DRUG ABUSE AND

DRUG ABUSE RESEARCH

The FIRST in a SERIES of

TRIENNIAL REPORTS to CONGRESS

from the SECRETARY,

DEPARTMENT of HEALTH and

HUMAN SERVICES

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JANUARY 1984

147120

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DHHS Publication No.   (ADM)85-1372
Printed 1984

ACKNOWLEDGMENTS

We also wish to acknowledge the important contributions of two staff members at the National Institute on Drug Abuse's Addiction Research Center: Dr. Charles Gorodetsky and Dr. Jack Henningfield.

Whenever specific questions of scientific judgment arose in the preparation of this report, we deferred to the expertise of the researchers contributing to individual chapters.

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INTRODUCTION

The problem of drug use and abuse in the United States is
pervasive. In fact, it is widely thought that the levels of
use and abuse of drugs in our society are equal to or higher
than those found in any other industrialized country. The
drug abuse problem is also exceedingly diverse. Virtually
every community in every State has, at one time or another,
felt its impact, some more acutely than others. Drug abuse
rates vary from community to community and, within communi-
ties, the rates often vary considerably from neighborhood to
neighborhood. While there are some differences in the
degree to which drugs are abused by sex, race-ethnicity,
social class, and other personal and psychological charac-
teristics, no segment of the population is immune to the
problem. Further, the drug abuse problem spreads and
changes with remarkable speed. For example, the phencycli-
dine (PCP) epidemic of the 1970s arose almost overnight and,
just when research on this drug began to make some strides,
the problem decreased dramatically.

Stated simply, the problem of drug abuse in the United
States is an extremely complex and almost constantly
changing phenomenon. The more we learn about the problem,
the more cognizant we are of the impact drug abuse has on
individual lives, on the functioning of families and
communities, and on the health and well-being of the entire
society.

THE RESEARCH PROGRAM AT NIDA

The Federal agency responsible for monitoring drug abuse
trends and sponsoring research on this complex problem is
the National Institute on Drug Abuse (NIDA). It was estab-
lished in September of 1972 and given statutory authority in
1973. Thus, NIDA has been in existence for less than a
decade. For most of this time, it has operated under an
extremely broad mandate that included providing direct
financial assistance for drug abuse education, training,
treatment, and rehabilitation, as well as funding and

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conducting intra- and extramural research. However, since the advent of the Alcohol and Drug Abuse and Mental Health Services Block Grant program in fiscal year 1982, NIDA no longer provides direct financial assistance to treatment and prevention programs although it does conduct research in these important subject areas.

The Epidemiological Research Program provides the Institute with an understanding of the incidence of, prevalence of, and trends in drug abuse for the general population as well as for specific subgroups within the population. It is organized around several statistical reporting systems that monitor changes in some of the consequences of drug abuse, e.g., medical emergencies, drug overdose deaths, admissions to treatment, and it regularly surveys the correlates, causes, and consequences of drug abuse in various segments of the population (i.e., households, high school seniors, etc.).

Prevention and treatment research are not seen as totally separate entities. Rather, they are thought to exist on a continuum of prevention. The Prevention Research Program includes the design, delivery, and evaluation of different school, peer, family, media, and community-based strategies. The primary purpose of these studies is to learn the most effective means to teach young people how to choose healthy alternatives to drug use. Much of the research in the area of primary prevention involves learning how young people make decisions and learning how to influence that decision-making process. The Treatment Research Program at NIDA is focused on those persons who are already heavily involved in drug abuse and who are suffering the consequences of that involvement. Treatment research seeks to design and evaluate the best mixture of treatment strategies for persons with differing kinds of drug abuse problems, the ultimate goal being prevention of further drug abuse and its attendant consequences. The fourth and final segment of the research program at NIDA is Drug Specific Research. This type of research is usually "basic" in nature because the bulk of it deals with the chemical and pharmacological properties of specific drugs and their effects on organisms.

About half of NIDA's program consists of basic research, seeking to develop new knowledge about the mechanism of action of drugs; their sites of action, especially in the brain and central nervous system; and their pharmacology. Recent advances in receptor research under sponsorship of NIDA grants have done much to advance the field of basic knowledge about how drugs act in the body and how their effects are produced.

Other drug-specific research focuses on the hazards of various drugs, and ranges from the adverse biological effects of drugs on body systems to psychobehavioral effects, including effects on learning, performance, and cognition, and to social effects, such as crime. Chemical research focuses on the development of new compounds, prediction of drug action from structure-activity relationships, determination of metabolic pathways of drugs, and the development of assay methods of detecting drugs in body fluids.

SIGNIFICANT RESEARCH CONTRIBUTIONS

In somewhat less than 10 years NIDA has established a strong program of research in the four categories. Significant contributions have been made in each area. A host of longitudinal studies, i.e., studies of the same people at different points in time, have provided a much clearer understanding of the factors influencing the initiation, continuation, progression, and cessation of drug use. The Institute has sponsored tightly controlled and comprehensive studies of various prevention strategies delivered in schools, e.g., drug education courses, teacher training, decisionmaking courses. There are clear differences in how effective these strategies are in changing student attitudes about drugs and their use of drugs. An extensive series of studies has begun to reveal which types of treatment are most effective for particular types of individuals with serious drug problems. Over the past several years, NIDA-sponsored research into the chemistry and metabolism of various drugs, i.e., the ways in which the drug is broken down and chemically transformed in the body, has shed new light on the role played by endorphins, the body's own pain-fighting substance. This line of research has relevance for all of medicine. NIDA has also played a key role in the development and testing of new and more effective treatment agents, most notably LAAM, naltrexone, and buprenorphine, all of which have unique properties that contribute to better treatment for opiate addicts. Research on the dependence liability and addictive potential of tobacco has led to a new understanding and appreciation of why people who smoke cigarettes have such a difficult time quitting.

