The YEAR BOOK of

Drug Therapy

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Introduction

Putting together the YEAR BOOK OF DRUG THERAPY follows a cyclic pattern. Early in the year, the editors have a short rest for 2 or 3 months. After that respite, a continuing series of articles is received and assigned to the most appropriate editor. Selections of the most interesting or pertinent articles are made over the next several months. Then the articles are abstracted. Finally, each editor receives the selected abstracts for review and comments. The work of all 3 editors is collated and sent off for publication. And so the cycle goes. With a little luck, we have made a balanced selection of articles that will let our readers keep abreast of current trends in drug therapy. Let us know if you feel that any areas have been unduly neglected, or how this goal might be better attained.

The special article this year deals with some of the hazards of social drugs. Most of the adult population of developed countries uses some social drug. We might deny that we use nontherapeutic drugs. We commonly do not think of caffeine, ethanol and nicotine as drugs, especially when they are taken as coffee, wine or cigarettes. The younger generation would feel the same way about cannabis. Evidence continues to mount that these social drugs, even when not seriously abused, may have adverse effects on health. We try more to prevent, rather than to treat, illness, and we try to make patients more responsible for maintaining their own health. Therefore, we thought you would like to know more about the possible hazards of drugs your patients take that you do not prescribe.

Progress in drug therapy has been substantial over the past 25 years and the pace ever quickens. The importance of drug therapy is evidenced by the fact that roughly one third of the questions on the examination for certifications by the American Board of Internal Medicine are directly related to drug therapy. We would like to think that this YEAR BOOK is read primarily because our readers want to make the most effective use of drugs for treating their patients. Whatever your many possible motives for buying and using this volume, we hope it will serve your needs.

A further personal note. Daniel Azarnoff, who has edited the last three editions of the YEAR BOOK OF DRUG THERAPY, has resigned from the editorial committee for personal reasons. Doctors Hollister and Shand will continue on the committee, with the probable addition of a new editor—still to be chosen—and wish to express their appreciation to Doctor Azarnoff for his labors and guidance during these past 3 years. We hate to see him leave.

DANIEL L. AZARNOFF, M.D.
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DANGERS OF SOCIAL DRUGS*

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Introduction

If our legislators were perfectly rational, one would expect that they would restrict the sale and use of dangerous drugs more than that of innocuous drugs. In the United States, the drugs with the most severe restrictions, such as heroin, are those listed in the Controlled Substances Inventory List (United States Department of Justice, 1977). By contrast, the socially acceptable drugs today – caffeine, alcohol and nicotine – are not even considered drugs and are exempted from control by the Food and Drug Administration. Despite this distinction, they remain pharmacologic agents and follow the same laws of nature as digitalis and penicillin. Of course, even the most "dangerous" drugs are not dangerous at all times. For example, heroin and lysergic acid diethylamide (LSD) are usually considered extremely dangerous, and phencyclidine (PCP) is a popular villain. But the toxic effects of all drugs follow a dose-response relationship: all drugs are safe below a certain level, and all drugs are dangerous above a higher level. A low dose of hydrocyanic acid inhaled by a passive smoker may be perfectly innocuous, whereas a high dose is obviously lethal. Caffeine, nicotine and alcohol can all effectively kill if given in high enough doses for a long enough time.

Drug popularity changes with the times. At the turn of the century, millions of people throughout the world were socially accepting drugs that today are censured. In China they smoked opium, in India they ate cannabis, in the East Indies they chewed betel nut, in Peru they chewed coca leaves, in the South Pacific they drank kava (which is not a brand of coffee, but a hallucinogen), throughout South America and Central America and the West Indies they used epéna and cohoba snuffs, Mexican and North American Indians took psilocybin and mescaline, Ethiopians and Yemenites used khat and Americans and Europeans bought opium products in grocery stores. Any user of these substances will tell you that they are satisfying and produce some type of pleasure. It still remains for scientists to determine the mechanisms whereby different types of drugs produce reinforcement, i.e., the tendency to repeat behavior associated with taking a drug.

