism responsible for alcoholic cardiomyopathy (Alexander 1967). Electron microscopic studies clearly show degenerative changes of the mitochondria in response to chronic drinking (Alexander 1967; Alexander et al. 1977b). Other subcellular structures also may be abnormal, leading to depression of mitochondrial respiration, liberation of mitochondrial enzymes, and a reduction of energy-providing ATP in the heart (Alexander et al. 1977a).

In contrast, some epidemiological studies have indicated that alcohol in moderate doses may have a health enhancing effect on the risk for coronary heart disease (Klatsky 1980). However, it has also been shown that at mildly intoxicating doses alcohol adversely affects left ventricular function (Ahmed et al. 1973). Larger doses actually impair the ability of the heart muscle to contract. Thus, alcohol depresses the heart muscle function at blood

concentrations found during alcohol intoxication. Gimeno and coworkers (1962) observed such depression in rats at concentrations of alcohol as low as 0.1 percent. Spann and his colleagues (1968) found that heart contractions of left ventricular muscles, obtained from both normal cats and those with chronic heart failure, are slowed by alcohol. As the alcohol dose is increased, the heart muscle contractions continue to be slowed. Nakano and Moore (1972) observed a similar heart muscle velocity/alcohol dose relationship in guinea pigs.

Delgado and his associates (1975) observed that consuming one to two drinks of Scotch whisky affected the heart in normal subjects 30 to 90 minutes following ingestion. Similarly, Ahmed et al. (1973) found that whisky ingested over 2 hours by normal subjects resulted in a reduction of the duration of systole.

The peripheral circulatory and neurohormonal effects of alcohol tend to obscure the unfavorable action of alcohol on the heart. Both acetaldehyde and acetate (metabolites of alcohol) have been shown to have direct effects on the vascular system resulting in vasodilatation (dilated blood vessels) (Liang and Lowenstein 1978). Acetate also increases cardiac output and left ventricular peak pumping rate and reduces the resistance of peripheral blood vessels, all varying with the alcohol dose (Liang and Lowenstein 1978).

Interestingly, alcohol cannot be metabolized by the heart because alcohol dehydrogenase is absent in the heart (Lochner et al. 1969). Acetaldehyde dehydrogenase is present, however, and thus acetaldehyde can be and is metabolized by cardiac muscle (Forsyth et al. 1973). Despite this lack of alcohol metabolism, Regan and his associates (1969) have shown that following alcohol administration to dogs various ions and enzymes usually found only inside cells are released by heart muscle into the blood. This leakage of cellular contents presumably indicates cellular damage, suggesting that alcohol itself is toxic to the heart. Moreover, Swartz and coworkers (1974) have reported that calcium uptake and binding in the heart, which is needed for muscle contraction, is inhibited by alcohol. Furthermore, Williams and his coworkers (1975) have demonstrated a dose-dependent inhibition of the sodium-potassium-ATPase activity of blood vessel membranes isolated from guinea pig hearts, with both alcohol and acetaldehyde. The enzyme plays a critical role in controlling the amounts of sodium and potassium, nec-

essary for muscle contraction, in the cell.

Cardiac arrhythmias (heart beat irregularities), such as ventricular fibrillation and palpitations, are common in individuals with alcohol-related disease and, in particular, during alcohol intoxication (Ettinger et al. 1978; Greenspon et al. 1981). Gould and his coworkers (1969) have suggested that sudden death probably caused by cardiac arrhythmias may be relatively common among young adults who are found, at autopsy, to have large fatty livers, presumably due to alcohol abuse. It is likely that these alcohol-induced cardiac arrhythmias are due to the direct effects of alcohol upon the heart muscle as well as to the adverse effects of acetaldehyde upon the conduction system. As little as 2 ounces of whisky, consumed by individuals with existing organic heart disease, can suppress the heart's ability to generate muscle contractions that pump the blood throughout the body (Newman and Valicenti 1971). Moreover, another study has indicated that alcohol intoxication can result in a complete heart block (absence of heart beat), requiring pacemaker therapy (Leier et al. 1974).

Finally, it appears that patients with existing heart disease are sensitive to adverse myocardial effects of alcohol or acetaldehyde (Conway 1968; Gould et al. 1971).

Skeletal Muscle

Myopathy, the disease of skeletal muscle, has been associated with alcohol abuse for about 120 years. Modern concepts of alcoholic myopathy began, however, in 1955 with the studies of Ekbom and his associates (1964), who first described a syndrome of muscle weakness without evidence of other signs or symptoms in alcoholics. Eventually, a wide spectrum of alcoholic myopathy has come to be recognized, from the completely asymptomatic to the near fatal (Hed et al. 1962).

Subclinical myopathies occur in more than one-third of alcoholics. Some alcoholics will have a history of muscle cramps, weakness, and occasional episodes of dark urine (myoglobinuria) which is thought to be due to the presence of myoglobin released by damaged muscle tissue (Faris et al. 1967).

The development of muscle weakness in any alcohol-abusing individual could imply acute alcoholic myopathy. Such individuals may experience a sudden attack of muscle pain or a rapid progression of a previously diagnosed chronic myopathy. Such attacks can be fatal. Generally, the muscles are exquisitely tender

during attacks, and are centered in one group of muscles, although on occasion the effect can be diffuse. Fortunately, if alcohol use is discontinued, the disease and its symptoms disappear.

Smooth Muscle

Alcohol's effects on smooth muscle have been recognized only recently. Previously, when alcohol was used as an analgesic for pregnant women, the uterine muscles occasionally stopped contracting. This led researchers to speculate that alcohol directly inhibited smooth muscle contractions (Chapman and Williams 1951). This concept was challenged, however, when Fuchs and Wagner (1963) reported that alcohol interfered with the release of oxytocin, a hormone responsible for uterine contractions, and that this inhibition of hormone activity was the major factor responsible for the diminished uterine contractions. However, more recently, several research teams have shown that alcohol in low concentrations does indeed directly depress uterine contractions (Gimeno et al. 1971; Laversen et al. 1973).

Moreover, Fischer et al. (1965), Winship and his associates (1968), Hogan et al. (1972), and Kjellen and Tibbling (1978) have reported that alcohol reduces sphincter (a smooth muscle) pressure in the lower esophagus. Even more recently, Altura and colleagues (1976, 1978) have shown that both alcohol and acetaldehyde consistently enlarge the peripheral blood vessels, by relaxation of the smooth muscle in the vessel walls.

Alcohol and Blood Disorders

Prolonged protein deprivation and deficiency of B vitamins, particularly riboflavin, pyridoxine, and folic acid, play a role in reducing the formation of new blood cells. In animal studies, protein deficiency or the removal of even a single essential amino acid from the diet can produce anemia with reduced blood formation in the bone marrow, which recovers after resuming a normal diet (Ghitis et al. 1963). Thus, protein deprivation probably plays an important role in the production of both the anemia and the abnormal iron levels seen in alcoholics, particularly those with liver disease.

The close relationship of folic acid deficiency to chronic alcoholism has been recognized for years. Consumption of a folate-poor

diet for several months will deplete body stores, and the diet of most alcoholics contains significantly less than the daily minimum requirement of this vitamin (Wu et al. 1975). Therefore, folic acid deficiency is the primary cause of megaloblastic (abnormal red blood cells) anemia in alcoholics (Sullivan and Herbert 1964; Hines and Cowan 1974). Because folic acid deficiency causes ineffective production of red blood cells, it is associated with increased iron turnover in the blood and a delayed red blood cell incorporation of iron. Therefore, folic acid deficiency leads to increased iron absorption and may be responsible for the increased iron stores in some chronic alcoholics. Impaired liver function may also contribute to these effects. Not only is folate intake reduced, but in individuals with alcoholic liver disease, folate may be released from stores in the liver and lost in the urine, therefore further reducing folate stores (Cherrick et al. 1965). Thus, folate deficient alcoholics may need to be treated with folic acid in therapeutic doses much larger than the amount needed to simply maintain normal function.

The symptoms of riboflavin deficiency, which include anemia, underdeveloped bone marrow, and abnormalities in developing blood cells, are identical to those seen in chronic drinkers. Thus, riboflavin deficiency may also contribute to the anemia present in alcoholics.

Vitamin B₆ is ineffectively converted to its active coenzyme form in alcoholics (Lumeng and Li 1974). The coenzyme deficiency appears to cause several clinical problems in alcoholics, including some forms of anemia as well as changes in the bone marrow, peripheral neurological disease, convulsions, and worsening of liver disease (Davis and Smith 1974; Hines 1975).

Finally, it is possible that alcohol itself may inhibit heme (a constituent of hemoglobin) synthesis in red blood cells (Moore 1974; Ibrahim et al. 1979).

Most alcoholics without iron deficiency have enlarged red blood cells (macrocytosis), a recognized but poorly understood disorder (Bingham 1960). Such blood cell dysmorphology may be the result of a variety of underlying mechanisms, including (1) folate deficiency, (2) increased numbers of immature red blood cells, and (3) increased deposition of cholesterol and phospholipids in red cell membranes, associated with liver disease.

Unger and Johnson (1974) were the first to report that, during routine screening of employees of an insurance company, a number of

alcoholics were discovered to have an elevated MCV (mean corpuscular volume, or average blood cell size) in the absence of other changes usually associated with alcoholism, such as folate deficiency, increased numbers of immature red blood cells, or significant liver disorder. Since then, many reports have confirmed their observations (Buffet et al. 1975; Morin and Porte 1976; Davidson and Hamilton 1978; Wright and Ree 1978). An increased MCV has been found in about 90 percent of alcoholics, which suggests that the MCV may be useful as a marker for alcoholism (Unger and Johnson 1974; Buffet et al. 1975; Morin and Porte 1976). Furthermore, in several large population studies, the number of alcoholic drinks taken daily correlated with the MCV (Whitehead et al. 1978; Eschwege et al. 1978). Even with abstinence, little or no change in the MCV occurs for many weeks; usually 2 to 4 months of abstinence are required before the MCV returns to normal (Unger and Johnson 1974).

Leukopenia (a reduced number of white blood cells) is relatively common in alcoholics (Cowan and Hines 1971). Eichner et al. (1972), for example, observed leukopenia in 8 percent of their cases. Other studies found 1.6 percent (Eichner 1973) and 8.5 percent (Liu 1973) of subjects with leukopenia.

Bone marrow smears obtained from such individuals consistently show a decreased number of cells with markedly decreased numbers of mature granulocytes. The leukopenic episodes in alcoholics tend to be transient, lasting 2 to 4 days, and usually followed by rapid recovery and an increased number of white blood cells.

As long ago as 1938, Pickrell noted in rabbits that white blood cells (which kill intruding bacteria) were inhibited from moving into sites of bacterial infections within the skin and lung during alcohol intoxication. He noted also that the white blood cells attacked the bacteria normally. Similar results have been obtained in mice (Louria 1963) and in humans (Brayton et al. 1970). MacGregor and his associates (1974; Gluckman et al. 1977) have shown that alcohol inhibits the movement of human white blood cells. Alcohol consumption for as short as 6 to 8 days can result in such inhibition. The mechanism by which alcohol impairs such white blood cell functions remains unclear, although it has been suggested that increased intracellular concentrations of cyclic AMP (adenosine monophosphate) after consuming alcohol may be partly responsible for this phenomenon.

There is additional evidence of altered immunologic activity of white blood cells in alcoholics. Studies of animals and humans during periods of alcohol ingestion found that the immunologic response of the skin was reduced (Gluckman et al. 1977). Also, many patients with alcoholic hepatitis have an altered immunity to liver antigens (Young et al. 1979). Furthermore, lymphocytes (one type of white blood cell) from patients with alcoholic liver disease may attack the patients' own liver cells (Paronetto and Lieber 1976). In summary, these observations suggest that abnormalities of lymphocytic function occur in alcoholics and that immunologic mechanisms may account for some of the liver damage induced by alcohol even after abstinence (Lue et al. 1979).

The natural tendency for the blood to coagulate and seal a bleeding wound is disrupted in alcoholics, principally as a complication of advanced liver disease. These changes are similar to those occurring in patients with other chronic liver diseases. Most often, the levels of the clotting factors dependent on vitamin K are decreased. Moreover, the clotting compounds themselves may be abnormal in alcoholics (Weinstein and Deykin 1978; Conoso et al. 1979).

Alcohol and Kidney Disease

Alcoholics with liver disease may have enlarged kidneys with increased fat, protein, and water (Van Thiel et al. 1977). Seven to 14 percent of alcoholics, about 20 times the rate of nonalcoholics, suffer tissue loss in their kidneys (Edmondson et al. 1966; Longacre and Popky 1968). In one study, 12 of 20 alcoholics suffered kidney tissue loss during their first attack of acute kidney infection, with the lower urinary tract the source in most cases. These infections occurred in alcoholics without cirrhosis, suggesting that alcohol abuse and not liver disease was the cause. Such a conclusion is warranted because kidney infection does not accompany other types of severe liver disease.

Alcohol and Pulmonary Disease

Chronic obstructive pulmonary disease is common among alcohol-abusing males, especially smokers (Rankin et al. 1969). Other pulmonary problems such as pneumococcal pneumonia are more likely to occur in alcoholics than in the general population. It is

possible that poor dental health, combined with recurrent abnormal respiration (aspiration) during intoxication, may be responsible for the increased prevalence of bacterial lung abscesses in alcoholics. Tuberculosis is a well-recognized health problem in malnourished alcoholics, and impaired connections between the arteries and veins in the lungs of alcoholics, especially those with advanced liver disease, can cause cyanosis (reduced hemoglobin), hyperventilation, and hypoxia.

Alcohol and the Endocrine System

Gonadal and Adrenal Effects

Low levels of androgens (male hormones) are found in alcoholic men. Thus, 70 to 80 percent experience decreased libido and/or impotence (Van Thiel 1980). In addition, 70 to 80 percent of such men show both testicular atrophy and infertility (Van Thiel and Lester 1979a).

Not only do alcoholic men produce fewer androgens, but such men also produce excess estrogens, the female hormones. Fifty percent of alcoholic men with cirrhosis develop feminine pubic hair patterns, and 20 percent develop enlarged mammary glands (Van Thiel and Lester 1979a). These signs of chronic alcoholism, unlike the transient impotence commonly experienced with an acute alcoholic bout, persist even in the absence of intoxication and are due in large measure to alcohol-induced tissue injury.

Until recently, liver disease was considered to be a primary cause of the sexual dysfunction present in alcoholics. During the past 10 years, however, this concept has been severely challenged, and a diametrically opposite view has gained currency (Van Thiel and Lester 1979a). This recent view is the result of evidence showing that sexual dysfunction can be present in alcoholic men with essentially normal livers (Van Thiel et al. 1974b). Plasma levels of testosterone, a male hormone, are reduced in men within hours after drinking enough alcohol (approximately seven drinks) to produce a hangover (Ylikahri et al. 1974). Many of the features of alcohol-induced sexual dysfunction can be produced in experimental animals with normal livers (Van Thiel et al. 1975a, 1979a). Furthermore, alcohol reduces testosterone levels in mice and rats (Van Thiel and Lester 1979a). Thus, the concept that the sexual changes observed in alcoholic men are the result of alcohol per se, rather than the

indirect consequences of alcohol-induced liver disease, has gained considerable credence.

The specific mechanisms by which alcohol adversely affects testicular function are being unraveled slowly. Vitamin A is essential for creating sperm, and alcohol may interfere with vitamin A activation in the testes (Van Thiel et al. 1974a). Alcohol metabolism may shift the balance between essential enzymes in the testes as it does in the liver, thereby limiting the generation of testosterone (Van Thiel and Lester 1976a). Similarly, acetaldehyde, either produced in the testes or entering the testes from the blood as a result of alcohol metabolism outside the testes, may have deleterious effects upon testicular mitochondria, subcellular organelles that are critical for generating steroids (Gavaler et al. 1983). Indeed, the conversion of cholesterol to the steroid pregnenolone, a reaction that occurs in mitochondria, is inhibited when mitochondria are exposed either to alcohol or to acetaldehyde. Several studies have found a reduced capacity to produce steroids in the testes obtained from alcohol-fed rats (Chiao et al. 1981; Cicero et al. 1980).