ORGANIZATION OF THE FIRST TRIENNIAL REPORT

This first triennial report to the U.S. Congress is organized to reflect the four foci of NIDA's research program. Following this introduction, Chapter 2 includes a review of some of the latest findings on the extent of drug abuse in

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the United States and on selected social consequences of drug abuse, such as medical emergencies and drug overdose deaths, vehicular accidents attributed to drug use, the impact of drug abuse in the workplace, the relationship between drug abuse and crime, and the impact of early drug use on subsequent use of other drugs. Included in Chapter 3 are a review of what is known about the factors that promote drug use relative to adolescent development and the effectiveness of various educational and psychosocial approaches to preventing drug use and abuse among adoles- cents. Chapter 4 focuses on the relative effectiveness of different treatment approaches, including detoxification, methadone maintenance, residential, outpatient drug free, and other treatment modalities. Chapters 5 through 10 will deal with specific drug classes and what is known from basic research about their mechanisms of action and the health hazards associated with use and abuse of these drugs. The final chapter summarizes the emergent knowledge about a new class of drugs, endogenous opioids such as endorphins and enkephalins, and recent research about drug receptors in the central nervous system. This line of research has great potential not only for the field of drug abuse but also for neurology, mental health, cardiology, and alleviating pain.

It would not be possible in a short report to review everything that has been done in each of these research areas. The purpose of this first triennial report is to provide an overview of some of the more important recent research on drug abuse and on the health and other consequences attributable to drug abuse.

EXECUTIVE SUMMARY

Section 2(b)(7) of Public Law 98-24, the Alcohol and Drug
Abuse Amendments of 1983, require the Secretary of Health
and Human Services to submit to the Congress a report
summarizing the health consequences and extent of drug
abuse. Also included in this report are current research
findings, such as the health effects of marijuana and the
addictive property of tobacco. In an effort to provide the
most current information available, the National Institute
on Drug Abuse (NIDA) drew upon experts from the field in
each of the various areas covered to prepare the material
used in the report.

Recent epidemiological data provide evidence that, as a
general trend, the extent of drug use in the Nation has
stabilized or is decreasing. Nonetheless, illicit drug use
in the United States remains at a level probably exceeding
any nation in the western industrialized world. Drug abuse
clearly is a major public health problem, demanding continu-
ing priority attention and concern. Twenty years ago less
than 2 percent of the Nation's young people had tried an
illicit drug. Today about two-thirds have tried an illegal
drug before they graduate from high school. In 1960 less
than 7 percent of college-age young adults had tried
marijuana; by 1982, 64 percent reported some use of the
drug. There has been a 400 percent increase in heroin use
since 1960. The adverse cost to society, particularly of
drug-related crime and corruption, also remains unacceptably
high. Studies have shown the total annual cost of drug
abuse to society to be close to $100 billion. Of this
figure, approximately $10 to $16 billion is conservatively
attributable to the impact of drug abusers on the health
care system, the law enforcement system, the employment
market, and the general welfare and social services.
Another $70 to $80 billion in annual costs result from the
costs of criminal drug trafficking.

The mission of the Department of Health and Human Services in combatting this extremely serious problem is primarily that of demand reduction. The Department, and within it the Alcohol, Drug Abuse, and Mental Health Administration and the National Institute on Drug Abuse, is involved in a variety of activities intended to eliminate drug use by (1) dissuading the nonuser from experimenting with drugs and progressing to habitual abuse of drugs, and (2) making the most effective treatment available to help those who are drug abusers become drug free. In carrying out this mission, the Institute is involved in four major areas of activity: research, epidemiology, prevention, and communications. NIDA's research program, on which this report focuses, has five major components: epidemiology, prevention, treatment, pharmacology of drugs of abuse, and neurosciences.

EXTENT AND CONSEQUENCES OF DRUG ABUSE

● The National Survey on Drug Abuse, conducted periodically in a nationally representative sample of American households, revealed a general downturn in lifetime and current use of marijuana between 1979 and 1982. There was also a slight decrease in use of hallucinogens, stimulants, sedatives, tranquilizers, and analgesics as a group. Cocaine use appeared relatively stable between 1979 and 1982.

● The Monitoring the Future Studies, a series of annual surveys of a nationally representative sample of high school seniors, also revealed a downturn in marijuana use from 1979 to 1983. Use of other drugs also declined. For example, the 1983 survey continued to chart declines in reported use of cocaine, stimulants, and methaqualone which had first been reported in 1982. Drinking levels appeared constant, and there was a slight upturn in levels of smoking from 1981. A parallel study of seniors in schools for military dependents overseas produced generally comparable rates of drug use.

● The decreases in drug use shown by both surveys reported above are particularly significant in that they represent the reversal of a trend of year-to-year increases. This trend reversal should not be viewed as anything but the beginning of success since overall levels of drug use are still tragically high.

● The decrease in overall prevalence represents important trend reversals; however, within this larger pattern, the

trends in use of particularly dangerous types of drugs by specific subpopulations are increasing. Thus, the drug abuse problem may appear to be worsening in some areas, despite the general downward trend in most categories.

● Current information from the Drug Abuse Warning Network (DAWN), which reports on drug-related cases from emergency rooms and medical examiners throughout the United States, supports the notion that the drug epidemic of the 1960s and 1970s has begun to recede, but alerts that the negative health consequences associated with drug use have not abated. For example, over the past 3 years, from July 1980 to June 1983, emergency room visits related to heroin increased in many cities. Over the same 3-year period, there were also increases in emergency room visits related to cocaine in most cities. Since June 1983, however, the overall consequences of cocaine and heroin abuse show some signs of improving or stabilizing, with the exception of increased emergency room mentions in several large cities.

● Preliminary data indicate that vehicular accidents are closely correlated both with the use of alcohol and with the combined use of alcohol and marijuana.

● It is thought that drug abuse significantly affects the workplace in the United States. However, a great deal more research is needed to understand the extent and specific features of its effect.

● Many recent studies have clarified the relationship between drug abuse and criminality. Those studies also document the effective use of treatment in reducing associated criminal activity. More specifically, it now appears that each of the approximately half-million heroin addicts in the United States is responsible for approximately 350 crimes per year when actively addicted. However, when an addict is in treatment or remission, the number of crimes committed is reduced by approximately 84 percent. Said another way, the addict in treatment commits only one-sixth as many crimes as the addict not in treatment.