*This work was supported by the Medical Research Service of the Veterans Administration and the American Cancer Society, Inc., grant PDT 2K and National Institute on Drug Abuse, grant DA-01986-01.

All the drugs that human beings self-administer can be put into two classes: those that are self-administered by lower animals and those that are not. Drugs that are unequivocally self-administered by animals are the sympathomimetic stimulants, opioids and sedative hypnotics. Nicotine is equivocally self-administered and is clearly different from these others. Caffeine is not self-administered, nor are any of the hallucinogenic drugs. Apparently the latter group is reinforcing for different reasons in human beings than in animals. It has been suggested that animals do not have the intellectual capacity to appreciate the perceptual changes that are produced by drugs such as marihuana or LSD, and this may also be true of caffeine.

One of the consequences of the social acceptability of caffeine, nicotine and alcohol is that their use is less likely to be associated with crime and with disease than is the use of "illicit" drugs not subject to quality control.

The very term "drug" has acquired derogatory connotations. Tobacco products, alcoholic and caffeinated beverages are produced by reputable manufacturers who almost never refer to their wares as "drugs." In common parlance, a "drug problem" refers to illicit drugs such as heroin, cocaine and marihuana, which are taken for their reinforcing properties. The socially approved drugs are considered either foods (e.g., as contained in coffee or in wine) or recreational products (such as cigarettes). All of them are readily available in markets and all are used at the dinner table. Nonetheless, they are drugs and may be dangerous under specific circumstances.

Alcohol

Ethyl alcohol is undoubtedly the oldest tranquilizer, and its origins are lost in prehistory. There are stories of animals becoming intoxicated with fermented fruits and seeking them out, as reported by Siegel (1977). An interesting experiment in the use of social drugs was performed by the United States government with the passage of the Eighteenth Amendment to the United States Constitution. The prohibition amendment was passed in 1920 and repealed in 1933. Criminalization of alcohol use resulted in bootlegging and the evolution of a gigantic underworld industry that is still with us. The lack of quality control caused the substitution of other drugs such as methanol, which resulted in blindness and death. Until 1978 the state of Kansas retained prohibition of the sale of alcoholic beverages, and it appears that religious factors still play a role in determining regional regulations concerning alcohol use (Trillin, 1978). During prohibition the incidence of cirrhosis of the liver and other alcohol-related diseases declined precipitously. However, repeal of prohibition became necessary when it was evident that the cost-benefit ratio was too high. Enforcement was expensive and relatively ineffective, just as it is for heroin and other dangerous drugs today. Effective drug control has only succeeded in countries where police corruption is impossible and law enforcement is adequate (e.g., Japan, China and the Soviet Union).

Therapeutic Uses

Although alcohol has been given intravenously as a general anesthetic, its therapeutic index is much too low. Until the Arabs introduced distillation into Europe in the Middle Ages, alcoholic beverages were highly diluted. It was always difficult to attain high blood concentrations of alcohol with beer and wine. However, with distilled beverages, fatal concentrations can be achieved with extremely low volumes ingested, although incoordination through intoxication provides a protective negative feedback mechanism. Alcohol is an official United States Pharmacopoeia preparation, and whiskey, brandy and sherry wine were formerly official preparations. Alcohol is still the most popular skin disinfectant, and absolute alcohol is sometimes injected to destroy nerves. Alcoholic beverages, especially wine, have been widely prescribed by physicians, even during prohibition, as stomachics to improve the appetite and also as tranquilizers, particularly in elderly persons (Mishara et al., 1975). It must be noted that influential textbooks of pharmacology (e.g., Goodman and Gilman, 1975) treat the use of alcohol rather benignly.

Alcohol is self-administered primarily as a sedative, occasionally as a hypnotic and also as an analgesic agent. Most parties and social events use alcohol as a "social lubricant." The change of state produced by alcohol does make people with anxieties and depression feel better and probably largely accounts for its tremendous popularity. It would appear that the reinforcing effects of alcohol differ for different persons. Cultural factors are obviously involved in such differences, but there is also a strong genetic factor involved in the habitual use of alcohol or in alcoholism (Goodwin, 1978).