Not only is testicular testosterone production inhibited as a result of alcohol exposure, but recent studies have demonstrated that alcohol interferes with gonadotropin (a substance that stimulates the gonads) binding to testicular tissue. Furthermore, chronic drinking is associated with a pituitary-endocrine defect for gonadotropin secretion (Van Thiel et al. 1978c). Alcoholics thus have low gonadotropin concentrations in their blood and respond inadequately to stimuli such as luteinizing hormone releasing factor that provoke gonadotropin release (Van Thiel et al. 1978c). Similar inadequate gonadotropin responses can be demonstrated in chronic alcohol-fed rats and after acute alcohol administration to normal rats (Van Thiel et al. 1979a). The cumulative evidence suggests that chronic drinking induces gonadal injury through its direct effects on the gonad, as well as through indirect effects on the hypothalamus (a part of the brain that integrates endocrine activity) and the pituitary gland.

In addition to having reduced gonad performance, alcoholic men also have relatively high levels of estrogens (Van Thiel and Lester 1976b, 1979a). As noted earlier, they show many of the secondary sex characteristics of women. Such feminization results from increases in estrogen-responsive proteins and the hormone neurophysin (Van Thiel et al. 1975b). The increases in the hormone prolactin

lins and endorphins) on the control of pituitary releasing factors. Such opiates appear to inhibit CRF and thereby ACTH release. They therefore might contribute to reduced ACTH release seen during alcohol intoxication and withdrawal (Morley et al. 1980). This hypothesis is consistent with other observations that opiates alter some of alcohol's effects. For example, the opiate antagonist, naloxone, improves the psychomotor impairment and depressed level of consciousness induced by alcohol (Jeffcoate et al. 1979; Jefferys et al. 1980).

The urine of patients with cirrhosis, especially those with edema, contains increased amounts of the steroid aldosterone, which controls the amount of fluid and salt in the body (Bongiovanni and Eisenmenger 1951). Individuals with cirrhosis are likely to have an increased secretion rate and blood levels of aldosterone (Coppage et al. 1962).

Chronic liver disease is associated with a significantly decreased blood flow in the liver, the site where aldosterone is metabolized. As a result, the clearance of aldosterone from the body is reduced and the duration of the activity of the hormone is prolonged (Coppage et al. 1962). It should be noted, however, that the resultant elevated blood levels of aldosterone in cirrhotic individuals reflect not only a decreased metabolic clearance but also an increased secretion rate of the hormone occurring, at least in part, in response to an increased production of angiotensin, which stimulates aldosterone secretion.

The state of the hypothalamic-pituitary-adrenal axis during alcohol withdrawal has been studied extensively in animals. After alcohol is withdrawn from mice, they are likely to be hyperactive, with seizures and increased corticosteroids in the blood (Goldstein 1972). Chronic alcoholics also experience increased corticosteroid levels during alcohol withdrawal (Stokes 1973).

Interestingly, the pituitary reserve of ACTH in alcoholics experiencing withdrawal is frequently reduced (Wright et al. 1975). Alcoholics who abstain from drinking often show persistent abnormalities of the hypothalamic-pituitary-adrenal axis (Oxenkrug 1978).

In addition to altering steroid hormone release by the adrenal gland, alcohol stimulates the secretion of catecholamines, e.g., epinephrine and norepinephrine, and increases the adrenal content of catecholamine synthesizing enzymes (Pohorecky 1974). Studies in rats have suggested that acetaldehyde is principally responsible for these observed changes in

catecholamine secretion in response to alcohol (Walsh and Truitt 1970).

The Thyroid

The most consistent effect of alcohol on the function of the thyroid is to moderately decrease the hormone thyroxine (T_4) levels in the blood and to markedly decrease the hormone triiodothyronine (T_3) in the blood (Israel et al. 1979). It has been suggested that the low T_3 levels after alcohol consumption reflect injury to the liver and reduced ability of the liver to remove iodine from T_4 (Orrego et al. 1979). Despite the considerable data suggesting that alcohol affects the thyroid (and its interactions with the hypothalamus and pituitary) indirectly via the liver, alcohol can directly cause an increase in the thyroid uptake of iodine, which is needed to synthesize the thyroid's hormones (Yadav et al. 1970). Moreover, Wright (1978) and Van Thiel et al. (1979b) have reported a diminished thyroid stimulating hormone (TSH) response to thyrotropin releasing factor (TRH) in alcoholics.

Growth Hormone and Prolactin

Considerable evidence suggests that alcohol blocks the release of growth hormone. Early studies of laboratory animals suggested that alcohol produces degenerative changes in the pituitary (Sanchez-Calvo 1941). More recently, the acute administration of large doses of alcohol to rats has been shown to abolish spontaneous growth hormone secretion (Redmond 1980). Alcoholics with cirrhosis, in contrast, have elevated levels of growth hormone and frequently respond abnormally to stimuli of growth hormone (Van Thiel et al. 1978b).

Two studies (Torro et al. 1973; Earll et al. 1976) have reported that a single dose of alcohol had no effect on prolactin (a hormone associated with milk-stimulation as well as other functions). However, Loosen and Prange (1977) reported reduced prolactin levels, but with minimally impaired prolactin responses to TRH during alcohol withdrawal. Jung and Russfield (1972) reported an increased prevalence of prolactin-secreting cells in the pituitaries of male and female patients who died of alcoholic liver disease. Ylikahri et al. (1976) noted increased prolactin responses to TRH in alcoholics, a finding confirmed by Van Thiel and his coworkers (1978a, b, c, d). Van Thiel and his associates (1978a, b, c, d) also reported that elevated prolactin levels occur in cir-

rhosis, and that cirrhotics have reduced prolactin responses to TRH. In contrast, individuals with fatty liver have reduced prolactin levels and exaggerated prolactin responses to TRH. Preliminary studies in the rat also suggest that alcohol increases prolactin levels in the blood (Gordon and Southren 1977).

Vasopressin and Oxytocin

Alcohol produces diuresis, which seems to occur because the hormone vasopressin, the body's antidiuretic hormone, is inhibited. Indeed, several groups have found reduced vasopressin levels after acute alcohol administration (Linkola et al. 1977; Helderman et al. 1978). Little or no tolerance to the diuretic effects of alcohol or its inhibition of vasopressin release has been observed in alcoholics (Marquis et al. 1975). Alcohol's suppression of vasopressin release appears to originate in the hypothalamus. Thus, stimuli applied directly to the hypothalamus can override the diuretic effects of alcohol. Alcohol may, however, inhibit the electrically evoked discharges of the hypothalamus (Raiha 1960).

More recently, studies showed that vasopressin was suppressed while blood alcohol levels were increasing. After the maximum blood alcohol levels were attained, the vasopressin levels increased (Marquis et al. 1975).

On the basis of bioassay data, alcohol would appear to inhibit the release of the hormone oxytocin, which is the principal uterine-contracting and lactation-stimulating hormone of the pituitary gland (Wagner and Fuchs 1968). No data, however, are available on the actual blood levels of oxytocin during alcohol administration and withdrawal.

Parathormone

Alcohol causes hypocalcemia (reduced blood calcium) in both dogs and rats (Peng et al. 1972). Parathormone, the parathyroid hormone that controls blood calcium levels, does not reverse this hypocalcemic effect of alcohol (Peng and Gitelman 1974). The fall in calcium may be related to the shift of calcium ions out of the blood (Peng et al. 1972). Some studies in normal volunteers and in alcoholics have suggested that alcohol produces an increased urinary excretion of both calcium and magnesium (Kalbfleisch et al. 1963; Jones et al. 1969). Alcohol has been shown to reduce the transport of calcium in the duodenum (Krawitt 1975). The defect in calcium stability found in alcoholics with hypocalcemia, however, is

most likely due to an alcohol-induced decrease in blood magnesium levels (Estep et al. 1969). Magnesium is well known to be important in the regulation of parathormone secretion and in the mediation of the hormone's peripheral action (Rasmussen 1974). Both malabsorption of calcium and a primary dietary deficiency of vitamin D probably are responsible, at least in part, for the hypocalcemia in individuals with advanced alcoholic cirrhosis. Finally, Williams and his coworkers (1978) recently have reported that alcohol results in an increased level of the hormone calcitonin, which may play a role in developing hypocalcemia.

It is of some interest that a decreased density of tibial bone has been reported in rats chronically fed alcohol (Saville and Lieber 1965). Alcoholic patients do have a decreased bone mass and an increased incidence of fractures (Nilsson 1970). Finally, low phosphate in the blood, which also is common in alcoholics, may contribute to the development of the metabolic bone disease seen in alcoholics (Knochel 1977).

The Endocrine Pancreas

Several studies have shown that alcohol increases insulin secretion in response to glucose (Singh and Patel 1976; Shah et al. 1977). Interestingly, alcohol increases the insulin response to other compounds that stimulate secretion as well as to glucose (Kuhl and Anderson 1974).

Glucose intolerance is common in individuals with alcoholic liver disease, particularly those with portal hypertension (Phillips and Safrit 1971; Kreisberg et al. 1972). Insulin and especially glucagon (a hormone that ultimately increases blood glucose) levels are increased in such individuals (Marco et al. 1973). It is thought that the glucose intolerance in such individuals is due primarily to raised levels of glucagon in the blood. However, abnormal glucose tolerance can occur in alcoholics due to chronic pancreatitis as well as to advanced liver disease.

The syndrome of fasting alcoholic hypoglycemia (low blood sugar) develops within 6 to 36 hours after ingestion of alcohol by a previously malnourished or fasting individual. No age group appears to be exempt from this type of alcohol-induced reaction, but children and women seem to be particularly susceptible. Several studies have reported that alcohol is capable of producing severe and conceivably fatal hypoglycemia in susceptible subjects (Marks and Medd 1964; Arky and Fienkel

1966). In addition to children, athletes are at particular risk for the development of severe hypoglycemia following the combination of alcohol ingestion, fasting, or exercise (Arky et al. 1968).

Alcohol and Cancer

Evidence for the strong associations between chronic alcohol consumption and cancers of the mouth, pharynx, larynx, and esophagus has existed for many years (Lieber et al. 1979). In addition to the cancers of the upper respiratory and alimentary tracts, more recent studies indicate that alcohol may play a role in cancers of the liver, pancreas, stomach, large intestine, rectum, breast, and malignant melanoma (Williams and Horm 1977; Rosenberg et al. 1982; Tuyns 1978).

There are no supporting data from animal studies to clearly show that alcohol by itself is carcinogenic. This issue is further clouded by the fact that, either by accident or as a result of the production process, carcinogenic materials were formerly found in various alcoholic beverages. These substances include nitrosamines, polycyclic hydrocarbons, fusel oils, and asbestos fibers (McGlashan et al. 1968; Wehman and Plantholt 1974; Spiegelholder et al. 1979).

While the basis for the relationship between alcohol and cancer is unknown, it is estimated that alcohol by itself, or in combination with substances such as tobacco, is associated with 3 percent of the cancer deaths in the United States (Rothman 1980; Doll and Peto 1981).

The interaction between alcohol consumption and tobacco is particularly striking in terms of cancers of the mouth, pharynx, and larynx, where the total risk is increased in a synergistic manner (Rothman and Keller 1972; Tuyns 1978; McCoy and Wynder 1979; Schottenfeld 1979). As an example, one study indicated that alcohol consumption and heavy smoking produced up to a fifteenfold increase in the risk of oral cancer, compared with the chances of people who neither drank nor smoked. Heavy smoking alone increased the risk by only twofold to threefold (Lemon et al. 1964; Lyon et al. 1976; Phillips 1980).

Despite the absence of a known mechanism of action, it is clear that heavy alcohol consumption is a risk factor for the development of cancer. To account for this action, several

hypotheses have been generated, including: alcohol acting as a solvent to increase the entry of carcinogens into cells (McCoy and Wynder 1979); alcohol-induced enzyme changes leading to the conversion of procarcinogens (noncarcinogenic substances) into active carcinogens (Seitz et al. 1981a,b; Garro et al. 1981); and repeated alcohol-induced cellular damage promoting cancer in the liver (Lieber 1969).

Summary

Chronic alcohol consumption leads to ubiquitous toxic effects in the body, with medical consequences ranging from slight functional impairment to life-threatening disease states. The most common site of injury is the liver, the organ most responsible for ridding the body of alcohol.

In the early stages of alcoholic liver disease, the liver becomes fatty, a condition that may progress to hepatitis. After an extended period of chronic drinking, the liver structure may be affected, followed by a breakdown in its functional capacity. The result is cirrhosis--an often fatal disease.

Because the liver is so essential for metabolism and detoxification, many organs and body systems may be adversely affected indirectly by alcoholic liver disease. Excessive alcohol also may directly injure the gastrointestinal tract, muscles, and pancreas. As alcohol and its metabolites travel through the body in the blood stream, they may affect the major body systems, including the cardiovascular system, the nervous system, and the endocrine system. Furthermore, there is evidence of a strong association between chronic alcohol use and cancer of the stomach, large intestine, pancreas, and liver.

Many of alcohol's deleterious consequences are the result of effects on the endocrine system hormones. For example, fewer androgens are produced in alcoholic men, often leading to a feminization of their appearance, decreased libido, and infertility. Alcoholic women are affected also, frequently with ovarian dysfunction. Alone, and in conjunction with dietary deficiencies frequently associated with alcoholism, alcohol abuse can produce nutrition-related deficits in the body. These deficits result in altered protein metabolism and vitamin-related disorders such as anemia.

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Chapter V

The Effects of Alcohol on Pregnancy Outcome

Clinical reports and experimental studies published in the past 10 years leave little doubt that prenatal alcohol exposure poses a threat to the health of the unborn child. This threat ranges from miscarriage and newborn death, to a cluster of abnormalities called fetal alcohol syndrome (FAS), to subtle behavioral disturbances such as hyperactivity, which may occur in the absence of observable physical abnormalities.

This chapter represents a selective review and status report on current knowledge concerning the effects of alcohol on pregnancy outcome. It is not intended to be exhaustive. A number of recent more detailed reviews have dealt with a full range of issues involving alcohol-related pregnancy complications and birth defects (see, for example, Rosett and Weiner 1981; Rosett et al. 1981; Sokol 1981, 1982; Abel 1982a; Randall 1982). In addition, overviews of fetal alcohol research are contained in the Third and Fourth Special Reports to the U.S. Congress on Alcohol and Health (USDHEW 1978; USDHHS 1981).

The present survey examines current findings about alcohol and pregnancy and needs for future research. The first section begins with a brief historical introduction. This is followed by an examination of data documenting alcohol as a teratogen (a substance that can cause birth defects). Some specific alcohol-related pregnancy complications and birth defects are then examined, with particular emphasis on new information about brain damage and behavioral disorders. The need for further information about time of exposure, patterns of drinking, type of beverage, determination of dose/response relations and thresholds, and host susceptibility are discussed in conjunction with ways of improving pregnancy outcomes by preventing alcohol-related birth defects.

It should be noted that this chapter uses, where appropriate, the terms alcohol-related birth effects as well as alcohol-related birth defects. Birth defects include entities such as organ anomalies. The term birth effects, as

used in this chapter, is more inclusive and contains, in addition, pregnancy complications and outcomes such as small-for-gestation-age weight. These factors usually place the infant at higher risk for an adverse health occurrence, but are not in their own right anomalies.