● Studies have illuminated the relationship between early experimentation with one drug and later involvement with others. Researchers have found that there are distinct and progressive stages of drug use and that involvement at one stage increases the probability that other drugs will be used during subsequent stages. The progression

of drug use appears to be: (1) beer or wine; (2) ciga-
rettes or hard liquor; (3) marijuana; and (4) illicit
drugs other than marijuana, such as cocaine. The more
extensive the involvement with drugs at an early stage of
development, the greater the likelihood that the behavior
will be continued or reinitiated at subsequent stages of
development.

PREVENTION RESEARCH

● An increased knowledge of influences leading to drug use,
which are generated by peers, the media, and much of
one's environment, offers new approaches in developing
skills to resist these pressures. These new approaches
will replace the traditional education approaches because
recent research has determined that "affective educa-
tion," which provides factual drug-related information or
broader enrichment for personal and social development,
is not very successful in drug abuse prevention.
Instead, the new approaches, such as positive structuring
of peer influence, offer more promise in the drug abuse
prevention area.

● Further research is needed to refine new approaches and
to document in detail their applicability to the preven-
tion of drug abuse.

TREATMENT RESEARCH

● Several recent, large-scale treatment outcome studies
have shown that each of the treatment modalities produces
substantial improvement in the social functioning and
employment of clients and decreases in drug use and
criminality.

● Detoxification programs, which account for 13 percent of
clients in treatment nationwide, serve mostly opiate
abusers. Modest but significant improvements in client
functioning have been documented by this treatment
approach.

● Methadone maintenance programs, which include 12 percent
of drug treatment clients nationally, are able to attract
heroin addicts into treatment, retain them in the
program, and show significantly favorable outcomes.

● Residential programs emphasize self-help and rely heavily
on ex-addicts as staff. Approximately 14 percent of all

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clients are in residential programs which are quite effective for many drug abusers.

● The most varied and widely used treatment programs (48 percent of all clients) are categorized as outpatient drug free. Recent studies have shown positive client improvement resulting from the care received in this modality.

● New treatment approaches under study include family-oriented treatment; long-acting narcotic drug maintenance, e.g., LAAM; and use of narcotic antagonists, e.g., naltrexone and buprenorphine. More research is needed on diagnostic criteria so that when people present themselves for treatment they can be matched with a treatment modality.

MARIJUANA AND CANNABINOIDS

● There has been significant improvement in chemical analytic methods for qualitative and quantitative detection of marijuana constituents in biological fluids and tissues.

● Studies being conducted among laboratory animals have shown a relationship between marijuana consumption and the production of reproductive hormones.

● A number of recent studies have shown that marijuana use during pregnancy has a high correlation with health consequences to the fetus.

● Chronic cannabis smoking has noxious effects on the lung, effects probably greater than those of tobacco smoking.

● In general, persuasive evidence indicates that consistent and regular use of marijuana poses hazards to personal and public health.

TOBACCO

● Research indicates that cigarette smoking is a prototypic dependence process, having both pharmacologic and psychological effects. In addition to being the most widespread example of drug dependence in this country, cigarette smoking is also the largest single preventable cause of illness and premature death in the United States.

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- Converging lines of research indicate that cigarette smoking is strongly related to the onset of marijuana smoking and the subsequent use of other drugs. In a representative sample drawn in 1982 of all teenagers, current cigarette smokers were 11 times more likely to be current marijuana users and 14 times more likely to be current users of heroin, cocaine, and/or hallucinogens than nonsmokers. These findings have promoted research on the hypothesis that delaying or preventing cigarette smoking by youth will result in predictable reductions in later use of other drugs.

- Many of the characteristics typically associated with severe drug dependence have now been shown to be associated with tobacco use, including peer pressure introduction, maintenance of drug-seeking behavior in the absence of social factors, tolerance and dependence, and relapse.

- Recent studies indicate that both humans and animals, when allowed to self-administer nicotine, tend to keep the dose almost constant.

- Nicotine functions as a reinforcer in both animals and humans and has been shown to produce euphoriant effects in man.

COCAINE AND STIMULANTS

- Preliminary evidence suggests that cocaine may be one of the most dangerous and potentially addicting drugs of all the substances currently being abused. Cocaine is highly reinforcing in both animals and man. Experimentation can lead to an increased frequency of use and rapid escalation of dose. A severely dependent state can occur, associated with a compulsive drive to repeatedly administer the drug.

- Single-dose effects of amphetamines may be due to bio-chemical mechanisms different from those associated with long-term chronic effects. Chronic use of amphetamines may lead to schizophrenic-like behavior.

SEDATIVES AND ANTI-ANXIETY AGENTS

- The use of barbiturates as sedative-hypnotic agents has significantly decreased over the past two decades. The use of another class of sedative-hypnotics, the benzo-diazepines (which include Valium and Librium), continued

to increase through the mid-1970s, but since that time has also shown a marked decline. An exception to this general decreasing trend in benzodiazepine use has been florazepam (Dalmane).

● Benzodiazepine tranquilizers are among the safest drugs when used legitimately to control anxiety. However, they have significant hazards associated with their misuse or abuse. The hazards include psychomotor impairment, dependence with possibly severe withdrawal, and overdose (both accidental and purposeful).

HALLUCINOGENS AND INHALANTS

● Hallucinogens are a diverse group of chemicals, primarily of plant origin or synthetic, which produce hallucinations, i.e., sensory experiences which originate in the brain rather than being based on objects in the external environment.

● The chemical structure of LSD-25 is similar to that of serotonin and dopamine, which are naturally occurring neurotransmitters in the brain. LSD-25 has also been shown to interact with subsets of both serotonin and dopamine receptors.

● Receptors for PCP have been identified in brain tissue and some cross-reactivity has been shown with a group of hallucinogenic opioids. There is also evidence that endogenous PCP-like peptides may exist in the brain.

● Inhalant use has decreased in recent years but remains unacceptably widespread among certain populations. The inhalants are especially dangerous because of their introductory role to other drugs and because of non-reversible toxic effects.

HEROIN AND NARCOTICS

● It is now known that opiates react with several types of opioid receptors. There is evidence for the existence of at least three types of opioid receptors in the human brain.

● Opioid-like peptides have been identified as normal constituents of human and animal brains. These peptides may be involved in many physiologic processes.