Tolerance to alcohol occurs after chronic use, and there is cross tolerance with numerous sedative hypnotic drugs. These also show cross dependence and are effective in counteracting the alcohol withdrawal syndrome. Evidently there is some physiologic mechanism common to drugs such as barbiturates, benzodiazepines, meprobamate and general anesthetics.

Goodwin (1977) describes the four stages of alcoholic intoxication as jocose, bellicose, lachrymose and, finally, comatose. Generally speaking, when the blood concentration of alcohol is 20–30 mg/100 ml, the effects of intoxication first become manifest. At 150 mg/100 ml, about half of drinkers are grossly intoxicated, and the average concentration of blood alcohol in persons who have died from it is 400 mg/100 ml. Intoxication depends greatly upon the way alcohol is ingested. According to Goodman and Gilman (1975), 44 gm alcohol taken orally may give blood levels ranging from a maximum of 92 mg/100 ml if taken as distilled spirits on an empty stomach, down to 23 mg/100 ml if taken as beer with a mixed meal. Blood alcohol falls, on the average, at the rate of about 18 mg/100 ml/hour.

Toxicity

There is great disagreement about the safety of alcohol in moderation. Are there dangers from ingestion of alcohol in doses low enough to prevent an illegal level of intoxication? From a medicolegal viewpoint, the blood level of alcohol is used to determine intoxication. With a blood level less than 50 mg/100 ml, a person is considered not under the influence of alcohol. Above 100 mg/100 ml, he is generally considered "under the influence." In the intermediate zone, a judgment of intoxication is usually at the discretion of the court. However, there are individual differences in susceptibility to intoxication by alcohol that may push these limits greatly. Extremely susceptible persons may have judgment and motor coordination impaired by much lower doses, and very tolerant persons apparently can function quite well despite much higher blood levels of alcohol.

The real problem with the drinking of alcoholic beverages is that there is a tendency to escalate the dose, particularly if positive reinforcement occurs. Although most alcohol users are not alcoholics, there are some persons who are genetically predisposed not to drink because the effects of alcohol are aversive (Wolff, 1972). The ready availability of alcohol and the fact that it makes so many people feel so good is the reason for its widespread use. It is estimated that in the United States, two thirds of the adult population use alcohol at least occasionally, and 12% of users are considered heavy drinkers.

The alcoholic beverage industry, including producers of beer, wine and spirits, is an exceedingly important part of our economy. It provides employment for many people. However, its cost to our economy is estimated at approximately $15 billion a year, measured in the results of automobile accidents, absence from work, illness (such as cirrhosis of the liver) and death.

A major danger of social drinking is that it precedes alcoholism. There has been much controversy about whether the alcoholic is so vulnerable to the reinforcing effects of alcohol that even moderate drinking will inevitably escalate to excessive drinking. A report from the Rand Corporation (Armor et al., 1978) indicated that under appropriate conditions, former alcoholics can be taught to handle alcohol and to drink moderately. Most organizations for alcoholics, however, insist that ex-alcoholics remain totally abstinent for the rest of their lives and regard even a single drink as a possible precipitant of relapse into alcoholism.

The moderate use of alcohol is also correlated with the use of our two other social drugs—nicotine (or tobacco) and caffeine (or coffee). In addition, problem drinkers tend to use other sedatives such as barbiturates, as well as stimulants such as amphetamines. Also, alcohol is sometimes the second drug of choice and is used when heroin addicts or barbiturate addicts are unable to obtain their preferred drug (Freed, 1973). The two other socially approved drugs, nicotine and caffeine, are generally considered stimulants and might be used to counteract the effects of alcohol (Myrsten and Andersson, 1978).

The moderate drinker, in contrast to the alcoholic, tends to maintain

his nourishment and is therefore less likely to suffer the medical complications of alcoholism, including cirrhosis of the liver, avitaminosis, alcoholic gastritis and pneumonitis.