Historical Perspective

Although even during ancient times alcohol may have been considered a pregnancy risk, by the 1700s a link between alcohol and birth defects was strongly suspected. In 1759, for example, the London College of Physicians petitioned the British Parliament to reinstate taxes on gin so that it would be less available and, therefore, would constitute less of a risk to pregnant women and their infants (Warner and Rosett 1975). Despite reinstatement of these taxes, a steady outpouring of warnings about drinking during pregnancy continued, indicating that the problem did not disappear after the law was changed.

In 1899, a report appeared in England which documented in a novel way many of the adverse effects of alcohol during pregnancy (Sullivan 1899). Six hundred offspring of 120 alcoholic women in a Liverpool jail were compared with offspring born to 28 nondrinking female relatives of these women. Infant mortality and stillbirth rates for the alcoholics' children were 2-1/2 times higher than the rates among offspring of the comparison group. Even more dramatic was the finding that many of those alcoholic women who previously had infants with severe and often fatal complications gave birth to healthy children when forced to become abstinent because of imprisonment. The obvious inference drawn by the author was that alcohol is toxic to the fetus.

Although several relevant studies pointing to fetal damage from prenatal alcohol exposure were performed during the early 20th

century, interest in alcohol and pregnancy notably decreased during Prohibition, and only sporadic reports can be found in the world literature from the succeeding 50 years (Sokol 1982; Abel in press). Modern recognition awaited the publication of two key papers in 1973 by Jones, Smith, and their colleagues. These investigators reported that 11 children of chronically alcoholic mothers were growth-retarded and had craniofacial and cardiac defects, as well as developmental delay (Jones and Smith 1973; Jones et al. 1973). Perhaps, in retrospect, the major contribution of these papers was the coining of the term fetal alcohol syndrome, which refocused interest on important scientific and public policy questions. These reports gave particular impetus because they appeared during a period of increased public and professional concern with maternal/fetal/infant health. If alcohol consumption represented an important and potentially avoidable pregnancy risk, perhaps pregnancy outcomes could be improved when the risk had been recognized.

Fetal Alcohol Syndrome and Alcohol-Related Birth Effects

Numerous cases of fetal alcohol syndrome from all over the world have now been described in the scientific literature, e.g., from Australia, Belgium, Brazil, Canada, Chile, Czechoslovakia, France, Germany, Hungary, Ireland, Italy, Japan, South Africa, Spain, Sweden, Switzerland, and the United States (Abel in press). Because standardized criteria were not used for many of the diagnoses, the Fetal Alcohol Study Group of the Research Society on Alcoholism proposed specific criteria in 1980 (Rosett 1980). These criteria require that at least one feature from each of the following three categories be present for a diagnosis of fetal alcohol syndrome:

- Growth retardation before and/or after birth
- A pattern of abnormal features of the face and head, including small head circumference, small eyes, or evidence of retarded formation of the midfacial area, including a flattened bridge and short length of the nose, and flattening of the vertical groove between the nose and mouth, i.e., the philtrum

- Evidence of central nervous system abnormality, including, for example, abnormal neonatal behavior, mental retardation, or other evidence of abnormal neurobehavioral development

None of these features alone is specifically characteristic of fetal exposure to alcohol. In fact, many other nonspecific abnormalities are seen in conjunction with FAS, as well as in isolation, which makes diagnosis difficult. These include eye and ear defects; heart murmurs, which are often associated with septal defects (openings between the chambers of the heart); genitourinary anomalies, such as undescended testicles; hemangiomas (a type of birthmark); fingerprint and palmar crease abnormalities; and other anomalies, such as hernias. Any of these abnormalities may be seen individually, even without maternal drinking. However, when these conditions are seen in conjunction with a pattern of abnormalities consistent with FAS, the diagnosis of FAS may be made. Alcohol-related birth effects are complications of pregnancy, risk associated pregnancy outcomes (e.g., small-for-gestation-age weight), and birth defects that can be attributed to alcohol use after statistical analysis has corrected for the contribution of other possible factors.

Prevalence

The reported prevalence of FAS varies widely and no firm national data are as yet available. Depending on the location and the population under study, the overall prevalence has varied from 0.4 per 1,000 in Cleveland (Sokol et al. 1980) to 2.1 per 1,000 in Boston (Rosett et al. 1983). In Seattle, where the syndrome was first identified, one study indicated a prevalence of 1.3 per 1,000 (Hanson et al. 1978). Estimates from Europe have ranged from 1.6 per 1,000 in Sweden (Olegard et al. 1979) to 2.9 per 1,000 in France (Dehaene et al. 1977). It appears then that, calculated on the basis of total number of births, the overall prevalence of FAS is in the range of 1 to 3 per 1,000.

Estimates of the frequency of the full fetal alcohol syndrome, calculated on the basis of occurrence only among women who have been identified as problem drinkers or alcohol abusers, are somewhat more consistent and higher than the above figures, ranging from 23 to 29 per 1,000 (Hanson et al. 1978; Sokol et al. 1980; Rosett et al. 1983). Further, as might

be expected, alcohol-related birth effects have been reported considerably more frequently among alcohol abusers. However, the estimates vary widely, ranging from 78 per 1,000 to 690 per 1,000 (Ouellette et al. 1977; Hanson et al. 1978; Sokol et al. 1980). This wide range may be attributed to the differing criteria used for inclusion in this diagnostic category. Thus, although only a limited proportion of the offspring may have enough abnormalities to be diagnosed as FAS, some effects possibly attributable to alcohol appear to occur in relatively high proportions of infants born to women who drink heavily during pregnancy.

In general, about 65 to 70 percent of developmental defects have been noted to be of unknown origin (Wilson 1973). Sokol (1981) has calculated that about 5 percent of all congenital anomalies may be attributable to prenatal alcohol exposure, suggesting that alcohol may account for a significant proportion of previously unexplained anomalies and that it should be considered a major contributor to abnormal fetal development. In terms of mental retardation, which may be considered the most serious and damaging of all alcohol-related birth defects, Clarren and Smith (1978) have stated that maternal alcohol abuse during pregnancy "appears to be the most frequent known teratogenic cause of mental retardation in the Western World."

The high prevalence of alcohol-related birth defects is worth noting not only because of its impact on the affected individual and on society, but also because of its significant economic impact. While difficult to evaluate precisely, one study has estimated a lifetime cost of \$155 million for those born in a given year with FAS and alcohol-related birth defects in New York State alone (Russell 1980).

Problems with Human Fetal Alcohol Studies

The experimental administration of alcohol to pregnant women is clearly unethical. Studies of alcohol and pregnancy in humans are limited by virtue of the usual constraints associated with human subjects to clinical observation and nonmanipulative designs. Clinical reports have been of particular importance in special cases, such as in the birth of twins. For example, a case in which one fraternal twin was more severely affected with FAS than the other (Christoffel and Salafsky 1975) suggests that genetic factors are significant in determining fetal susceptibility to

alcohol's damaging effects. This may partially explain why only one of two women who consume the same amount of alcohol may give birth to a child with FAS.

Observational studies involving many patients rather than single cases, however, can be more difficult to interpret. Recent detailed critical reviews of such studies (Neugut 1981; Sokol 1980b) have identified two general problem areas, the first involving the issue of bias. In many published case reports and studies, the clinician diagnosing alcohol-related birth defects may have been aware of maternal alcohol abuse, leading to the possibility that some of the observed associations may have been affected by such knowledge. However, even when infants have been examined without knowledge of maternal alcohol history, as in the large prospective observational studies funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), alcohol-related pregnancy complications and birth effects, including lowered birth weight and congenital abnormalities, have been identified (Ouellette et al. 1977; Kuzma and Sokol 1982).

A second major problem in human fetal alcohol studies is called "confounding." Alcohol is but one of a multitude of possible pregnancy risks (cofactors) which include maternal characteristics, medical disorders, pregnancy complications, abuse of substances other than alcohol, and exposure to environmental contaminants. In observational study designs, complex statistical techniques are used to try to control and adjust for as many factors as possible to support the inference that any observed effect is attributable to alcohol. Many pregnancy risks remain unknown, however, and these statistical techniques are limited, making it almost impossible to adjust for confounding completely. While human studies can document associations between alcohol and adverse pregnancy outcome, they cannot demonstrate causality convincingly (Sokol 1980b). Experimental studies in animals have therefore proven to be valuable. If rigorously designed and performed, animal studies allow greater control and greater certainty in inferring a causative role for alcohol as a teratogen.

Animal Models

Alcohol-related birth defects comparable to those occurring in humans have been reported among mice (Randall and Taylor 1979), rats

(Abel 1979), beagles (Ellis and Pick 1980), sheep (Potter et al. 1980), miniature swine (Dexter et al. 1980), and monkeys (Altshuler and Shippenberg 1981). These studies in animals have documented direct dose/response effects of alcohol on perinatal mortality, infant weight, and soft tissue malformation and have shown that these effects cannot be attributed to other factors, such as undernutrition, often associated with alcohol abuse in humans. For example, Randall and her colleagues (1981), using a study design that equates the nutritional intake of alcohol-exposed and control animals, clearly demonstrated in mice that restricted caloric intake could not account for the teratogenic effects observed. However, nutritional factors, e.g., low protein intake, can interact with alcohol exposure, leading to higher blood alcohol levels and more severe alcohol-related birth defects, as suggested by the work of Wiener and her colleagues (1981). These findings indicate that nutritional factors alone did not account for the observed deficits. The alcohol present in the body rather than nutritional factors is the teratogen.

Other compelling evidence for a direct effect of alcohol as a teratogen comes from in vitro (literally in glass) studies of embryonic tissue. In these experiments, rat embryos have been directly exposed to alcohol (Brown et al. 1979). Compared with unexposed controls, embryos exposed to 0.15 or 0.3 grams of alcohol per 100 ml of culture medium (an intoxicating dose) had decreased crown-rump and head lengths and decreased total cell counts, as well as retarded development, after only 24 hours of exposure. The rat embryo at this stage cannot metabolize alcohol to its primary metabolite, acetaldehyde; thus, this study strongly supports a causative role for alcohol as an agent directly toxic to the fetus but does not rule out the possibility that acetaldehyde also may be a teratogen (Popov et al. 1981).

Additional support for a direct effect of alcohol in inducing aberrant fetal development is provided by a notable study performed in mice. Sulik and her colleagues (1981) administered early in pregnancy two large closely spaced doses of alcohol on a single day, such as might occur in binge drinking. They were able to produce abnormal facial features in the mouse fetus that appear remarkably similar to those observed in human FAS. However, certain methodological issues raise questions as to the immediate applicability of such findings to humans. Nonetheless, this study

both supports the concept of a causative role for alcohol in inducing fetal malformation and raises questions about the critical periods of exposure for specific effects and the ability of fetal tissues to recover from exposure to toxic levels of alcohol early in pregnancy.

Specific Adverse Pregnancy Outcomes

Exposure to intoxicating levels of alcohol over prolonged periods is clearly associated with a range of specific adverse fetal outcomes. Some of these outcomes have been described in detail in the Third and Fourth Special Reports to the U.S. Congress on Alcohol and Health (USDHEW 1978; USDHHS 1981) and therefore will be reviewed only briefly.

Spontaneous Abortion

The risk for spontaneous abortion (miscarriage or early pregnancy loss) is increased approximately twofold in pregnancies complicated by maternal drinking, although perhaps only among the heaviest or most frequent drinking 3 to 5 percent of women (Harlap and Shiono 1980; Kline et al. 1980; Sokol 1980a; Sokol et al. 1980). Pregnant monkeys also tend to abort early in pregnancy following alcohol exposure (Altshuler and Shippenberg 1981), as do rodents, as indicated by an increased rate of resorption, the analog of spontaneous abortion in humans (Chernoff 1977; Randall et al. 1981). With respect to later pregnancy loss, i.e., the stillbirth rate, the data are less clear. A statistically significant increase in the stillbirth rate was detected in an initial study from France for women consuming three or more drinks per day (Kaminski et al. 1978), but not in a subsequent study by this group (Kaminski et al. 1981). Also, no increase in the stillbirth rate was noted in a large study from the Cleveland area (Sokol et al. 1980). Studies in animals are likewise equivocal with respect to alcohol and stillbirths (Ellis and Pick 1980; Abel et al. 1981b).

Physical Congenital Anomalies

Virtually all of the congenital anomalies reported to be alcohol-related birth defects in humans have now been duplicated in animals prenatally exposed to alcohol, although probably only when blood alcohol levels exceeded 0.1 percent--the legal level of intoxication in most States (Randall 1982). Acute intragastric

administration (directly into the stomach) of alcohol to mice on one day of pregnancy did not result in a significant increase in birth defects, compared with two nutritional control groups (Lochry et al. 1982). Thus, it appears that duration as well as level of exposure are important determinants of alcohol-related physical birth defects.

Lowered Birth Weight

Lowered birth weight is the most reliably observed effect attributable to in utero alcohol exposure in humans and animals. Based on a review of more than 300 reported cases of FAS, the average birth weight of such children was 2,000 grams (Abel 1982b), compared with the median birth weight for all infants in the United States of more than 3,300 grams (NCHS 1980). Further, decreased birth weight has been observed even in the absence of full FAS (Ouellette et al. 1977; Sokol et al. 1980). These findings are of concern because lowered birth weight is widely recognized as being associated with significant increases in risk for fetal and infant mortality and long-term abnormalities in neurologic development and intelligence. Lowered birth weight may be the result of preterm delivery (prematurity) or intrauterine growth retardation, or both.

Preterm delivery.--Effects of alcohol on pregnancy duration are unclear. Alcohol-related prematurity was not identified in one study of more than 12,000 pregnancies (Sokol et al. 1980). Two more recent studies, however, suggest that preterm delivery may result from prenatal alcohol exposure. Berkowitz (1981), in a study of 175 mothers of preterm infants and 313 mothers of term infants, found that alcohol consumption prior to the third trimester of pregnancy was associated with preterm delivery. Furthermore, in a more detailed analysis of the same data, Berkowitz and her coworkers (1982) found that heavier alcohol consumption (an average of two or more drinks every day) during pregnancy was associated with an approximately threefold increase in risk for preterm delivery; no increased risk was identified for lighter drinking.

In a recent study from Boston City Hospital of 1,690 births, maternal drinking prior to pregnancy was found to be associated with shortened gestation (Hingson et al. 1982). It is interesting to note that preterm delivery does not occur in pregnant animals that are given alcohol—in fact, parturition may be delayed (Bond 1982).

Intrauterine growth retardation.--In contrast to the data involving prematurity, the evidence linking in utero alcohol exposure and decreased fetal growth is very strong. For example, in their study of more than 12,000 pregnancies, Sokol and his colleagues (1980) found that with alcohol abuse birth weight was decreased by about 190 grams, in the absence of any effect on pregnancy duration. Similarly, in another group of approximately 5,000 women in a different part of the country, Kuzma and Sokol (1982) detected about a 100-gram decrement in birth weight, limited to the most frequently drinking 3 percent of women. Little (1977) noted a statistically significant decrease in infant birth weight of 91 grams for women reporting average alcohol use of 1 ounce (two drinks) per day for the prepregnancy period, and a 160-gram decrement for late pregnancy consumption at that level.

Prenatal growth retardation associated with maternal alcohol consumption has been observed in numerous animal studies (Ellis and Pick 1980; Lee and Leichter 1980). The extent of this retardation appears to be dose-dependent with exposure during the third trimester having a more severe effect on birth weight than did exposure earlier in gestation (Abel 1979; Lochry et al. 1982). The decrease in birth weight can be seen even after a single administration of alcohol shortly before term (Greizerstein and Abel 1979; Lochry et al. 1982). These observations are consistent with studies in humans that indicate that drinking continued through the third trimester is associated with decreased infant weight (Little 1977; Rosett et al. 1978).