- The understanding of opioid chemistry has become very well developed. Drugs are now being developed and tested that have greater selectivity of action and less potential for abuse.

- The mechanisms of pain perception and its modification, possibly involving endogenous opioid peptides as well as other neurohumors, are undergoing intensive and rigorous scientific study.

BASIC RESEARCH ON ENDORPHINS AND ENKEPHALINS

- Much basic research in the drug abuse area has focused on the endogenous opioid peptides, the endorphins, and the nature of opioid receptors.

- Three major branches of the "super-family" endorphin have been identified: pro-opiomelanocortin family, pro-enkephalin family, and pro-dynorphin family.

- The mapping of the anatomical location and relationships among various endogenous opioids, different opioid receptors, and related neuronal pathways is presently the subject of intense investigation. This line of inquiry will have broad implications for many medical problems.

- The role of the endogenous opioids in normal physiologic functioning, their possible relationship to pain, and the actions of exogenous narcotic drugs are in need of further study.

EXTENT AND CONSEQUENCES OF DRUG ABUSE

SOCIOEPIDEMIOLOGICAL SURVEYS

The diverse methodologies used to understand the drug abuse
phenomenon range from pharmacological investigations with
nonhuman species in laboratory settings to studies of human
patients in clinical settings. Insights beyond those
available from laboratory or clinical studies are provided
by social epidemiological studies (Kandel 1982a; Kandel and
Davies 1982; Clayton and Voss 1981; Kaplan et al. 1982).
Such studies seek to combine the classical epidemiologists'
terminology and care in tracing the origins and spread of a
disease through a population with the social scientists'
survey methodology and sensitivity to the sociocultural
contexts of drug abuse. The most useful epidemiological
surveys are based on representative samples of the general
population. In such surveys, data concerning the distri-
bution of drug use and abuse, and on changes in drug use
patterns over time and among different groups, can be gen-
eralized from the sample to everyone represented by the
sample. By directing attention to the general population
rather than to the heavy drug users found in most clinics,
socioepidemiological surveys allow us to understand better
what kinds of people use which drugs, and how they differ
from each other and from nonusers.

Surveys that include persons of widely different ages pro-
vide valuable information about cohort differences in age at
onset of drug use and in patterns of use of various drugs.
The detailed year-by-year life history data obtained in some
surveys has shed new light on the course of drug-using
careers, showing how periods of abstinence are interspersed
with periods of heavy use and abuse (Ball et al. 1981) and
how drug abuse affects entry into and exit from various
adult roles (Yamaguichi and Kandel 1983a).

The portfolio of epidemiological research at the National
Institute on Drug Abuse (NIDA) includes a periodic national
survey of drug use in the household population (the National

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Survey on Drug Abuse) and an annual nationwide survey of drug use among high school seniors (the Monitoring the Future surveys). In addition, the Institute supports other surveys focused on different segments of the population. NIDA also maintains a nationwide drug-abuse monitoring system in hospital emergency rooms in 26 large urban areas and in a sample of hospital emergency rooms in smaller cities across the United States. This statistical system, known as the Drug Abuse Warning Network (DAWN), is designed to detect changes in drug abuse trends that may constitute a danger to public health. The DAWN emergency room data are supplemented, in many cities, with a DAWN medical examiner system designed to chart trends in deaths caused by or related to drug abuse.

The first section of this chapter will focus on the distribution (prevalence) and the changes (trends) that have occurred in drug abuse in the United States in recent years.

National Survey on Drug Abuse

This is a periodic survey of the household population of the continental United States. The 1982 survey (Miller et al. 1983) is the seventh in a series that began in 1971 and 1972 under the auspices of the National Commission on Marijuana and Drug Abuse. Since 1974, these surveys have been sponsored by NIDA. In 1982, interviews were conducted with a total of 5,624 persons: 1,581 youths, 12 to 17 years old; 1,283 young adults, 18 to 25 years old; and 2,760 older adults, 26 years old or older. These samples represent, respectively, 23 million youth, 33 million young adults, and 126 million older adults.

The percentage of youths 12-17 years old who had ever tried marijuana rose during the 1970s, from 14 percent in 1972 to 31 percent in 1979 (Fishburne et al. 1980). In 1982, the lifetime prevalence of marijuana use among youth was slightly lower, at 27 percent, a seeming reversal of the trend. A similar phenomenon appears among the young adults. Lifetime experience with marijuana was 48 percent in 1972. It rose to 68 percent in 1979, and then dropped to 64 percent in 1982. There is also a downward trend in the current prevalence of marijuana use (i.e., use in the month prior to the interview) for both youth and young adults. Among youth, use in the past month increased from 7 percent in 1972 to 17 percent in 1979. In 1982, past-month use of marijuana among youth dropped over 5 percentage points to 11.5 percent. Among young adults, use of marijuana in the preceding month rose from 25 percent in 1972 to 35 percent

in 1979. Between 1979 and 1982, it dropped 8 percentage points to 27 percent.

While these levels of marijuana use are still unacceptably high, the downturn in lifetime and current use rates from 1979 to 1982 is encouraging. For the first time in a decade, the percentages went down instead of up. Even so, it is still too early to know if this change is a one-time shift in direction, the beginning of a downward trend in use of marijuana, or merely evidence that use of marijuana in this society had reached a plateau or ceiling and had virtually nowhere to go but down.

In the older group of adults, those 26 years old or older, lifetime prevalence of marijuana use increased, from 20 percent in 1979 to 23 percent in 1982. This is primarily a result of the changing composition of the older adult population. Because a new cohort of persons enters the older adult category each year, this year's entrants include many who first used marijuana as a youth or young adult during the 1970s. Use during the month preceding the interview for older adults increased less than one full percentage point from 1979 to 1982, from 6 to 6.6 percent.

The downturn observed for use of marijuana between 1979 and 1982 also occurred in the use of other drugs such as the hallucinogens (e.g., LSD, peyote, PCP or angel dust). For example, lifetime prevalence of use of hallucinogens was 25 percent in 1979 for young adults. By 1982 it had dropped to 21 percent. Use of hallucinogens in the preceding month dropped from 4.4 percent among young adults in 1979 to 1.7 percent in 1982.