If people take alcoholic beverages to relieve themselves of anxiety, they may also use a variety of sedative hypnotics for the same purpose. Today, the benzodiazepines, chlordiazepoxide and diazepam are the most widely prescribed drugs in the world. They have some advantages over alcohol. For one thing, they have no caloric value and therefore will not cause obesity. They appear to have a lesser tendency to cause release of catecholamines.

The one important effect of alcohol that should temper its prescription to patients with cardiovascular problems, or to old or debilitated persons, is its ability to depress myocardial contractility in low doses. One must therefore weigh the risk of throwing a patient into cardiac failure against the relief of anxiety or insomnia that alcohol produces.

Although older investigators came to the conclusion that moderate amounts of alcohol have no effect on cardiac performance, newer studies using more sensitive measures do show impairment. For example, at blood alcohol levels of 74 mg/100 ml, in one study (Ahmed et al., 1973) there was an increase in preejection period, isovolumetric time and the ratio of preejection period to left ventricular ejection time. The depression of myocardial contractility was related to blood level of alcohol. By contrast, isocaloric sucrose produced just the opposite effect on myocardial contractility. It has already been shown that alcohol plays an important role in cardiomyopathy and could exhibit significant depression of ventricular function after alcohol (Regan, 1971).

Alcohol even in moderate doses does cause a release of catecholamines during the early stages of intoxication. There is a slight rise of blood pressure, transient hyperglycemia and pupillary dilatation which may be associated with the presence of catecholamines in the blood (Kalant, 1961).

Moderate evening intake of alcohol has been associated with nocturnal hypertriglyceridemia and hyperinsulinemia. Ethanol, 15 gm/kg, was taken between 5 and 9 P.M., resulting in average blood alcohol concentrations of 110 mg/100 ml. The hyperglycemic response is similar to that seen in type 4 endogenous hyperlipidemia.

Alcohol given in doses similar to those taken in social drinking modifies cardiovascular reflexes in a direction suggesting enhanced cardiovascular reflex modulation (Zsoter and Sellers, 1977). Doses of 0.3 and 0.6 gm alcohol per kg increased resting heart rates in nonalcoholic subjects and increased the heart rate response to a Valsalva maneuver. Vasoconstriction in the hands during and after hyperventilation was increased by this intake of alcohol. The changes are consistent with increased peripheral adrenergic activity, and a rise of serum dopamine β-hydroxylase activity occurs after 0.3 gm alcohol per kg. However, the degree of change in a healthy young population (average age, 27) was relatively small. The amount of harm produced by a one-time ingestion of alcohol in otherwise abstinent volunteers was evidently slight.

On the other hand, chronic use of alcohol seems to produce cardiovascular harm (Turner et al., 1977). There is still controversy whether

cardiomyopathy seen on autopsy in alcoholics is related solely to their alcohol intake. Paradoxically, however, alcoholics appear to be less prone to myocardial infarction. Even a moderate intake of alcohol seems to offer protection. Stason et al. (1976) found that persons drinking at least 30 oz. ethanol per month suffered fewer heart attacks than nondrinkers. Other studies seem to bear out this important finding.

In a number of studies a clear relationship between alcohol consumption and blood pressure has been demonstrated. Men and women who took three or more drinks per day had higher blood pressures than those who drank less. Alcohol use even in relatively moderate doses is therefore considered a risk factor for hypertension (Turner et al., 1977).

A number of investigators do advocate the prescription of moderate amounts of alcoholic beverages, particularly for the elderly (Mishara et al., 1975). It is possible that at extremely low doses the deleterious effects of alcohol on the heart may be slight enough so that they are outweighed by the tranquilizing and stomachic effects. Thus, one is faced with the paradox that alcohol decreases cardiac function, while at the same time it seems to offer protection against myocardial infarction. Only future studies will clarify the appropriate approach to alcohol, in view of such findings.