Studies in animals are also beginning to help identify mechanisms by which alcohol may decrease fetal growth. For example, animal embryos provide evidence for the direct effects of alcohol and acetaldehyde on fetal growth (Brown et al. 1979; Popov et al. 1981). In addition, alcohol exposure may lead to chronic fetal hypoxia (Abel 1982b), or to hypoglycemia, i.e., low blood glucose. Decreased fetal nutrition resulting from hypoglycemia induced by high blood alcohol levels could contribute to fetal growth retardation (Tanaka et al. 1982). Other studies suggest that alcohol may affect fetal cell growth by interfering with the passage of amino acids across the placenta (Henderson et al. 1981). With inadequate transport of amino acids to the fetus, protein synthesis and growth would be inhibited. Moreover, decreased incorporation of amino acids into protein in alcohol-exposed fetuses has also been reported (Henderson et

al. 1979, 1980). Although alcohol-related decreased absorption of zinc has also been suggested as a contributor to growth retardation, the evidence on this issue is contradictory (e.g., Samson and Diaz 1981; Flynn et al. 1981; Ghishan et al. 1982).

Based on these results, it is reasonable to conclude that alcohol is associated with lowered birth weight, related possibly to both shorter gestation and decreased intrauterine growth. Diminished prenatal growth is dose-related and may be more severe when alcohol is consumed in the third trimester.

Abnormal Neurobehavioral and Neural Development

In surviving fetuses, the most severe alcohol-related birth defects are those involving the central nervous system. Congenital anomalies, even those that are very severe, e.g., heart defects, are often repairable. Brain damage, however, is permanent and irreversible. Alcohol-related anatomical, electrophysiological, and biochemical abnormalities in the brain have now been identified and may underlie the observed behavioral deficits.

Behavioral development.--The adverse effects of alcohol on behavioral development may be divided into three main categories: abnormal neonatal behavior, as reflected in sleep problems and state regulation disorders; childhood hyperactivity; and mental retardation, as indicated by lowered IQ scores (Abel 1981a).

Infants born to heavy drinkers or alcoholics have been found to be more restless during sleep and not to sleep as much as other children (Rosett et al. 1979). Abnormal electroencephalographic (EEG) activity during sleep has been noted for as long as 6 weeks after birth in some of these children.

Hyperactivity in children with FAS has been noted in several clinical case studies (Abel 1981a). It has also been noted in 15 children who had physical abnormalities consistent with FAS, but whose IQ scores were within normal limits. All 15 of these children eventually received recommendation for special education services because of their restlessness, short attention spans, and distractibility (Shaywitz et al. 1980).

Lowered IQ scores in conjunction with heavy prenatal alcohol exposure have been noted in other countries. In the United States, the average IQ scores for a group of patients with FAS was found to be 65, reflecting moderate

mental retardation (Streissguth et al. 1978a), and when the same individuals were retested, the IQ scores did not change (Streissguth et al. 1978b). Similar results were obtained in the study from Sweden in which children with physical signs of FAS were found to have an average IQ below 70 (Olegard et al. 1979).

Two studies of mental and motor development identified infants exposed in utero to alcohol and investigated those who did not exhibit full FAS. Streissguth and her coworkers (1980) administered an infant development test to a group of infants at the age of 8 months. They recorded significant trends toward lower scores on mental and motor tests related to increased maternal alcohol use during pregnancy.

Golden and her colleagues (1982) evaluated neurobehavioral development in 12 infants with physical alcohol-related birth defects and a history of maternal alcohol abuse and compared them with 12 normal infants. These two groups of infants were examined at a mean age of 1 year without knowledge of the prenatal drinking history. Both the mental and motor scores were 20 points lower in the alcohol group, a notable difference. Furthermore, the alcohol group had significantly higher frequencies of postnatal growth retardation and microcephaly, i.e., abnormally small heads. Although it was not possible in this study to adjust for the confounding effects of maternal smoking, there was strong evidence that the abnormal neurobehavioral development of the infants was attributable to alcohol alone or in combination with cigarette smoking.

Landesman-Dwyer and her coworkers (1981) studied 272 offspring of women without alcohol problems and found that at age 4, the children with greater in utero alcohol exposure generally were less attentive and less compliant with parental commands. More recently, Streissguth and her colleagues (1983b), after observing 4-year-olds, found that maternal alcohol use during pregnancy is significantly related to decreased attention and longer reaction time. They suggested that alcohol use by pregnant women can have long-term behavioral effects in children.

As with physical anomalies, some studies in animals duplicate many of the behavioral abnormalities noted in humans with fetal alcohol exposure. For example, hyperactivity has been noted consistently in rats prenatally exposed to alcohol (Bond and DiGiusto 1976; Abel 1982c). Learning difficulties have also been identified in animals prenatally exposed to

alcohol (Bond and DiGiusto 1978; Riley et al. 1979a, b; Abel 1979). Riley and his coworkers (1979a, b) have proposed that many of the abnormal behavioral effects related to prenatal alcohol exposure suggest an underlying problem in response inhibition. The magnitude of this effect appears to be dose-related (Lochry and Riley 1980). On balance, the behavioral abnormalities found in animals are similar to those in children with fetal alcohol syndrome.

Neural development.—Neuroanatomic and biochemical abnormalities probably underlie alcohol-related abnormal neurobehavioral development; these areas are currently under study. Microcephaly, an important component in the diagnosis of FAS, indicates an overall decrease in brain growth. Moreover, anatomic abnormalities have been observed in brains of children born to alcoholic women as studied at autopsy, as well as in animals prenatally exposed to alcohol. These include hydrocephalus (increased fluid distending cavities in the brain), absence of the corpus collosum (the bundle of fibers connecting the two sides of the brain), and abnormal growth patterns of nerve and other brain cells (Clarren et al. 1978; Peiffer et al. 1979; Rasmussen and Christensen 1980).

Subtle changes in brain structure have been noted in animals following prenatal alcohol exposure. West et al. (1981) found that rats exposed to alcohol throughout gestation had abnormally distributed nerve fibers in the hippocampus (deep inside the brain), and Barnes and Walker (1981) identified a decrease in the cell content of rats' hippocampus. In addition, Davies and Smith (1981) identified a considerable decrease in the extent of the neural dendrites (parts of the nerve cell that receive signals) of the hippocampus in mice. Taken together, these anatomic abnormalities in the hippocampus may be the structural basis for some of the behavioral abnormalities observed in humans and animals, as this part of the brain is involved in learning/memory performance and in inhibitory control of behavior.

Alcohol Use, Abuse, and Dependence and Pregnancy

Drinking in Women

Approximately 60 percent of adult American women drink alcoholic beverages; 40 percent are abstinent. An estimated 6 percent of adult women in this country have been clas-

sified as problem drinkers (Clark and Midanik 1982). During the peak reproductive age range of 18-34, an estimated 5 percent of American women consume an average of 2 or more drinks per day or 14 or more drinks per week (Clark and Midanik 1982). Estimates of the proportion of women who drink at least this amount during pregnancy vary widely, ranging from a low of 0.5 percent in parts of California (Harlap and Shiono 1980) to a high of 16 percent in Buffalo (Russell and Bigler 1979), and a median of 2 percent (Abel in press). Because alcohol readily crosses the placenta, yielding levels of alcohol in the fetus almost identical to those in the mother, it is reasonable to conclude that a significant number of unborn children in the United States are exposed to the equivalent of two drinks a day.

Drinking Patterns in Pregnancy

The amount and timing of alcohol consumption that put the fetus at risk are still unknown. Scientists have considerable difficulty in addressing this issue because of problems in obtaining reliable drinking histories and in defining abusive drinking and dependence. Furthermore, drinking patterns often change during pregnancy.

Essentially all reported studies of drinking during pregnancy have relied on self-reports of patients. The inherent limitations of self-reports suggest that the alcohol intake information obtained must be understood in broad terms, rather than in precise measurements. The amount of alcohol actually imbibed in a drink might vary from 1 to 8 ounces, depending on the individual giving the history and the method by which the history is obtained (Rosett et al. 1983). A detailed recall of drinking behavior is likely to be inexact, particularly for the heavy or dependent drinker who may be unable or unwilling to recall specifically how much she drank. Self-reports of drinking during pregnancy are therefore of limited value. This in turn seriously limits the credibility of estimates relating a given number of drinks per day to a particular risk to the fetus. Moreover, it is likely that actual alcohol intake is underreported by the abusive drinker, the individual most likely to be at risk for giving birth to a child with alcohol-related birth defects (Sokol et al. 1981). This could lead investigators to overestimate the risk to the fetus of what might appear to be "two drinks a day."

All investigators studying drinking during pregnancy have been faced with the problems

of obtaining reliable drinking histories and have used a multitude of definitions of problem drinking, abusive drinking, heavy drinking, and alcohol dependence. For example, studies by Rosett et al. (1981), Streissguth et al. (1981), and Kuzma and Kissinger (1981) all used different criteria. Such variances in definition increase the difficulty of making comparisons across studies.

The stage of pregnancy is an important consideration in assessing women's drinking habits because women tend to decrease the amount they drink as pregnancy progresses, an observation first reported by Little et al. (1976) and subsequently corroborated by others (e.g., Rosett et al. 1978; Sokol et al. 1981; Weiner et al. 1983) and by the National Center for Health Statistics neonatal survey as discussed in chapter 1 of this report. Fried and his coworkers (1980) in a study of 217 Canadian women found that prior to pregnancy 18 percent of women were heavy (0.85 ounces per day) social drinkers, but that during the first trimester this proportion was reduced by two-thirds. The proportion of women who were drinking heavily continued to decrease during the last two trimesters of pregnancy. In the Cleveland study (Sokol et al. 1981), the heavier drinking group also was found to decrease its alcohol intake significantly as gestation progressed. These are encouraging findings, inasmuch as decreases in drinking would be expected to minimize birth defects. They point up the problem, however, of attempting to summarize a woman's drinking throughout pregnancy with a single number, e.g., "two drinks a day."

Paternal Drinking

Women who drink heavily tend to be married to men who drink heavily (Gomberg 1975). This suggests that some of the abnormalities described as alcohol-related birth defects might be related to paternal drinking. Long-term consumption by men of large amounts of alcohol is known to be associated with impotence, reduced sperm motility and ultimately loss of sperm, and abnormalities in sperm structure (Lester and Van Thiel 1977). Thus, fertilization with defective sperm is possible, which might result in fetal anomalies. Some investigators have argued that the male parent could contribute to alcohol-related birth defects (Anderson et al. 1981); however, no convincing evidence exists of such paternally mediated anomalies related to alcohol. Recently, Kuzma and Sokol (1982) examined 44

potential determinants of infant birth weight adjusted for gestational age and found no significant effect of paternal alcohol consumption. Similarly, Randall and her coworkers (1982) were unable to detect any effects of chronic paternal alcohol consumption on fetal growth and development in mice, in terms of the number of implantation sites, prenatal mortality, fetal weight, sex ratio, or the frequency of soft tissue malformation. These findings were confirmed by Bennett et al. (1982). Some studies reporting paternally mediated alcohol effects in conjunction with alcohol have had such methodologic flaws as lack of nutritional controls.

Knowledge and Attitudes

Public education efforts concerning risks associated with alcohol use during pregnancy have been actively pursued since the mid-1970s. Broad coverage in the media has been obtained for public health advisories from NIAAA, the American Medical Association, and the March of Dimes on a national level, as well as for an advisory from the Surgeon General (FDA 1981). Public education has also been attempted by many State governments. Most Americans have been exposed to such public health messages, and 90 percent of the respondents in a recent survey knew that drinking during pregnancy might be harmful. However, three-quarters of the respondents who thought abstinence is unnecessary believed that an average of more than three drinks per day was safe (Little et al. 1981). These findings suggest that current public education/prevention programs may not be fully adequate in permeating the public consciousness.

Although knowledge of potential adverse effects of alcohol on pregnancy outcome has changed, and public attitudes have shifted over the past 10 years, the question remains: Has the drinking behavior of women during pregnancy changed? The purpose of a recent study was to compare drinking patterns during pregnancy in the same population in Seattle over a 6-year interval (Streissguth et al. 1983a). Samples of pregnant women were interviewed in 1974-75 and in 1980-81. Although the proportion of women drinking during pregnancy was found to have decreased during the 6-year interval, the proportion of women drinking at least an ounce of absolute alcohol (two drinks) each day was relatively constant. Because precisely this limited proportion of the population incurs the highest risk for al-

cohol-related birth defects, these findings suggest cause for concern.

Conclusions

Although studies of drinking during pregnancy depend upon self-report and the reliability and precision of such data are limited, it appears that drinking during pregnancy is not uncommon. Many women who drink either decrease their drinking naturally or become abstinent during pregnancy. Public education efforts may well reinforce this change in behavior. However, persistently heavy drinking during pregnancy remains a problem for some women despite public education efforts.

Implications of Current Knowledge—Frontiers

The preceding sections have summarized the current status of information concerning risks for alcohol-related dangers to pregnancy and birth defects. Progress in scientific evaluation of these risks has clearly been very rapid over the past decade. However, it is equally clear that many questions remain.

Need for Further Research

Timing, pattern, and beverage source.—Because a reliable biochemical indicator for alcohol intake is not available, clinical investigators must depend on patient reports. However, as previously noted, human drinking is difficult to represent numerically in a single (and simple) measure of alcohol use; volume, frequency, and beverage source of alcohol intake must be considered. Also, other potential determinants of pregnancy outcome, e.g., other substance use, medical/obstetric factors, and socioeconomic status should be taken into account.

Improved measures of alcohol intake would heighten understanding of the stages of pregnancy when drinking is most dangerous to the fetus. Different alcohol-related birth defects might result from drinking during different critical periods, e.g., either early or late in pregnancy. Sulik and her colleagues (1981) suggest that heavy alcohol consumption early in pregnancy might contribute to such birth defects as abnormalities in the face and central nervous system. Studies of the relationship between early pregnancy drinking, particularly binge drinking, and physical congenital anomalies in the human could be valuable.

Heavy drinking in late pregnancy leads to an increased frequency of congenital anomalies (Rosett et al. 1978; Rosett and Weiner 1981). Although organogenesis, the development of the organs of the embryo, may be completed during very early pregnancy, nerve cells, for example, continue to make new connections through pregnancy. Heavy drinking could impair the growth of these connections. The results of animal studies suggest that after toxic substances are withdrawn, the fetus may compensate for earlier impairments with accelerated growth and repair before development is completed (Snow and Tam 1979; Anders and Persaud 1980). Further basic science studies in animals and clinical research in humans regarding critical periods of exposure and the capacity of the unborn offspring for compensatory growth and repair are needed, because the results of such studies might be useful in counseling patients whose fetuses have been exposed to significant levels of alcohol during early pregnancy.

Beverage source (wine, beer, whisky, etc.) may affect infants differentially. Animal studies have been few and inconclusive (Abel 1981b; Abel et al. 1981b). Nonetheless, possible relationships between beverage source and pregnancy outcome have been reported (Kaminski et al. 1978; Kuzma and Sokol 1982; Berkowitz et al. 1982).

Moderate drinking.—Moderate drinking may increase the risk for lowered birth weight (Little 1977), abnormal neurobehavioral development (Streissguth et al. 1980), and spontaneous abortion (Harlap and Shiono 1980; Kline et al. 1980). However, others (Rosett 1980; Sokol 1980b, 1982) have questioned whether the women manifesting these increased pregnancy risks are in fact moderate drinkers. They note that the women with alcohol-related pregnancy risk constitute only the heaviest drinking (5 to 10 percent) of pregnant women. As research continues to expand knowledge, the answers to this important clinical question will emerge.