There are four classes of drugs (stimulants, sedatives, tranquilizers, and analgesics) that are usually obtained via prescription for legitimate medical purposes. Questions are asked in the National Survey on Drug Abuse about nonmedical use of these substances (i.e., use that does not comply with medical instructions about time and frequency of use). Differences in the way these questions were worded in various surveys make accurate descriptions of long-term trends in use difficult. However, nonmedical use of any of the stimulants-sedatives-tranquilizers-analgesics increased slightly for youth (7 percent in 1979 versus 10 percent in 1982). The respective lifetime rates of use of any of these drugs for young adults was 30 percent and 28 percent, a small decrease from 1979 to 1982; and for older adults, 9.2 and 8.8 percent, a small decrease as well.

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Heroin use and abuse is extremely rare. Because this survey
represents the household population, missing the transient
and street populations, reported use of heroin in the study
is low. Among the young adults, where levels of drug use
are traditionally the highest, only 1.2 percent in 1982
report ever having tried heroin, down from 3.5 percent in
1979. In contrast, the use of cocaine seems to be high and
relatively stable. Among the young adults, lifetime
experience with cocaine increased from 9 percent in 1972 to
27.5 percent in 1979. It rose slightly to 28.3 percent in
1982. Use of cocaine during the preceding year decreased
for young adults between 1979 and 1982, from 19.6 to 18.8
percent, while reported use in the past month dropped from 9
to 7 percent. Among youth, lifetime, past year, and past
month use of cocaine is relatively rare. All have remained
stable since 1979. As expected, the lifetime and past-year
rates of use of cocaine among older adults increased
somewhat between 1979 and 1982, reflecting the passage of
new cohorts into that age group. It is too early to know
whether the relative stability in levels of cocaine use
among young adults will take a downward turn as marijuana
did, or will move upward as the economy improves and levels
of discretionary income increase.

Monitoring the Future Surveys

Since 1975, under the auspices of NIDA, researchers at the
University of Michigan have surveyed approximately 18,000
high school seniors each year. The students are chosen from
about 140 public and private high schools, to represent all
current high school seniors. The findings and trends in
drug use from these studies (Johnson et al. In press) are
remarkably consistent with those obtained from the National
Survey on Drug Abuse.

The proportion of seniors ever having tried marijuana has
not changed much since 1979, when it was 60 percent. Fifty-
seven percent of the class of 1983 had tried marijuana at
least once. However, the percentage reporting use in the
month preceding the study dropped from 37 percent in 1979 to
27 percent in 1983. Of perhaps more significance from a
public health perspective, daily use of marijuana (use on 20
or more occasions during the past 30 days) decreased signi-
ficantly. Between 1975 and 1978, daily use of marijuana
among high school seniors increased from 6 to 11 percent.
However, the decline since 1978 has been almost as dramatic.
In 1983, active daily use of marijuana (5.5 percent) had
fallen to below its 1975 level of 6.3 percent. About one in
every eighteen seniors in the United States in 1983 used

marijuana daily. Part of this decline can be attributed to increasing concern about health consequences. In 1978, only 35 percent of seniors attached "great risk" to regular use of marijuana. By 1983, 63 percent were concerned that regular use of marijuana might be damaging to their health. This is equal to the percentage who saw great risk in smoking one or more packs of cigarettes a day. Another reason for the decline in daily marijuana use may be attributed to a change in attitudes about marijuana. Among seniors from the class of 1983, some 83 percent disapproved of regular use of marijuana (compared to 68 percent in 1978) and 78 percent said their friends disapproved of regular use.

Marijuana was not the only drug for which a decline in use was observed. For example, the proportion of seniors who had used PCP, or angel dust, in the preceding year decreased from 7 percent in 1979 to 3 percent in 1983. The nonmedical use of sedatives during the preceding year declined from 12 percent in 1975 to 8 percent in 1983 while nonmedical use of tranquilizers decreased from 11 percent in 1977 to 7 percent in 1983. No significant changes were observed in the past-year use of heroin (about one-half of one percent) or the amyl and butyl nitrites (drugs in the inhalant class known by such street names as snappers, poppers, Locker Room, and Rush). Past-year use of these drugs was 7 percent in 1977, and has remained between 3 and 4 percent since 1981.

Use of cocaine, stimulants, and methaqualone (known as ludes or Quaaludes on the street) began to decline for the first time in 1982. Cocaine, which had shown a dramatic increase in lifetime prevalence (from 9 percent in 1975 to 17 percent in 1981), dropped slightly to 16 percent in 1983. Past year use of cocaine, which had increased from 6 percent in 1975 to 12.4 percent in 1981, decreased to 11 percent in 1983. Stimulants, primarily amphetamines used nonmedically, were second to marijuana among the drugs used illicitly by high school seniors. Measurement of levels of use of these drugs has been somewhat confounded in recent years by the appearance of the so-called "look-alikes." The annual prevalence of use of stimulants stands at about 25 percent. The prevalence of use of methaqualone decreased slightly from 7.6 percent in 1981 to 5 percent in 1983, the first decline registered for this sedative or the sedative class of drugs.

The decline in daily cigarette use that occurred between 1977 and 1981 (from 29 to 20 percent) halted in 1982 when 21 percent reported smoking cigarettes on a daily basis. Data from the 1983 survey show that this rate had not changed. Over 93 percent of high school seniors had tried alcohol and

most (69 percent) reported having used it during the preceding month. Daily drinking was at about the same level it was in 1975 (5.5 percent). For the first time, the 1982 survey of high school seniors included questions about use of over-the-counter diet pills. In the 1983 survey, among senior girls, over 45 percent had tried them and 14 percent, about one in seven, could be considered current users of diet pills.