There is no question that heavy drinking decreases life expectancy. There seems to be some controversy, however, whether moderate drinking has this effect. Goodman and Gilman (1975) maintain that there is no difference in the life expectancy of abstainers compared to temperate drinkers. The life expectancy of Seventh-Day Adventists and Mormons who abstain from alcohol is distinctly longer than that of the average American. However, members of these groups abstain from the use of all three of the socially approved drugs (Lemon et al., 1969). The use of alcohol by patients who have liver disease, particularly infectious hepatitis, remains controversial. Some clinicians prohibit alcohol forever to patients who have suffered from hepatitis, whereas others feel that ingestion of alcohol has no effect on the course of the disease. Modest amounts of alcohol may have additive or synergistic effects with a variety of drugs. Alcohol can potentiate the toxic effects of halogenated compounds on the liver. Also, relatively small amounts of alcohol combined with other sedative hypnotic drugs such as barbiturates or benzodiazepines may cause coma and death.

Although alcohol itself is not carcinogenic, alcohol intake in combination with cigarette smoking significantly increases the risk of cancer of the larynx, oral cavity and esophagus. There appears to be a synergistic effect between tobacco and alcohol, with alcohol acting as a promoter. The interaction between smoking and amount of alcohol is evident; moderate drinking (one to six alcohol units per day) increases the risk of laryngeal cancer in smokers (Wynder, 1977).

The mechanism whereby alcohol produces its characteristic intoxication and also its reinforcing effects is by no means clear. There certainly appears to be evidence that ethanol has nonselective depolarizing action on excitable membranes, and more so than do barbiturates (Okamoto, 1978). In addition, various putative neurotransmitters have

been implicated in the action of alcohol. These include acetylcholine, norepinephrine, dopamine, serotonin and γ-aminobutyric acid (GABA). There has been particular interest in GABA because it is thought to be a naturally occurring depressant substance, and the hypothesis has been put forth that alcohol and other sedative drugs may either potentiate or mimic its action. The evidence supporting this hypothesis is still equivocal.

Most animals will not drink alcohol solutions except at extremely low concentrations. However, there are certain strains of species that may show preferences. For example, the C57BL mouse seems to prefer 12% alcohol. Similarly, the ALKO strain of rat selects 10% alcohol solutions and has been called "alcohol addicted." The Syrian hamster is said to prefer 5% alcohol (Myers, 1978). It would be useful to find biochemical differences between individuals who like alcohol and those who do not.

Catecholamines are clearly influenced by alcohol drinking. Ewing et al. (1975) found that volunteers with high plasma levels of dopamine β-hydroxylase appear to be more tolerant to alcohol and derive more pleasure from it. There has been much interest in recent years in the possibility that some common mechanism underlies addiction to alcohol and to morphine. Whereas this is an intriguing theory, it is evident that there is little, if any, cross tolerance between the two types of addiction, and the evidence for a common mechanism is still inconclusive.

Lithium has been purported to reduce the craving for alcohol or the tendency to ingest it (Judd et al., 1979). However, a truly effective agent for the treatment of alcoholism has not yet been found. One of the foremost investigators in alcohol research has indicated "progress in the sense of understanding why and how alcoholism occurs and how to change it" has not yet occurred (Mello, 1977). She points out with great perspicacity that definitions of abnormal drinking are highly varied according to different sociocultural or pharmacologic criteria. Problem drinking in Saudi Arabia is very different than in Ireland.

Mello questions the prevalent theory that induction of euphoria is the primary reason why people drink. Clinical studies of alcoholics during intoxication demonstrate increases in depression, anxiety and dysphoria. However, there does seem to be a transition phase from sobriety to elation to depression. In fact, in Mello's view, it appears to be a paradox that alcoholics drink without inducing positive affect or relieving dysphoria.

A fetal alcohol syndrome appears to be well established. Children born to chronically alcoholic women show a variety of birth defects, including growth deficiency, swollen head size with mental subnormality and characteristic facial abnormalities (Hanson et al., 1976). Even moderate drinkers (those consuming alcohol more than once a month but less than 45 ml a day) showed increased incidence of congenital abnormalities in their offspring (Ouellette et al., 1977). These effects have also been seen in animals administered alcohol with nutrition well controlled.

In view of the dangers to the fetus evident in mothers who drink, it is surprising that infusions of alcohol have been used to retard labor.