Susceptibility.—Different species and different strains within a species of animal may differ in their susceptibility to alcohol-related birth defects. Also, differences among animals in the same exposed litter are commonly observed. As noted earlier, human fraternal twins may not be equally affected by alcohol exposure (Christoffel and Salafsky 1975). Such findings suggest the possibility of differential susceptibility on a genetic basis. Interactions

of alcohol consumption with other pregnancy risks, such as poor nutrition, other substance use, or medical illnesses, may also alter susceptibility. Information about interacting risks would help in designing more focused and potentially more effective prevention strategies. A profile of patients particularly at risk for the adverse effects of in utero alcohol exposure also would aid the practitioner in giving direct patient care.

Prevention and Treatment

Problems.—Although major progress has been made over the past decade in understanding the risks of alcohol use during pregnancy, much remains unknown. Methods are being developed to identify and treat pregnant women with alcohol problems (Rosett et al. 1981; Sokol et al. 1981). Education programs aimed at professionals may modify attitudes and clinical behavior (Weiner et al. 1982; Little et al. 1983). Professional education, based on firm scientific evidence concerning risks for alcohol-related birth defects, effective methods of detection of abusive drinking, and treatment methods for abusive drinking and alcohol dependence, appears to be a promising avenue for the prevention of alcohol-related birth defects and other anomalies.

Current statements and recommendations.—Based on currently available information, some broad statements with prevention and treatment implications appear to be warranted. Extensive public education efforts have alerted women to the dangers and fewer American women appear to be drinking during pregnancy. However, the frequency of heavy or abusive drinking may not have decreased. It can be stated with some certainty that those pregnant women who are the heaviest (most frequent) drinkers (about 5-10 percent) are exposing their unborn children to a significant risk. If these women abstain or significantly decrease their drinking during pregnancy, the evidence from both animal and human studies suggests that they can have healthier babies.

Effective prevention strategies for alcohol-related birth defects, including FAS, remain elusive. More information is needed about alcohol abuse and dependence in young women, so that more focused approaches to prevention can be developed. Professional education of

physicians, nurses, and other health care providers may afford a rational and cost-effective approach to prevention of alcohol-related birth defects. If these individuals can be educated to take an active role in influencing the drinking habits of their patients, it may be possible to decrease the occurrence of alcohol-related birth defects and improve the probability of successful pregnancies.

Summary

Heavy drinking during pregnancy adversely affects organic and behavioral fetal development and increases the risks of miscarriage. When consumed in large amounts, alcohol can result in fetal alcohol syndrome. It appears that the overall prevalence of FAS is in the range of 1 to 3 cases per 1,000 births. Alcohol-related birth defects occur more frequently than FAS.

Alcohol can induce abnormal fetal development that varies in intensity, depending on dose, genetic susceptibility, nutritional status, and other as yet unknown factors. Heavy maternal drinking may affect the fetal nervous system, which may result in abnormal neonatal behavior, childhood hyperactivity, and mental retardation.

Alcohol probably affects all organ systems of the fetus, but many questions remain as to the mechanisms and their potential reversibility. Many variables, such as the amount of alcohol and the time during pregnancy of consumption, may influence the nature and degree of adverse effects. Studies in animals suggest that, at high alcohol levels, birth anomalies are directly related to the amount of alcohol exposure.

Public education efforts concerning risks associated with alcohol use have been actively pursued over recent years. These education efforts have encompassed media messages, public health advisories, and programs at the State level. Most Americans have been exposed to public health messages; however, the impact on heavier drinking in pregnancy has been less than desired. One study found that while the proportion of women who drank during pregnancy decreased over the past 6 years, the proportion of women drinking at least two drinks a day had not changed.

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Chapter VI

Adverse Social Consequences of Alcohol Use and Alcoholism

Heavy drinking and chronic alcoholism contribute to a variety of social problems. In addition to accidents involving various modes of transportation, accidents occur in the home, at work, and during recreational activities. Alcohol use also contributes to loss of work productivity, homicide, suicide, and assaultive behaviors. In a 1982 national Gallup survey, one-third of persons interviewed said alcohol had caused problems in their families (Gallup 1982).

Research on the contribution of heavy alcohol consumption and alcoholism to social problems varies in quality. Although the causal link is sometimes weak or nonexistent, the best evidence available strongly suggests that many of these problems are much more likely to arise among alcoholics or heavy drinkers than among other persons. Moreover, the potential for some of these problems to occur may be heightened by even moderate consumption (Moore and Gerstein 1981, pp. 44-45). Since moderate drinkers outnumber heavy drinkers, moderate drinking may actually contribute substantially to social problems. Because most individuals do not believe they personally will experience drinking-related problems, it has been difficult to sensitize the public to social problems caused by moderate drinking.

Alcohol and Accidents

Traffic Accidents

Traffic accidents across the country resulted in 49,268 deaths in 1981 (USDOT 1983). Nearly 150,000 persons are permanently disabled each year in automobile accidents, and 1.8 million persons sustain injuries that restrict their activities for at least 1 full day after a crash (National Safety Council 1982). During the past decade, more than 450,000 traffic accident fatalities constituted the fifth leading overall cause of death in the United

States and the leading cause of death in the 1- to 35-year-old age group (Ross 1982).

After analyzing case reports, simulated driving conditions, and epidemiologic data, researchers have consistently and unequivocally concluded that alcohol contributes significantly to traffic accidents. The higher the amount of alcohol consumed, the greater the likelihood that an accident will occur and that the accident will be serious or fatal.

In a report to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Cameron (1977) cited 23 studies showing that at least one-third of the drivers in fatal accidents had blood alcohol concentrations (BACs) exceeding .10 percent. This effect roughly equals that in a 155-pound man who consumed at least five or six drinks or more within an hour. Estimates place the annual number of deaths in traffic accidents in which at least one driver had been drinking at 16,000 to 30,000 (Roizen 1982). Between 20 and 40 percent of people killed in these drinking-driving accidents were persons other than the drunk driver (Reed 1981).

Borkenstein and colleagues (1974) interviewed Indiana drivers about their drinking and tested their blood alcohol contents. Regardless of the frequency with which drivers reported drinking, elevated BACs increased crash probabilities. Studies comparing drivers in fatal accidents with drivers not involved in accidents in similar locations at similar times suggest that drivers with BACs above .10 percent are 3 to 15 times more likely than nondrinking drivers to be involved in a fatal crash (Cameron 1977). For young drivers, in particular, the risk of a fatal crash increases sharply with increasing BAC levels (Perrine et al. 1971; Wagenaar et al. 1981). For further discussion of this topic, see tables 4 and 5 in chapter 1 of this volume.

Because of the high risk of fatal accident involvement after heavy drinking, the risks posed by driving after moderate drinking are sometimes overlooked. According to studies in New York City (McCarroll and Haddon 1962)

and Vermont (Perrine et al. 1971), even drivers with BACs of .05 percent to .099 percent are 1.25 to 3.25 times more likely to be involved in fatal accidents than nondrinking drivers. According to the U.S. Department of Transportation (Fell 1982), while 50 percent of fatally injured drivers had BACs above .10 percent, 12 percent had elevated BACs between .01 percent and .10 percent. Reed (1981) has estimated that if all drivers in this country in 1977 were only exposed to the risk of drivers who do not drive after drinking, there would have been 24 percent fewer accidental deaths (11,700 deaths prevented) and 156,000 to 300,000 fewer injuries.

Alcohol contributes to traffic accidents by affecting cognitive and behavioral function, often in multiple ways in the same accident. Alcohol in the blood at levels above .10 percent is known to (1) lower divided attention performance, (2) reduce dynamic visual activity, (3) reduce adaptation to brightness and glare resistance recovery, and (4) reduce ability to see flickering lights, e.g., turn signals (Perrine 1974). Some researchers believe alcohol also interferes with the brain's ability to process large quantities of information at one time (Moskowitz 1974). Still others cite the sedating, fear reducing, and disinhibitory effects of alcohol on aggressiveness or self-destructiveness. Cognitive effects such as short-term memory loss or learning deficits may also contribute to accidents (Barry 1974). Those willing to drive after heavy drinking, of course, may generally engage in high risk-taking behavior and may be impulsive and careless (Jones and Joscelyn 1978). This may place them at increased risk for highway accidents regardless of their drinking behavior.

Most researchers concur that chronic heavy drinkers or alcoholics are more likely than light drinkers or nondrinkers to be involved in traffic accidents (Fell 1982). Estimates vary widely, however, on the proportion of accidents involving each category, largely because of variable criteria for diagnosing alcoholics. Klatsky et al. (1981) compared 2,015 Kaiser Permanente plan members who averaged six or more drinks daily with 6,045 light drinkers and nondrinkers matched by age, sex, race, cigarette use, and city. Those who reported drinking more than six drinks daily were three times more likely than the rest of the sample to die in a traffic accident during the subsequent 10 years.

Although persons with a previous driving-while-intoxicated (DWI) arrest run a higher accident risk than other drivers, they are in-

involved in only a small fraction of fatal accidents. Sterling-Smith (1976) reported that of drivers known to be responsible for fatal accidents in the early 1970s in Massachusetts, only 4 percent had a previous DWI arrest, about one-tenth of those in the study with a BAC above .05 percent. The implication is that even highly successful rehabilitation programs aimed at the arrested drunk driver may influence only a small minority of drunk drivers. If the percentage of drunk drivers who are arrested increases, however, these successful rehabilitation percentages may increase.

Despite widespread awareness of its risk, drunk driving occurs relatively frequently. Researchers have estimated that at any given time 2 to 3 percent of the driving population are legally intoxicated, and that the percentage doubles at night or on weekends, the hours during which accidents are most frequent (Damkot et al. 1977; Haddon and Blumenthal 1981). As many as 20 percent of nighttime drivers randomly stopped have been found to have measurable BACs (Damkot et al. 1977). Statewide random sample surveys of nearly 1,000 adults in Massachusetts in 1981 indicated that 29 percent of drivers report driving after drinking at least four times in the prior month, and 4 percent report driving after six or more drinks at least four times a month. Males, persons who are unmarried, and those under age 25 most often reported driving after drinking heavily (Hingson et al. 1982a, 1983).

At least three reasons explain why people drive after drinking. First, a considerable number of people who drink do not know the level of drinking that makes individuals legally too intoxicated to drive. The 1981 Massachusetts survey indicated that 10 percent of the respondents who drive did not know the level of legal intoxication, and 17 percent felt that a person can drink six or more drinks without being legally too drunk to drive. Second, even though the relative risk of accident involvement for persons who drive under the influence is much higher than for nondrinkers, the probability of an accident during a trip when the driver is under the influence is still quite low, only about 2 per 1,000 trips (Ross 1982). The risk of arrest is roughly comparable, after which the drunk driver would still stand only a 50-50 chance of being punished (Jones and Joscelyn 1978; Ross 1982). Finally, driving after drinking has long been considered socially acceptable behavior. While political and social pressures have prompted 34 States to change their drunk driving laws during the past

2 years (Volpe 1982), it is not clear whether this will substantially alter public complacency about drunk driving and the frequency of its occurrence.

Pedestrian Accidents

At least 8,000 pedestrians are killed and 100,000 injured each year by motor vehicles. Research indicates measurable BACs among fatally injured pedestrians ranging from 35 to 74 percent (Blomberg et al. 1979).

Only two studies compared fatally injured pedestrians with noninjured pedestrians who passed the same spot at a similar time of day and day of week (Haddon et al. 1961; Blomberg et al. 1979). In the more recent and more extensive study (Blomberg et al. 1979), between July 1972 and March 1976, postmortem BAC results were obtained on all 86 fatally injured pedestrians taken to a New Orleans hospital. All 180 injured pedestrians taken to the same hospital between March 1975 and March 1976 were also tested. Pedestrians who passed the same site within 30 minutes of the accidents on the same day of the week and year were also stopped; 1,208 of 1,469 eligible control respondents were given blood alcohol tests and interviewed.

Thirty-six percent of the injured pedestrians had BACs over .10 percent, as did 45 percent of the pedestrians who died. Only 13 percent of controls had BACs at that level. Compared with age- and sex-matched nondrinkers, the risk of accident involvement for pedestrians was two times higher with BACs above .10 percent and five times higher for those with BACs above .20 percent. The relative risk rose rapidly as the blood alcohol concentration increased beyond .20 percent.

Driver error was less frequently the cause when the pedestrian had been drinking. Alcohol-involved accidents were more frequent among male pedestrians aged 20 to 49 and tended to cluster on weekends and at night.

Airplane Accidents

Alcohol is also a factor in aviation accidents (U.S. National Transportation Safety Board 1979). In 678 fatal plane crashes nationwide in 1979, alcohol impairment was identified in 30 pilots, most of whom had BACs above .10 percent. Because the proportion of pilots who fly after drinking and the proportion of flight time under the influence are not known, however, the relative risk of aviation accidents at various drinking levels is yet unclear.

Occupational Accidents

Work-related accidents were responsible for 13,000 fatalities in 1980, and 80,000 persons were permanently disabled, partially or totally (National Safety Council 1982). National survey data suggest that yearly 25 percent of workers sustain some sort of injury on the job (Quinn and Shepard 1974). About 35 percent of the work-related fatal accidents are represented in the traffic accident statistics already cited.

Accidents on the job are not as extensively researched as traffic accidents; less is known about their occurrence and contributory factors (including alcohol). Baker and associates (1982) indicated that in 1978, 148 Maryland workers died in job-related accidents. Blood alcohol concentration levels were obtained on 79 percent of those from whom BACs could technically have been obtained. About 11 percent of both motor vehicle fatalities and fatalities from other causes had BACs above .08 percent. In contrast, according to a national survey of workers (Quinn and Shepard 1974), only 2 percent of the working population can be expected to drink on the job on any given day. Although the types of jobs and worker characteristics in a national sample may systematically differ from those in Maryland, these data suggest that people who have fatal accidents on the job were much more likely than other employees to drink at work.

Given the well-established relationships between blood alcohol levels and poor coordination, faulty judgment, and lengthened reaction time, it is plausible that alcohol often contributes to accidents at work. Of course, the risk may well vary with the type of work.

Some data also suggest that alcoholics are more likely than other workers to experience work-related accidents, but the results have not been consistent. Shain (1982) studied one firm located in the eastern United States and found that alcoholics are two to three times more likely than other employees to be involved in work accidents, but alcoholism was not adequately defined in this study. Trice (1965) compared 72 alcoholic employees with "normal" employees and found no relation between alcoholism and accident involvement during the 5 years preceding and 1 year following diagnosis.

Additional research is needed on alcohol use and alcoholism as they affect accident involvement at work. Research priority should be given to (1) national or regional surveys to

determine the prevalence of on-the-job drinking and the incidence of accidents after drinking, (2) systematic BAC testing on all occupational fatalities, and (3) case control studies comparing alcohol use by employees involved in occupational accidents with that of employees who work at similar jobs but were not involved in accidents.

Valid data may be difficult to obtain because of legal questions concerning financial responsibility for defective products as well as worker compensation when the worker had been drinking prior to the accident. Furthermore, other characteristics that contribute to drinking on the job (job boredom, stress) could independently relate to accident involvement.

Home and Recreational Accidents

Nationwide, in 1980, 22,800 persons died and another 90,000 were permanently injured in home accidents. Falls accounted for about one-third of home accident deaths, and burns or injuries resulting directly from fires comprised another 20 percent. Outside the home, 21,000 persons died and 60,000 were permanently injured in non-motor-vehicle accidents such as falls, drownings, and other recreational accidents. From 1970 to 1980, the sharpest declines in fatal accident rates--about 25 percent--were recorded in these groupings (National Safety Council 1982).

The role of alcohol is less well understood in home and nontransportation accidents than in traffic accidents because on-the-scene investigations are less frequently conducted and most studies are undertaken in hospital emergency clinics. Moreover, because these accidents encompass a wider variety of circumstances, identifying specific causes for each accident type is more difficult. Since different researchers use different taxonomies, it is difficult to combine the results into effective generalizations.