Seniors in Overseas Schools for Military Dependents

In 1982, a parallel survey was conducted with a representative sample of about 2,400 high school seniors, dependents of military personnel who attended 33 overseas schools administered by the Department of Defense (Johnston et al. 1983). Exactly the same proportion as their stateside counterparts had tried any illicit drug or an illicit drug other than marijuana. Lifetime prevalence rates in the two populations were nearly identical for certain drugs (marijuana, hallucinogens, sedatives). Rates of use by the overseas seniors were lower for cocaine, stimulants, the amyl and butyl nitrites, and methaqualone. However, the use of inhalants other than nitrites, tranquilizers, sedatives, heroin, and opiates other than heroin were somewhat higher among the overseas seniors. Daily use of marijuana was lower (4 percent compared to 6.3 percent), while daily drinking (8.5 compared to 5.7 percent) and daily cigarette smoking (26 compared to 21 percent) were higher abroad. Students in the Department of Defense schools expressed somewhat less disapproval of all types of drug use than stateside seniors did. They also indicated that most illicit drugs were less available to them than did stateside seniors, with three exceptions: heroin, opiates other than heroin, and tranquilizers. Students stateside and overseas perceived about the same level of risk for drug users, with two exceptions. Regular marijuana use and daily drinking were not perceived as being as risky by overseas as by stateside seniors.

The unprecedented increase in levels of drug use that occurred during the 1970s seems to have reached a rather high plateau. As noted above, preliminary evidence suggests some downward movement in prevalence rates during the 1980s, especially for youth and young adults. There has been less research attention, but growing concern among parents, educators, and health professionals about a decrease in the average age at onset of use of illicit drugs. The Monitoring the Future surveys provide the only solid data available on this issue. Initial experimentation with most

illicit drugs begins in the 10th grade or later. Marijuana is an exception. For those high school seniors who have ever used marijuana, nearly 6 out of 10 began use prior to the 10th grade. The ratio is the same for initial use of alcohol, 6 out of 10 prior to the 10th grade. Almost 2 out of 3 seniors who have ever smoked cigarettes daily began such use prior to the 10th grade. The more recent classes initiated drug use, primarily use of marijuana, earlier than the less recent classes. As an example, 37 percent of the class of 1975 had used some illicit drug prior to the 10th grade compared to 52 percent of the class of 1982.

World Wide Survey Among Military Personnel

In 1980 (Burt and Biegel 1980) and again in 1982 (Bray et al. 1983), surveys were conducted with a worldwide random sample of U.S. military personnel: 15,268 in 1980 and 22,005 in 1982. The general prevalence rates for use during the past 30 days have decreased for all drugs. For example, among all lower ranked (E1 through E5) personnel studied, 37 percent in 1980 reported having used marijuana or hashish during the 30 days prior to completing the questionnaire. The comparable figure in 1982 was 22 percent, a decrease of 15 percentage points. Decreases were noted for all serv- ices; from 40 to 31 percent in the Army, from 47 to 17 per- cent in the Navy, from 47 to 21 percent in the Marine Corps, and from 21 to 18 percent in the Air Force. The past-month use of stimulants dropped from 9 to 6 percent between 1980 and 1982 among all personnel. This compares quite favorably to the 30-day prevalence rates found in the Monitoring the Future class of 1982; 29 percent for marijuana and 11 percent for stimulants. The 30-day prevalence rates for 1982 for other drugs are almost identical to those observed among high school seniors in 1982. The exception is alco- hol. In 1982, some 83 percent of the E1-E5 military person- nel had used alcohol in some form during the preceding 30 days; a total of 13 percent reported use on 20 or more days, the usual definition of daily use. Among high school sen- iors in 1982, 70 percent used alcohol during the preceding 30 days, and 6 percent used it on 20 or more of those days.

SELECTED CONSEQUENCES OF DRUG ABUSE

Some who abuse drugs do so because they are physically and psychologically addicted to them. The acquisition and use of drugs dominates their lives. Others become habitual users. For them, drugs are fitted into their schedules as any other activity might be. It would be a mistake to assume that even the addicts and habitual users are entirely

driven by internal forces that are beyond their rational control. People take drugs primarily because of the effects they experience. While the effects sought by users are generally defined as positive ones, most drugs can also produce negative effects. The effects usually sought by users occur immediately, occur inside the individual, and do not endure long beyond the drug-taking episode. Therefore, in order to re-experience those effects, the individual must take the drug again and again. Alteration of the body through repeated use of a drug can have long-term consequences for the user's health and well-being. However, it is unlikely that these potential, long-term consequences carry much weight in decisions about drug use. Most users are cognitively aware of the potential detrimental consequences but place higher priority on the immediate effects, defined by them as positive, than on the long-term consequences that may be negative.

To avoid duplication of chapters devoted to individual drugs, more attention will be given here to social consequences than to drug-specific effects. Several types of consequences have been singled out: medical emergencies and drug-related deaths; the relationship of drug use to driving and vehicular accidents; and the effect of drug use and abuse in the workplace. These three categories of consequences were not selected because of the quantity or quality of available research evidence concerning them, but because of the real and potential social and economic effect they may have on our society.

Medical Emergencies

One clearly negative, health-related consequence of drug abuse occurs when a person overdoses, or takes too much of a certain drug or drugs. When this happens, he or she is often taken to a hospital emergency room for treatment. The Drug Abuse Warning Network (DAWN) system, sponsored by NIDA, was established to monitor emergency room episodes involving drug abuse. Data are gathered on up to four drugs that led to or caused the medical emergency. Thus, there are more drug mentions than there are drug episodes. For the 3-year period from October of 1979 through September of 1982, the annual number of drug-abuse episodes showed a net decrease of 1 percent (from 116,755 episodes in the 1979-80 period to 115,365 in the 1981-82 period). The annual number of drug mentions associated with these episodes showed a net increase of 2 percent (from 186,615 to 190,819) with an average of 1.65 drugs mentioned for each episode for the

latest reporting period (October 1981 through September of 1982).

In a sense, drug-related emergency room episodes in each of these 26 metropolitan areas provide a barometer of the nature of drug abuse in that community. The kinds of drugs being abused in different communities varies according to availability, the characteristics of the drug abusers, and where the community is located. New trends in drug abuse often start on one coast, bounce to the other, and then move toward the middle sections of the country. One notable exception is what is known as "T's and Blues" (i.e., the combination of pentazocine or Talwin and tripelennamine or Pyribenzamine), which started in the midwest.