The few studies available suggest that alcohol may contribute to some of these accidents. Wechsler et al. (1969) compared home accident admissions with emergency room admissions for other reasons, e.g., circulatory or digestive disorders. Twenty-two percent of 620 patients in home accidents had positive BACs compared with 9 percent of nonaccident patients. Eleven percent had blood alcohol concentration levels above .05 percent compared with 3 percent of nonaccident patients. The relationship was statistically significant even after adjusting for age, sex, and socioeconomic status of persons in each group.

In a review of the available literature, Wingard and Room (1977) identified only a half dozen U.S. reports since 1950 on alcohol and fatalities from falls, drowning, and fire-related injuries. Since studies showed a considerable variation in the proportion of fatal accident victims in whom alcohol was present, it is not clear whether alcohol is more likely to be involved in certain types of accidents.

Haberman and Baden (1978), in a report on 121 falling, fire, and drowning deaths in New York City between 1974 and 1975, indicated that 43 percent of such victims had blood alcohol concentrations above .10 percent. That proportion actually exceeded the proportion of motor vehicle and pedestrian accidents involving blood alcohol at that level during the same time period. Only about half the accidents in each of those categories during that time period were available for study. Yet, even if all the omitted accidents did not involve alcohol, 20 to 25 percent of the falls, burns, and drownings would still have occurred to persons with BACs above .10 percent. In contrast, on any given day one can expect only 3 percent of the population in a large urban area to consume the equivalent of five or more drinks, the amount needed to achieve a BAC of .10 percent (Hingson et al. 1981). However, the proportion of persons in similar social and demographic groups as those in accidents who consume that much has not been determined.

Alcohol's contribution to accidents may vary by type of accident. In some, such as falls, alcohol may reduce sensory motor coordination. In drownings, alcohol may contribute by increasing the risk-taking behaviors of swimmers or boaters or by reducing coordination so that capsizing is more likely. Once the person is in the water, alcohol may hasten a loss of body heat (Stanley and Siegal 1981). Alcohol may prompt smokers to fall asleep and risk cigarette fires (Levine and Radford 1977).

Some studies compare death rates from accidents of alcoholics or heavy drinkers with those of the rest of the population. When Brenner (1967), Nicholls et al. (1974), and Schmidt and de Lint (1972) compared alcoholic samples with matched age- and sex-specific populations, they found a 5 to 13 times greater risk of dying from falls among alcoholics. Schmidt and de Lint also reported a tenfold increase in death rates in fires among alcoholics. Social class and possible living environment differences between the groups were not, however, controlled in these studies. In the study of 2,015 Kaiser Permanente Health

Plan members (Klatsky et al. 1981), heavy drinkers were 2.7 times as likely as the overall sample to die in an accident (other than traffic accident) during the subsequent 10 years. Specific comparisons on the types of accident were not made and none of these studies examined alcohol consumption immediately prior to the accident.

Of course, using alcohol or being alcoholic is only one of many factors that contribute to such accidents, and its presence does not necessarily imply a causal role. Research is needed to assess when alcohol may have an independent effect beyond other factors such as age, architecture, poverty, poor housing, and smoking. The national fire survey does not query fire witnesses and victims about alcohol, even though drinkers are much more likely than nondrinkers to smoke and smoking is well known to relate to the incidence of fires (FEMA 1982). Case control studies that compare persons in falls with persons passing similar locations at similar times of day who do not fall would help establish the relative risk for intoxicated persons.

Alcohol and Crime

Homicide

In 1980, there were 22,516 murders in the United States or 9.8 per 100,000 inhabitants. The rate per 100,000 inhabitants rose 11 percent since 1976 (USDOJ 1981).

It has long been recognized that alcohol is frequently present in both perpetrators and victims. Wolfgang's landmark study (1958) in Philadelphia indicated that either the victim or the offender or both had been drinking in nearly two-thirds of the slayings he studied, and in 44 percent, both parties had been consuming alcohol.

Roizen and Schneberg (1977) identified 11 studies that reported a range of alcohol involvement in from 28 to 85 percent of arrested offenders. Greenberg's review (1981) of 28 studies indicated that a majority of victims or offenders or both drank prior to the crime. Reports of involvement varied somewhat by type of study. Studies of police reports and arrested populations identified alcohol in 66 percent of cases, whereas 9 prison studies identified its involvement in 44 percent of cases. In 4 of 5 studies reviewed by Greenberg (1981), at least 20 percent of the individuals who committed murder also had an alcoholism problem.

These findings have prompted some researchers to hypothesize a direct causal relationship between heavy alcohol consumption or alcoholism and murder. Numerous theories attempt to explain how alcohol may be directly related to violent crime (Pernanen 1981). To cite a few:

- Alcohol may reduce inhibition and release violent impulses.
- Alcohol may alter neurotransmitter activity.
- Chronic excessive alcohol use may lead to temporal lobe dysfunction, which in turn may contribute to violent behavior.

Still others argue that alcohol use contributes to violence only in the presence of such conditions as hypoglycemia, produced by poor nutrition among chronic heavy drinkers, or persistent lack of REM (rapid eye movement) sleep activity as a result of prolonged drinking. Either of these factors may produce heightened irritability among drinkers.

However plausible these theories may be, no studies to date provide clear evidence that alcohol is an independent causal factor in murder. According to Collins (1981), "the number of scientists arguing for direct and simple relations between the presence of alcohol and crime has decreased as the complexity of logic and sophistication of designs has increased." MacAndrew and Edgerton (1973), using cross-cultural analyses, suggest that behavior while intoxicated may depend more on what is considered socially acceptable while intoxicated than on disinhibitory effects.

Several researchers have also noted that some variables simultaneously contribute to both alcohol use or alcoholism and crime, possibly making the alcohol-crime relation coincidental rather than causal. For example, heavy drinking is more apt to occur in marital situations in which neither partner is satisfied or happy (Hingson et al. 1981). While such situations may also be more likely to result in murder, it is difficult to say whether alcohol and/or the underlying unhappiness contributed to such murders.

Similarly, Wolfgang (1967) has cautioned that drinking is a part of the mores of low-income young males, the group involved in most murders. But tension and frustration may also be more common among this subgroup, which in turn prompts some to commit murder as well as to drink. Also, alcohol use and vio-

lence are both more likely to be found in settings (e.g., bars) where low-income young males congregate. It is difficult to establish whether alcohol contributes to violence, or whether it at times even helps avert violence and murder by relieving tension and frustration.

Few studies in this area attempt to control for these possibly confounding factors. Of 35 studies on crime reviewed by Greenberg (1981), only 5 controlled for age, sex, and race, factors related not only to the incidence of murder but also to drinking.

Other methodologic limitations of the existing research on this topic have been discussed by Roizen and Schneberk (1977). Distinctions are seldom drawn between presence of alcohol and actual intoxication, and length of time since alcohol ingestion is rarely indicated. Data are collected at different points in the judicial process: arrest, court, and prison. The limited data available suggest that murderers who had been drinking and are caught are more likely to be convicted and hence overrepresented in prison populations (Greenberg 1981). In all studies of murder, the definition of the crime itself may be blurry; for example, manslaughter and homicide may be combined.

The presence of alcohol in the victim is not clearly and adequately understood. The few studies of victims suggest that they were frequently drinking. It is possible that drinking victims who had been drinking either lacked adequate judgment to avoid antagonizing the offender or were unable to modify the offender's anger in some way (Braucht et al. 1980). It is also possible that intoxication rendered victims less able than sober persons to defend themselves or to avoid an attack.

In studies of homicide and alcoholism, the presence of alcohol at the scene and time of the crime is seldom identified. Moreover, alcoholics are more likely to have court records such as DWI offenses, loitering, etc., and hence to be known by police. This has prompted some researchers to ask: Are alcoholic criminals more likely to get caught? (Roizen and Schneberk 1977).

It should be kept in mind that the majority of criminal offenders are not alcoholics and the majority of alcoholics never commit serious crimes (Collins 1981). Even explanations that identify alcohol as a potential contributor to violence cite other contributors as well, e.g., hereditary factors, brain dysfunction, availability of guns, media violence, and numerous other social and psychological factors

(Collins 1981; Menuck and Voineskos 1981). According to Blum (1981), "Under no circumstances will alcohol be a sole cause of violence."

In sum, alcohol use is part of the lifestyle of low-income young males, those most apt to commit or be involved in murder. Even if drinking may have disinhibitory effects or long-term effects on mental functioning that in turn contribute to violence, it is unrealistic to cite alcohol as the major cause of the frustration and anger in this population that also contribute to high murder rates. Nor, however, is it realistic to dismiss alcohol as irrelevant. Alcohol may alter perceptions, cognitive performance, moods, emotions, and response capabilities and preferences. The frequent association of alcohol among murderers and their victims suggests it is more than coincidental.

It is reasonable to expect that alcohol is more likely to contribute in some types of murders than in others, e.g., quarrels among family members, friends, and acquaintances that escalate into murder. Alcohol is less likely to be involved in premeditated murders in which the perpetrator makes careful plans to avoid detection. At this point, because of inherent difficulties in studying murder and limitations in available research about alcohol and murder, one can conclude only that alcohol may be one of numerous factors that at times may independently contribute to some types of murder.

Rape

In 1980, there were 36.4 forcible rapes reported per 100,000 persons in the population, or 82,088 rapes (USDOJ 1981). This rate has steadily increased 38 percent from 1976 to 1980 in part because of changing public and law enforcement attitudes, the push from women's groups to encourage victims to report rapes, and the general increase in violent crime in the United States.

Rape is an extremely difficult crime to investigate (Rabkin 1979). Local legal codes, police enforcement, and public attitudes toward rapists and victims vary greatly by region, resulting in different reporting and recording rates. Low reporting and conviction rates limit inferences about the characteristics of rapists. In general, studies of rape draw from interviews and other data collected from apprehended rapists, who may differ from undetected rapists.

In a study of violent crime in Western Canada (Gerson and Preston 1979), 60 percent of the rapes in a 12-month period were considered to be alcohol related; either the victim or the defendant had been drinking, and the crime involved violation of an alcohol statute or occurred in a licensed alcohol establishment. Groth (1979) found that 50 percent of a group of men who raped older victims reported being high on alcohol or on alcohol and drugs.

Rada and his colleagues (1978), in a study of 382 rapists in a State mental institution, found that 81 percent of the alcoholics and 25 percent of the nonalcoholics drank before the assault. In another population, 53 percent of mentally disturbed sex offenders reported drinking heavily (Rada et al. 1978). In contrast, in a general urban population 36 percent of males can be expected to drink on any given day (Hingson et al. 1981). A more appropriate comparison would match nonrapists with rapists on other social and economic characteristics to see whether their drinking levels differ.

Few studies have examined the related question of frequency of alcoholism among rapists. Rada et al. (1978) found that 33 percent of 77 rapists had a history of alcoholism. Twenty-seven percent of 82 rapists in another group of subjects (Barnard et al. 1979) were identified as alcoholics. The proportion of alcoholics in the general population is much lower.

These studies suggest that people who commit rape are disproportionately likely to have been drinking or to be alcoholics. However, the reasons for this alcohol-rape connection are not well understood. Wilson (1981) reviewed two major theories. Disinhibition theory suggests that alcohol releases otherwise well-controlled sexual or aggressive behaviors. An alternative explanation based on social learning principles suggests that behavior after consuming alcohol is determined by past learning about the effects of alcohol on actions and by personal expectations about the consequences of a certain course of action. A social learning model of alcohol-associated rape might suggest that alcohol consumption is seen as a way to disavow responsibility for actions and thereby avoid external punishment, social disapproval, or internal guilt for attempting rape.

In conclusion, it appears that alcohol consumption and rape may be associated, but this link may have been overstated. Some rapists may actually plead drunkenness or alcoholism as a way to avoid legal responsibility for the

crime. Thus, the role of alcohol in rapes is still poorly understood.

Other Crime

The relationship of alcohol to other crime is even less clear. Data on the characteristics of perpetrators should be considered with much greater caution than those of murder offenders since a lower proportion reach the attention of the police.

Fewer studies have been undertaken on alcohol involvement in other crimes than in murder. Table 1 indicates the relative alcohol involvement for these crimes in contrast to murder (Greenberg 1981). Compared with murder, the proportion of these crimes with alcohol involvement appears to be lower. Because, with the exception of aggravated assault, most of these crimes are premeditated and carried out with the intent of avoiding arrest, it is unlikely that alcohol will be as strong a potential contributor as in crimes of passion and violence.

Alcohol and the Family

Separation and Divorce

The annual divorce rate in 1977 in the United States among women over the age of 15 was 21 per 1,000. These rates have been climbing steadily since 1967 (USDHHS 1980). Evidence suggests that the rate of separation and divorce among alcoholics and their spouses is seven times that of the general population (Paolino and McCrady 1977). Forty percent of family court problems involve alcoholism in some way (Jacob and Seilhamer 1982), and it is estimated that 33 percent (Jacob and Seilhamer 1982) to 40 percent (USDHEW 1975) of intact alcoholic couples have poor marital relationships.

Alcohol is clearly associated with disrupted family functioning, but the marital and family problems may precede the alcoholism, may occur solely as a result of the alcoholic's drinking and behavior changes, or may be part of a complex interaction between preexisting weaknesses of the family or of individuals in the family and the drinking of one family member.

Family Violence

The abuse of children by their parents, and the abuse of spouses by their marital partners,

Table 1. Alcohol involvement in criminal events, by type of crime

Percentage of crime victims or offenders in whom alcohol was present during criminal event ^a	Frequency of studies							
	Homicide	Sexual offenses	Aggravated assault	Robbery	Burglary	Larceny	Auto theft	Forgery/ bad checks
0 - 10	2	-	-	-	-	1	-	-
11 - 20	4	-	1	1	1	-	-	-
21 - 30	-	2	2	-	-	-	-	-
31 - 40	2	1	-	-	2	-	-	-
41 - 50	2	3	1	-	-	1	1	1
51 - 60	4	1	-	1	1	1	1	2
61 - 70	4	1	3	2	1	1	1	-
71 - 80	2	-	-	1	-	1	-	-
81 - 90	7	-	-	-	1	-	-	-
91 - 100	1	1	1	-	-	-	-	-
Total studies ^b	28	9	8	5	6	5	3	3

^a These percentages reflect the presence of alcohol, as defined in a variety of ways, immediately prior to or during the crime. The number upon which the percentages are based are therefore either total cases (victims) or total offenders. In studies in which drinking on the part of both victims and offenders is reported, the percentage of victims only is reported in this table.

^b This table is based on the findings of 35 studies. The grand total does not add to 35 because some studies include data on only one type of crime, while others include two or more types of crime and therefore appear in more than one column.

Source: Greenberg 1981.

have received increasing attention in the media and in the professional literature. Self-help groups for parents who abuse their children (e.g., Parents Anonymous) and shelters for battered women have proliferated throughout the country.

The study of family violence, however, is an extremely sensitive, emotionally laden, and difficult pursuit. The definitions of abuse vary widely, and incidents of abuse are markedly unreported. Research in this area is hampered by the traditional sanctity of the family and the blurred lines between acceptable family behavior and abuse.

Most studies that have attempted to understand causes for family violence, or the links between violence and alcohol use, have

sampled individuals in treatment. Such individuals represent only that fraction of the abusing population who have admitted they have problems, or whose abuse has become severe enough to come to the attention of outside authorities, who required that they undergo treatment.

Finally, many attributions of violence are based on retrospective reports of the abuser, the victim, or a third party. Recall may be faulty, making attribution of violence to drinking or drunkenness suspect. One party may place primary emphasis on drinking that another would see as immaterial, or alcohol use may be presented as an excuse for violent behavior. Aarens et al. (1977) noted in one study of domestic violence that the com-

plainant stated that the abusive party was drinking or drunk much more often than was noted by the police. Finally, alcohol consumption may be irrelevant or coincidental or may have created or contributed to a conflict that culminated in violence.