While there is substantial variability in drug abusing patterns from community to community and in each community over time, the ranking of drugs that cause emergency room visits is fairly stable for the country as a whole. Usually ranked first is <u>alcohol-in-combination</u>. The DAWN system does not record an emergency room visit in which alcohol is the only drug mentioned. Between October of 1979 and October of 1982, there was a 5 percent increase in the alcohol-in-combination mention, from 26,623 to 27,928 mentions. To illustrate the amount of variability across communities, alcohol-in-combination increased 220 percent over the 3-year period in New Orleans, while decreasing 22 percent in Detroit.

<u>Heroin/morphine</u> is usually ranked second in DAWN mentions. Mentions for heroin/morphine increased 48 percent over the 3-year period from 7.784 in 1979-80 to 11.538 in 1981-82. This coincides with recent reports of a large increase in the availability of relatively high quality heroin in the northeastern corridor of the United States. The drug usually ranked third in DAWN mentions is the country's most widely prescribed anti-anxiety drug, <u>diazepam</u> ("Valium"). Over the 3-year period, mentions of diazepam as a causative factor in emergency room episodes decreased 21 percent, from 16,620 mentions in 1979-80 to 13,047 mentions in 1981-82. This coincides with a dramatic reduction in the number of prescriptions being written for diazepam, and with responsible action by the medical community regarding refills. <u>Cocaine</u> mentions increased 55 percent over the past 3 years, from 3,757 mentions in the first year to 5,830 mentions between October of 1981 and October of 1982. During the 3-year span, cocaine mentions increased 172 percent in Los Angeles and 167 percent in San Francisco. Cocaine mentions were down 37 percent over the 3-year period in Miami.

<u>Nonnarcotic analgesics</u> are usually ranked fifth in causing medical emergencies from drug abuse. The two principal substances involved are aspirin and nonaspirin substitutes containing acetaminophen. In the 3-year span, there was a 17 percent increase in emergency room mentions of nonnarcotic analgesics. However, the increase was only 3 percentage points for aspirin, compared to 27 percentage points for acetaminophen.

Virtually every substance, even aspirin or the nonaspirin substitutes that are found in practically every medicine cabinet, can be damaging to one's health or even life threatening if used indiscriminately. This is particularly clear in the DAWN emergency room data.

From the standpoint of the economic costs of health care (Cruze et al. 1981), additional research is needed to see what happens to persons presenting themselves in emergency rooms. Are those who appear for drug-related reasons more, less, or equally as likely as other persons to be admitted as inpatients? What happens to them after admission? Relatively speaking, are drug abusers more likely to stay in the hospital longer, utilize more of the hospital's services, and be less likely to have part of their expenses covered by third-party insurers? These are important questions in a society where the rates of drug abuse are too high, the costs of health care are increasing rapidly, and the financial and other strains on community and private hospitals are reaching crisis proportions.

Drug-Related Deaths

It is axiomatic that the ultimate consequence of drug abuse may be death. Drug-related deaths are classified as either suicide or accidental overdose. The National Institute on Drug Abuse has a nationwide DAWN medical examiner reporting system for drug-related deaths of both types--suicide and accidental overdose. The sample of medical examiners is not inclusive. Therefore, it is not possible to generalize the findings from this data system to the entire country. However, the data are useful for understanding drug abuse trends and for monitoring changes in the patterns of drug abuse.

There have been two previous peaks in health-threatening drug abuse episodes. The first occurred in 1969 and was nationwide in scope. The second occurred during the 1974-76 period and was also nationwide. Between 1969 and 1974 and again between 1976 and 1982, there were general declines in

drug-related deaths, medical emergencies, and other indica-
tors of drug abuse. In 1982 there was a resurgence in some
of these indicators, but the trends seemed to be regionally,
rather than nationally, operative.

Using data from the DAWN medical examiner system for the
period from April 1978 to March 1981, the annual number of
drug mentions associated with deaths has shown a slight
increase -- 7,157 mentions, 7,249 mentions, and 7,450
mentions respectively. The change between the first and
second year was 1 percent. The increase between the second
and third years was 3 percent. Mentions for alcohol-in-
combination increased a total of 11 percent over the 3
years. Mentions of heroin/morphine increased a total of 40
percent: 563, 687, and 787 mentions respectively. Amitrip-
tyline (an antidepressant) decreased a total of 18 percent
over the 3 years, while mentions of methadone decreased 6
percent from 1978 to 1979 and then increased 3 percent in
the third year: 379, 356, and 365 mentions respectively.
Diazepam as a cause of death decreased 13 percent over the 3
years. Drug-related deaths from cocaine showed the largest
percentage increase for the 1978 to 1981 period. Cocaine
mentions increased 147 percent between the first and the
third years: 112 mentions in 1978-79, 148 mentions in the
1979-80 period, and 277 mentions in the 1980-81 period.

The data presented above are for the entire DAWN medical
examiner system. As mentioned earlier, there are some
recent, rather striking regional changes that are not
reflected in the comprehensive data. For example, in 1980-
81, the percent of heroin deaths in New York was higher than
the peak years of 1974-76. For Los Angeles, although there
has been a significant increase, the problem of heroin
deaths does not appear to be as severe as in 1974-76, yet.
This resurgence in New York appears to be connected with a
large amount of heroin-related activity occurring in the
northeastern corridor of the United States, where the
availability of high-quality/lower-price heroin has been
increasing.

Vehicular Accidents

A predictable effect of the use of almost any psychoactive
drug is a distortion of the perception of time, space, and
the location of objects within space. A corollary effect is
a dose-related reduction in physical coordination or psycho-
motor functioning. Normally easy tasks like placing a top
on a jar or walking become difficult to perform. The abil-
ity to visually locate objects in space, judge their

distance, and track them is impaired. In addition, the ability to judge the skill being performed diminishes in relation to the dose consumed (Ferraro 1981). In view of these effects, it is not surprising to find, from a study covering the years 1979 and 1980, that alcohol is involved in up to 55 percent of all fatal highway crashes. The data came from 15 states participating in the National Highway Traffic Safety Administration's Fatal Accident Reporting System, and revealed that 60 percent of fatally injured drivers (25 to 34 years old) and 43 percent of fatally injured teenagers (16 to 19 years old) had a blood alcohol content (BAC) above .10 percent.