Child abuse.--This discussion does not consider child neglect or failure to provide necessary food, shelter, or medical care but instead focuses on willful commitment of injury to the abused person. A national survey conducted in 1965 revealed that 2 to 4 percent of the adults surveyed personally knew families in which child abuse had occurred in the previous year (Gil 1970). Three literature reviews concerning drinking, alcoholism, and child abuse (Aarens et al. 1977; Hamilton and Collins 1981; Orme and Rimmer 1981) identified only three studies that determined the frequency of drinking during actual episodes of child abuse. Two of these note that 12 percent of abusers were drinking at the time (Gil 1970; Thomson et al. 1971), while only 3 to 6 percent were drinking in the third study (Scott 1973).

When considering the frequency of alcohol problems or alcoholism in child abuse cases, reports range from "no association" to 38 percent of abusers' having alcohol problems. The most frequently reported figures are that between 11 and 17 percent of abuse cases involve alcoholism.

Overall, the currently available evidence does not indicate a strong association between drinking or alcoholism and child abuse. As Orme and Rimmer (1981) concluded, "When estimates of alcoholism and alcohol problems in the general population were available, the prevalence appeared to be almost identical to that in child abusers" (p.284).

Spouse abuse.--Figures on spouse abuse tend to focus almost exclusively on the abuse of women by their husbands or lovers. During 1978, 6.6 percent of murder victims were women killed by either their husbands or their lovers (USDOJ 1981). Hamilton and Collins' (1981) review of 15 studies suggested that 17 to 35 percent of divorces involve violence.

Hamilton and Collins (1981) reported that most studies cite alcoholism or excessive drinking in 45 to 60 percent of spouse abuse. Most of these reports of alcohol problems come from the female victims of the abuse. These women may exaggerate or overestimate the seriousness of their partners' drinking or may prefer to believe their mates have a

drinking problem rather than accept other reasons for the abuse (Aarens et al. 1977; Hilberman 1980). Estimates of actual alcohol consumption at the time of abuse vary from 29 to 71 percent, although virtually all these figures are based on victim recall and were not verified by objective means such as BAC analyses.

Several theories have tried to explain the role of alcohol in spouse abuse. Gelles and Straus (1979) have suggested that alcohol is used as an excuse for violence because, when drunk, a person may deny responsibility for his or her actions. Denial of responsibility for actions when drinking is common in American society (Richardson and Campbell 1980). Social learning theorists (Wilson 1981) suggest that people learn to expect to behave more aggressively when drinking and therefore do so, even if the alcohol itself does not have a direct disinhibitory effect on their behavior. These two models are in direct contrast to disinhibition theory, which suggests that alcohol directly disinhibits people so that they express their real, underlying aggressive impulses. A fourth model suggests an interactive relationship between drinking and violence (Gelles 1972; Pernanen 1976). Arguments about a husband's drinking may escalate into arguments about many areas of marital problems. The alcohol may diminish the drinker's ability to reason and to control his behavior, resulting in a growing conflict that may culminate in violence.

Child Functioning in Alcoholic Families

The complexity of individual, family, and social factors that interact in a child's development makes it difficult to attribute a child's particular problems or personality solely to a parent's alcoholism. The study of children of alcoholics is further complicated by the methodologies usually employed. Children in treatment often form the basis of research samples, but they reflect only the fraction whose problems are serious enough to come to the attention of treatment agencies and who are able to find such agencies. Children whose parents are in alcoholism treatment are another common yet not fully representative sample, as many people with serious drinking problems never reach treatment (Hingson et al. 1981, 1982b). Attempting to gain access to children and their families who are not connected to the treatment or social services system, however, raises diagnostic and ethical issues. When asked about parents'

drinking, for example, a child may feel he or she is betraying the parent or may fear retaliation and therefore minimize parental drinking. Even if the situation is accurately identified, obtaining parental permission for the child to participate in a research study may be difficult. Ethical questions arise also if such children in the course of a study become labeled by a social institution (e.g., their school) as socially deviant by virtue of being the children of alcoholics.

Woodside (1982) has reviewed the available data on children of alcoholics. Hyperkinesis has been suggested as one consequence of parental alcoholism. Although early studies suggested that alcoholism was twice as frequent among parents of hyperkinetic children as among normal controls, more recent data fail to support this finding (Morrison 1980; Stewart et al. 1980). Children with at least one alcoholic parent are more likely to have a childhood history of school problems and anti-social behavior than other children (Sher and McCrady in press). Other studies reviewed by Woodside (1982) have found lower self-esteem, more emotional detachment, more anxiety symptoms, more social aggression, or more psychosomatic symptoms (such as headaches or stomach aches) among children of alcoholic parents than among control children. Most of these associations have not been replicated, however, and do not explore what mechanism may lead to the childhood problems or what protects some children from such problems.

Summaries of unstructured or semistructured interviews with children of alcoholics (Cork 1969) suggest that these children feel rejected by their parents, guilty or somehow responsible for the parent's alcoholism, resentful of the alcoholic parent, and in constant fear. However, most of these studies focus on the casualties of alcoholism--the children in trouble. One notable exception sought to understand what factors spare certain children (Wolin et al. 1980). They found that alcoholic families that maintained some predictable structures, particularly around the observance of family rituals (at meals, holidays, etc.), were less likely to produce alcoholic offspring than families with disrupted family rituals.

Alcohol and Suicide

About 27,000 Americans commit suicide each year (Hendin 1982), but 10 times as many persons make unsuccessful suicide attempts. The overall rate of suicide, at 12.5 per 100,000

persons, remained fairly stable from the 1940s to the 1960s and has increased only slightly since then. Suicide among young people 15 to 24 years of age has increased dramatically, however, by 250 percent among young women and more than 300 percent among young men. There are 100 to 200 suicide attempts for every completed suicide of a high school youth.

The other high-risk population group includes white men over 45 years of age, who commit 30 percent of all suicides each year, even though they represent only 10 percent of the population. Men who are alone or have suffered recent losses are at particular risk. Black men are at their highest risk for suicide between the ages of 20 and 34, rather than when they are older (Hendin 1982).

In some situations, alcoholism may contribute to a number of problems that may in turn precipitate suicide. Separation and divorce rates are high among alcoholics (Paolino et al. 1978). Depression is common among alcoholics during prolonged drinking bouts as well as during some phases of alcohol withdrawal, and alcoholism also causes numerous debilitating and life-threatening medical problems; suicide may become a response to any of these problems.

Because suicide has many causes, however, it is difficult to discern the contributory role of alcoholism when it coexists with other problems. As many as 25 percent of female alcoholics, for example, have diagnosable depression (Schuckit and Morrissey 1979). If such a patient commits suicide, it is impossible to determine to what the suicide should be ascribed--depression or alcoholism.

Individuals use alcohol in an attempt to cope with life problems. A person facing a divorce, the death of a parent, or a serious illness may drink and, in fact, may develop a serious drinking problem. If this person commits suicide, is the suicide a result of the alcohol abuse or of the original life problem?

A number of problems with research methods further muddy the waters. Social pressures often lead to underreporting of suicide, and family members may be reluctant to acknowledge the alcoholism of a deceased relative, thus obscuring the suicide-alcoholism association. Diagnosing alcoholism based only on survivors' reports is also difficult, especially when attempting to distinguish between alcoholism and other psychological disorders. Blood alcohol levels are not always determined when someone dies. Finally, the assessment of intent of a death is sometimes problematic.

For example, a person who dies from combined drug and alcohol ingestion may have planned his or her death, or may have been unaware of the way the substances could potentiate each other. Likewise, a person who dies in a single-car accident after drinking might have deliberately caused the accident or may have simply lost control of the vehicle.

Keeping in mind these research limitations, the Fourth Special Report (USDHHS 1981) cited studies indicating between 15 and 64 percent of suicide attempters and up to 80 percent of suicides had been drinking at the time of the attempt. The wide range of percentages makes it difficult to assess whether drinking is in fact causally linked with attempts. A review of violent deaths in the Cleveland area (Ford et al. 1979) found alcohol present in 25 percent of suicide victims. Of course, determining whether drinking is independently associated with suicide would require identifying populations of similar socioeconomic status, age, race, and sex as those who commit suicide. It is particularly important to compare populations with similar sociodemographic characteristics, as suicides occur disproportionately among the young and among older single males. The presence of alcohol in the blood stream of a suicide attempter at the time of the act provides insufficient data to conclude that alcohol is independently related to the attempt. Evidence is available that alcoholism or a history of drinking problems is more common among suicide attempters. Roizen (1982) indicates that most studies reported that more than 10 percent of attempters and completers had drinking problems.

Aarens et al. (1977) provide stronger data, comparing the proportion of problem drinkers or alcoholics in a random sample survey with Beck and associates' (1975) sample of suicide attempters in two large metropolitan hospitals. The survey data were standardized by age, sex, and marital status to match the suicide population. These data indicated that suicide attempters were four to six times more likely than the general population to report being problem drinkers or alcoholics.

Several studies have also shown that, as a group, alcoholics are more likely over the course of their lifetimes to commit suicide. Reviewing reports from 1935 to 1970, Miles (1977) estimated that 15 percent of alcoholics ultimately complete suicide. Another review suggests that 6 to 12 percent of alcoholics commit suicide, compared with 1 percent of the population. Klatsky et al. (1981) reported

that persons who consume more than six drinks a day as a group were twice as likely to die from suicide over a 10-year followup period than age- and sex-matched light drinkers and abstainers. It was not indicated whether these people were drinking at the time, but suicidal actions are more likely to be damaging when people have been drinking; combinations of alcohol with other drugs often have greater lethal potential (Eckardt et al. 1981).

Economic Costs of Alcohol Abuse

Alcohol and Work Productivity

Foregone work productivity is widely accepted to be an important component of the costs of alcohol abuse. The proliferation of occupationally based alcoholism programs may in part be attributed to increased employer awareness of excessive alcohol use and compromised job performance. No one has been able to precisely identify the worker productivity costs of alcohol abuse; the majority of studies have examined simple measures such as absenteeism.

A study of alcohol problems in seven railroad companies examined absenteeism as well as several empirical measures of lost productivity. Problem drinkers had almost twice the absenteeism of other workers and cost the company an estimated \$3.1 million, assuming 5.2 extra days of absence per year for the 8,670 employees for whom adequate attendance records were available and based on an average employee salary of \$18,000 (Mannello 1979).

Cost-benefit studies of occupational alcoholism programs generally support the claim that productivity losses attributable to alcoholic employees can be reduced. These studies generally focus on absenteeism rates among a treated group of alcoholic workers before and after an intervention. For example, Wood (1980) suggested that an occupational alcoholism program sponsored by New York Telephone Company saved the firm \$1.5 million, assuming that untreated alcoholics would have been absent 60 days a year (and also that they would have incurred \$2,000 in extra treatment costs). Jones (1977) attributed to Kennecott Copper Company's alcoholism program a 52-percent improvement in attendance, on average, among the 150 men who spent 12.7 months in treatment. Saxe et al. (1983) have recently reviewed similar studies of programs in the Philadelphia fire and police forces

(Jones and Vischi 1979), General Motors, and the U.S. Air Force (Orvis et al. 1981). All the studies indicate that reduced absences and cost-effectiveness are associated with those programs.

These studies focus primarily on absenteeism and illness costs (not productivity or working days), and they lack adequate controls that would suggest causal inferences. They explore only identified alcoholic employees and leave unresolved the crucial question of how these employees would have fared in the absence of treatment. Whether problem drinking causes substandard job performance or, conversely, substandard, unproductive, and hence unrewarded job performance contributes to problem drinking remains unanswered. Development of more precise estimates concerning the amount of work productivity lost because of drinking and the proportion that can be regained if employees with problems are identified and offered assistance should be a research priority in the 1980s.

Estimating the Costs of Alcohol Abuse

Given the numerous social problems associated with or caused by alcohol abuse, some attempts have been made to quantify its economic costs to society. Two major estimation procedures have been used. The population-specific approach (Berry and Boland 1977; Berry et al. 1977) compared per capita health care costs of alcohol abusers with those of nonabusers and multiplied the difference by an estimate of the prevalence of alcohol abuse, yielding a total cost of \$42.8 billion in 1975. This approach has been criticized because it fails to make corrections for other health risks more common among heavy drinkers. This would tend to inflate the estimates (Cruze et al. 1981).

The alternative approach identifies specific events or illnesses associated with alcohol abuse. For example, in calculating treatment costs, the illness-specific approach includes all expenditures for illnesses attributable solely to alcohol abuse and, for illnesses with multiple causes, only those expenditures that can be ascribed to alcohol abuse. This system would tend to produce a more conservative estimate.

Using this latter approach on 1977 data, Cruze et al. (1981) estimated the national economic costs of alcohol abuse at \$49.4 billion. "Direct core costs" (an estimated \$6.4 billion in 1977) are expenditures for hospitalization, outpatient care, professional ser-

vices, drugs and sundries, and other outlays involved in the diagnosis, treatment, continuing care, rehabilitation, and terminal care for alcohol-related illness and trauma. "Indirect core costs" (estimated for 1977 at \$36.8 billion) reflect the losses of productivity associated with alcohol-related morbidity (\$26.1 billion) and mortality (\$10.7 billion). Table 2 specifies the components of direct and indirect core costs.

"Other related costs," \$6.2 billion, include costs associated with motor vehicle crashes and fires and a proportionate share of society's expenditures for administering the systems of criminal justice, social welfare, fire protection, and highway safety. Also counted are productivity foregone by family and friends of alcoholics, productivity lost by 83,700 individuals in prisons in 1977 for crimes caused by alcohol abuse, and losses associated with automobile accidents experienced by individuals other than crash victims. Table 3 summarizes the breakdown of these other related costs.

Cruze et al. (1981) specified that when data are limited or unavailable, their estimates tend to err on the conservative side. When causal relations are imperfectly demonstrated between alcohol abuse and associated economic costs, on the other hand, their estimates tend to overstate the real costs. The issue of establishing causality was flagged by an advisory panel as "one of the most important factors in carrying out this study.... Failure to recognize the difference between causality and association will lead to unrealistically high estimates of the cost to society of alcohol abuse" (Cruze et al. 1981, p.D-3). The investigators nonetheless contend that, overall, their estimates "lean strongly in the conservative direction" (Cruze et al. 1981, p.6-1).

It is generally recognized that the total burden on society of alcohol abuse and alcoholism is substantially greater if social costs are considered. These include the pain and suffering of the alcohol abuser's family and a host of medical, psychological, and social consequences that a full accounting of costs would ultimately have to include in one way or another. Few studies do more than grant that these intangible costs would add billions of dollars to the overall economic costs to society, assuming they could be measured accurately in monetary terms (Cruze et al. 1981).

Nor has previous research ventured far into the analysis of the benefits of alcohol consumption, which from the standpoint of public

Table 2. Estimated core costs for alcohol abuse, 1977
(in \$ millions)

Total core costs	\$43,161
Direct	\$ 6,372
Treatment	5,637
Alcohol-abuse-specific illness	
—specialty setting	707
Alcohol-abuse-specific illness	
—general setting	2,001
Alcohol-abuse-related illness	
categories	1,711
Gastrointestinal tract	220
Liver disease	181
Nervous system	6
Heart	17
Endocrine system	608
Nutritional deficiency	108
Cancer	171
Mental disorder	293
Infectious disease	107
Alcohol-abuse-related trauma	1,217
Support	735
Research	28
Training and education	225
Construction	193
Health insurance administration	289
Indirect	\$36,789
Mortality	10,715
Direct primary causes—alcohol psychosis, alcoholism, alcoholic cirrhosis of liver, alcohol poisoning	2,617
Direct secondary causes—cirrhosis of liver—other, malignant primary liver neoplasms, other malignant neoplasms of gastrointestinal tract, pancreatitis, respiratory tuberculosis, other associated diseases	1,063
Indirect causes—motor vehicle crashes, falls, fires, other accidents, homicides, suicides	7,035
Morbidity	26,074
Lost productivity	23,593
Males	20,178
Females	3,415
Lost employment	2,481
Trauma	545
Residential treatment	328
Long-term disability	1,608

Source: Cruze et al. 1981.

policy could be considered relevant. Apart from the personal pleasures that prompt so many people to drink in the first place, the alcoholic beverage industry does make a substantial contribution to the economy. The Distilled Spirits Council of the United States, Inc., an association of producers, importers, and other industry representatives, reports that the industry paid \$15.7 billion in 1981 in taxes and other fees to Federal, State, and local governments and employed 826,000 people in 400,000 firms (DISCUS 1982). Additionally, as Gerstein (1981) points out, sales of alcoholic beverages provide not only contributions to government revenues and jobs in the economy, but also an important profit margin for many businesses.

The question for our society seems to be not whether the benefits outweigh the costs, but rather what can be done to reduce the considerable expense of alcohol abuse in terms of human lives, illness, and suffering.

Summary

In 1977, the last year for which there are reliable estimates, alcohol cost the Nation approximately \$50 billion—about \$26 billion in lost employment and productivity, \$17 billion in health care, and \$7 billion in property loss and crime. Although the costs are almost certainly much higher now after 5 years of inflation and sharply increased health care costs, alcohol's impact transcends monetary loss. In many fatalities, alcohol is an accessory before the fact.

Traffic accidents, especially those involving alcohol, continue to be a major problem in our society. According to one estimate, if no drivers drank in 1977, almost 12,000 deaths and perhaps 300,000 injuries would have been prevented. Drivers who drink in excess of the legal intoxication level are 3 to 15 times as likely as nondrinking drivers to be involved in a fatal crash. Even moderate drinking at legal levels can increase the likelihood of fatal accidents. Furthermore, pedestrians killed in traffic accidents are 3 times more likely to be intoxicated than noninjured pedestrians.

Although accidents in the home and workplace have not been as extensively researched as traffic accidents, evidence is ample and growing that alcohol contributes significantly to their incidence and severity. People who drink on the job are much more likely than their coworkers to have fatal accidents at work. Results indicate that alcoholics and

Table 3. Estimated other related costs
for alcohol abuse, 1977
(in \$ millions)

Total other related costs	\$ 6,213
Direct	\$ 4,441
Motor vehicle crashes	1,782
Crime	1,685
Public criminal justice system	1,479
Law enforcement	313
Legal and adjudication	139
Corrections	1,027
Private criminal justice system	191
Law enforcement	184
Legal and adjudication	7
Corrections	-
Property loss/damage	15
Social welfare programs	142
Fire losses	319
Fire protection	482
Highway safety	31
Indirect	\$ 1,772
Crime careers	-
Incarceration	1,418
Homicide	276
Felonious assault	120
Robbery	46
Burglary	49
Drug laws	0
Driving under the influence	287
Liquor laws	158
Public drunkenness	461
Other	21
Motor vehicle crashes	354

Source: Cruze et al. 1981.

heavy drinkers tend to be involved in fatal falls, drownings, and fires.

More alcoholics and heavy drinkers than abstainers are involved in homicides, as both victims and offenders. The alcohol association is somewhat weaker for other crimes such as rape, theft, robbery, and assault. While there are some statistical links between alcohol and crime, factors other than alcohol may explain the relationship.

Heavy drinking seems to affect family stability profoundly. In families with at least one alcoholic spouse, the rate of separation and divorce is seven times that of the general population. Although some researchers have speculated that the incidence of child abuse and spouse abuse may be alcohol-related, re-

liable data are difficult to collect. Suicides are higher among alcoholics, but drinking may be a result of depression or other problems that in turn lead to suicide.

More carefully designed studies are required to establish unequivocally the potential adverse consequences of alcohol. Meanwhile, there is clear reason for concern about the social effects of excessive alcohol consumption.

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Chapter VII

Treatment: Emerging Trends in Research and Practice

During the past decade, several issues surrounding the treatment of alcoholism have been subject to controversy. Does the unitary disease concept permit reliable diagnosis for the purposes of early detection and treatment planning? Is treatment effective and, if so, can the costs of treatment be contained? Are there distinct subgroups of alcoholic persons? Can treatment efficacy be improved by matching individual patients to specific types of treatment? Should abstinence be the singular goal of treatment or can some problem drinkers engage in nonabusive drinking? If some can, how can these individuals be identified? The issues raised by these questions imply much about the theoretical and practical challenges facing the treatment field.

This chapter will focus on the state of the art of alcoholism treatment, giving special attention to developments not covered in the Fourth Special Report (USDHHS 1981). These developments include innovations in diagnosis, improved procedures for screening and early intervention, new findings on the costs and benefits of treatment, a continuing debate on the use and viability of controlled drinking therapies, and emerging models of treatment efficacy. An encouraging development in recent years has been the enhanced investment in research and clinical training in the alcoholism field, and the concomitant emergence of a multidisciplinary research community actively involved in the problems of treating alcoholism. As the quality and sophistication of clinical research improve, it is likely that many of the unanswered questions will be solved.

Recent Advances in Diagnosis and Nomenclature

Diagnosis, the process of identifying and labeling specific disease conditions, uses precise attributes, or diagnostic criteria, to

classify a sick person as having a disease. The importance of diagnostic criteria derives from their usefulness in making clinical decisions, estimating disease prevalence, understanding etiology, and planning treatment. While the diagnosis of alcoholism may seem straightforward to the concerned layperson, it is in fact a complex process.

Limitations in current diagnostic procedures were recently reviewed by McIntosh (1982), who compared data collected in 31 studies of the prevalence of alcohol-related problems in general hospital populations. Variations in the use of diagnostic criteria, as well as lack of conceptual precision in differentiating alcohol dependence from related disabilities, have led to widely differing prevalence estimates of the number of alcoholic patients. In spite of the fact that these patients were in hospitals, most individuals with drinking problems had neither been diagnosed as such nor received appropriate treatment for their alcohol problems.

The traditional unitary disease concept of alcoholism has been challenged by the observation that there may be multiple patterns of dysfunctional alcohol use, which result in multiple kinds of disability. A corollary of the unitary disease concept has been the assumption that alcoholics could be clearly differentiated from nonalcoholics on the basis of their distinctive disease characteristics. Known as the binary classification rule, this assumption has led to the search for universal and singular criteria applicable to all alcoholics. This dichotomous approach has not been particularly helpful to programs interested in early intervention (namely, secondary prevention), nor has it been useful in differentiating prognoses within patient samples in ways that could clarify important questions about treatment efficacy. An alternative approach (Marlatt 1981) characterizes alcohol dependence along a continuum of severity, with no clear demarcation between the beginning of alcoholism and the end of social

drinking. An advantage of this approach is that early detection may be improved when levels of risk have been established.

An important development in the area of diagnosis has been the publication in 1980 of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1980), better known as DSM-III. As a major revision of the manner in which various disorders, including alcoholism, are diagnosed and classified, DSM-III introduced several innovations designed to address problems in earlier classificatory systems (Spitzer et al. 1980). In contrast to previous editions of DSM, alcoholism is now included within the separate category of substance use disorders rather than as a subcategory of personality disorder. Reflecting a trend toward increased semantic precision, the term "alcohol dependence" is used in preference to the more generic "alcoholism." In addition, a separate category of "alcohol abuse" is added to permit greater differentiation. As delineated in table 1, alcohol dependence is differentiated from alcohol abuse by the presence of tolerance or withdrawal symptoms. Both diagnoses include a pattern of pathological use or impairment in social or occupational functioning due to alcohol. Modeled after diagnostic procedures initially developed for research purposes (Feighner et al. 1972), these criteria provide a systematic, standardized approach to diagnostic decisionmaking.

DSM-III permits evaluation of the individual's condition in terms of five independent dimensions or axes. Axis I describes the major clinical syndromes, including substance use disorders, while Axis II is reserved for concomitant personality disorders. Axis III classifies physical disorders and conditions, a number of which can be coded as alcohol-induced, including alcohol intoxication, alcohol withdrawal, alcohol withdrawal delirium, alcohol hallucinosis, alcohol amnestic disorder, and dementia associated with alcoholism. Axis IV draws attention to the severity of psychosocial stress (e.g., occupational, interpersonal, physical) that may modify the course of the current disorder. Finally, Axis V permits the clinician to indicate the patient's highest level of adaptive functioning during the past year in terms of social relations, occupational functioning, and use of leisure time.

Preliminary evaluations of DSM-III suggest that it provides reliable and valid identification of alcoholics in clinical settings, but that it may be less useful in detecting alcoholics who are not institutionalized (Mulford

and Fitzgerald 1981; Helzer et al. 1981; Hesselbrock et al. 1982). Thus, while the DSM-III alcohol-related diagnoses contain many innovative features, the usefulness of this approach for early identification, epidemiological surveys, and treatment planning remains to be evaluated.

The recent development and successful field testing of two standardized interview schedules, the Schedule of Affective Disorders (Weissman et al. 1980) and the Diagnostic Interview Schedule (Helzer et al. 1981), represent a major advance in clinical diagnosis and psychiatric epidemiology. Both schedules provide objective, standardized procedures for diagnosing alcoholism and other clinical syndromes using DSM-III criteria. As these instruments are used with greater frequency to study clinical and population samples, they promise to advance basic knowledge about alcoholism and its relationships to psychiatric syndromes and personality disorders. Data from household surveys using the Diagnostic Interview Schedule in three National Institute of Mental Health Epidemiology Catchment Areas suggest that, at some time during their lives, one in seven adults 18 years of age or older met criteria for alcohol abuse or alcohol dependence.

A related development in the area of alcoholism diagnosis is the international program on diagnosis and classification sponsored jointly by the U.S. Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and the World Health Organization (WHO 1982). The purpose of this project is to recommend improvements in sections of the International Classification of Diseases (ICD) dealing with alcoholism, drug abuse, and mental health. The first phase was devoted to a systematic examination of concepts and nomenclature pertaining to alcohol and drug abuse (Edwards et al. 1981). Of particular interest to the alcoholism treatment field is the emerging set of concepts, definitions, and criteria that may well provide the basis for the next revision of ICD. Central to the WHO approach to alcoholism is the concept of a dependence syndrome that is distinguished from alcohol-related disabilities (Edwards et al. 1976, 1981). As outlined in table 2, the dependence syndrome is an interrelated cluster of cognitive, behavioral, and physiological symptoms. Alcohol-related disabilities, on the other hand, consist of those physical, psychological, and social dysfunctions that follow directly or indirectly from excessive drinking and dependence.

Table 1. DSM III criteria for alcohol abuse and alcohol dependence

Diagnostic criteria for alcohol abuse	Diagnostic criteria for alcohol dependence
A. Pattern of pathological alcohol use: need for daily use of alcohol for adequate functioning, inability to cut down or stop drinking, repeated efforts to control or reduce excess drinking by "going on the wagon" (periods of temporary abstinence) or restricting drinking to certain times of the day, binges (remaining intoxicated throughout the day for at least 2 days), occasional consumption of a fifth of spirits (or its equivalent in wine or beer), amnesic periods for events occurring while intoxicated (blackouts), continuation of drinking despite a serious physical disorder that the individual knows is exacerbated by alcohol use, drinking of nonbeverage alcohol. B. Impairment in social or occupational functioning due to alcohol use: violence while intoxicated, absence from work, loss of job, legal difficulties (e.g., arrest for intoxicated behavior, traffic accidents while intoxicated), arguments or difficulties with family or friends because of excessive alcohol use. C. Duration of disturbance of at least 1 month.	A. Pattern of pathological alcohol use: need for daily use of alcohol for adequate functioning, inability to cut down or stop drinking, repeated efforts to control or reduce excess drinking by "going on the wagon" (periods of temporary abstinence) or restricting drinking to certain times of the day, binges (remaining intoxicated throughout the day for at least 2 days), occasional consumption of a fifth of spirits (or its equivalent in wine or beer), amnesic periods for events occurring while intoxicated (blackouts), continuation of drinking despite a serious physical disorder that the individual knows is exacerbated by alcohol use, drinking of nonbeverage alcohol. B. Impairment in social or occupational functioning due to alcohol use: violence while intoxicated, absence from work, loss of job, legal difficulties (e.g., arrest for intoxicated behavior, traffic accidents while intoxicated), arguments or difficulties with family or friends because of excessive alcohol use. Either tolerance or withdrawal: C. Tolerance: need for markedly increased amounts of alcohol to achieve the desired effect, or markedly diminished effect with regular use of the same amount. D. Withdrawal: development of alcohol withdrawal (e.g., morning "shakes" and malaise relieved by drinking) after cessation of or reduction in drinking.

Source: American Psychiatric Association 1980.

According to the WHO dependence model, a complete description of an individual's alcohol-related pathology must include statements concerning the nature and severity of dependence, the kinds and degrees of disability, and the personal and environmental factors that influence the drinking problem. The WHO model departs significantly from DSM-III and the older binary classification schemes by em-

phasizing that both dependence and alcohol-related disabilities exist in degrees rather than in an all-or-none state.

In the brief period since it was first introduced, the dependence syndrome construct has received considerable attention from researchers and clinicians. A number of instruments have been developed to assess its usefulness (Stockwell et al. 1979; Skinner and

Table 2. Constituent elements of the alcohol dependence syndrome

Elements	Interpretation/examples
Narrowing of the drinking repertoire	The drinking pattern tends to become stereotyped around a regular schedule of almost continuous daily consumption.
Salience of drink-seeking behavior	Drinking is given higher priority than other activities in spite of its negative consequences.
Increased tolerance to alcohol	More and more alcohol is required to produce behavioral, subjective, and metabolic changes; large amounts of alcohol can be tolerated.
Repeated withdrawal symptoms	Tremulousness, sweatiness, nausea, etc., appear after short periods of abstinence.
Relief drinking	Withdrawal symptoms are relieved or avoided by further drinking, especially in the morning.
Compulsion to drink	Subjective awareness of craving for alcohol exists, as well as impaired control over quantity and frequency of intake.
Readdiction liability	The syndrome tends to be rapidly reinstated when drinking is recommenced after a period of abstinence.

Source: Adapted from Edwards et al. 1976, 1981.

Allen 1982; Hesselbrock et al. 1983). Research in both experimental and clinical settings suggests that the severity of dependence can correlate positively with attendance at a treatment clinic (Skinner and Allen 1982), cravings for alcohol after a "priming" drink (Kaplan et al. 1983), and failure to control drinking following relapse (Orford et al. 1976; Polich et al. 1981). While further research is needed, the dependence syndrome construct shows considerable promise for early detection, diagnosis, and treatment planning.

Differential Assessment

Both DSM-III and the WHO dependence model represent a general movement toward differential assessment as evidenced by the use of multiple criteria to provide a comprehensive evaluation for treatment planning. Ideally, specificity of diagnosis should lead to

specificity of treatment, an important goal in the delivery of treatment services for three essential reasons: (1) economy of cost, (2) avoidance of inappropriate or ineffective treatment, and (3) increased efficacy. Surprisingly, outside the area of personality assessment, little interest has existed until recently in differential assessment of the alcoholic person. This is due in part to assumptions about the unitary nature of alcoholism, and in part to the limited methods available to evaluate alcoholics.

Recent advances in evaluation methodology (Meyer et al. 1981) have stimulated research in this area, and a number of assessment procedures have been developed. In addition to those already discussed, several investigators (Skinner and Allen 1982) have demonstrated the usefulness of assessing drinking patterns and alcohol-related problems in an effort to identify individual differences related to