Marijuana is often used in combination with alcohol. The combined effects of these two drugs on psychomotor functioning may well be more disruptive than that posed by either used alone. While there is a dearth of available data concerning this problem, the data that are available give cause for alarm. The California State Department of Justice analyzed nearly 1,800 blood samples taken from drivers arrested for driving while intoxicated. Sixteen percent were positive for marijuana. Among those blood samples where alcohol was not present, marijuana was present in 27 percent.

The two studies discussed above dealt with drivers who were fatally injured or detected and arrested for driving while intoxicated. Very little is known about the prevalence of drinking, smoking, driving, and vehicular accidents in the general population. In a recent analysis of data from the Monitoring the Future Class of 1980, automobile accidents during the preceding 12 months were reported by 17 percent of the males who had not used alcohol during the year, 29 percent who had used alcohol on fewer than 40 occasions and 38 percent of those who had used alcohol on more than 40 occasions. For those in the latter group (i.e., those who had used alcohol on more than 40 occasions in the past year), 62 percent of the accidents were not reported as being related to drug use of any kind--the remainder, 38 percent, were reported as being drug related. Among the accidents that were drug related, half occurred after the person had been drinking alcohol, 1 in 10 occurred after the person had been smoking marijuana, and 4 out of 10 occurred after he had been using both alcohol and marijuana. These data, while limited exclusively to male high school seniors, a group already at high risk for automobile accidents, suggest a need for considerably more research on the relationship between drug use and driving. The leading cause of death and injury among teenagers is vehicular accidents. In

addition to the incredible amount of suffering and grief caused by the linkage between drug using and driving, which can't be measured, the economic and health-care costs associated with this phenomenon are measurably staggering.

Drug Abuse in the Workplace

Work occupies a larger portion of our daily lives than any other activity except sleep. More than any other, it is the role in which our identity as a person is grounded. Every day, over 100 million adult men and women in the United States go to work. Based on what is known about the extent and frequency of drug use in America, including alcohol, one would expect the effect of drug abuse in the workplace to be large, visible, and thoroughly studied. However, far more is known about drug abuse among students, who are not in the labor force, and among heroin addicts, whose primary sources of income are transfer payments, crime, and the drug distribution network. Very little is known about the extent to which drugs are used at work or what specific effects use has, either at work or outside of work, on various indices of job performance and productivity.

Several estimates of how much drug and alcohol abuse cost the American business community are available. For example, the Fourth Special Report to the U.S. Congress on Alcohol and Health estimated that half of the 10.2 million problem drinkers in the United States in 1981 were employed. Of these, 25 percent were thought to be white collar workers, 30 percent, manual workers, and 45 percent, professionals or managers. Although the specific effects of alcohol abuse in the workplace are still largely unknown, the economic effect was tagged at $43 billion in 1978. The estimated cost of drug abuse was put at $25 billion annually. These are considered conservative estimates, primarily reflecting lost productivity, wasted time and materials, on-the-job accidents, and absenteeism. They do not include excess disability payments, higher insurance rates, losses due to theft directly attributable to alcohol and drug abuse, or the lowered morale and productivity of workers fearful that their drug-impaired colleagues will cause an accident.

Societal level estimates of the economic costs of alcohol and drug abuse in the workplace serve a useful function. They underscore the magnitude of the problem and justify actions designed to deal with it. Unfortunately, it is relatively easy in economic cost studies to substitute assumptions where hard data from rigorously designed studies are unavailable. The much more difficult research task of

identifying the extent to which drug and alcohol abuse affect specific indices of job performance for individual workers (abusers compared with nonabusers) has not been done.

Existing data suggest that even heroin addicts are capable of maintaining gainful employment (Craddock et al. 1982). In addition, in laboratory experiments where subjects are allowed to "work" for drugs by pressing buttons (operant tasks), heroin, alcohol, and marijuana had little effect on performance. While intoxicated, the subjects continued to work for money as well as for drugs sufficient to maintain their preferred level of consumption (Mello 1981). This suggests that even heavy drug users may remain undetected by traditional performance measures until their level of drug consumption exceeds their capacity to compensate. If this conclusion is borne out in nonlaboratory conditions, it may explain why only a small proportion of respondents in large-scale surveys report having "problems at work" that they attribute to drug use. For example, in a nationwide survey of a representative sample of 2,510 men who were 20 to 30 years old, only 5 percent of those who had used alcohol and 3 percent of those who had used marijuana reported ever having problems at work because of their use of these drugs (O'Donnell et al. 1976).

Does this mean that the effect of drug abuse on workers and on various indices of job performance is overestimated? Perhaps, perhaps not! The fact is, very little is known about the complex relationship which undoubtedly exists between drug abuse, worker performance and productivity or the lack thereof, and how the work setting influences or is influenced by drug abuse. Considerably more research is needed on this relationship before definitive conclusions can be reached. Simply put, the number of unanswered questions currently far outnumbers the available answers. One such question is: what kinds of jobs are held by drug abusers? It is known that extent of marijuana use is associated with lower educational attainment, working in low status and low paying occupations, and a higher chance of being unemployed for varying periods of time (Kandel 1982b; Voss and Clayton 1983). The same is true for heroin use. In a recent nationwide study of clients enrolled in four types of treatment for drug abuse (e.g., methadone, out-patient detoxification, outpatient drug free, and residential), only 27 percent of the methadone and 13 percent of the residential clients were employed during the week prior to admission to treatment. When the employment status of all clients at admission to treatment was examined, 18

percent were employed full time, 8 percent were working part time, 18 percent were unemployed but seeking work, and 56 percent were unemployed and not seeking work. While these figures are not encouraging, perhaps the best predictor of future gainful employment is a past history of successful work experience. About 24 percent of the clients had held a job for more than 3 years, and over 56 percent had held at least one full-time job for a year. Only one-quarter of these addicts had not held a fulltime job during the 3 years prior to admission to treatment (Craddock et al. 1982).

The total economic effect of lower productivity among heavier drug abusers may be relatively small, since they constitute only a small proportion of the total labor force and work, for the most part, on the lower rungs of society's occupational ladder. However, even one drug-impaired decision by a heavy drug user holding a responsible position can have costly, even deadly consequences. This raises another question: how many people use drugs on the job? While there is no way to answer this question with existing data, enough anecdotal evidence exists to say--too many.

TWO OTHER CONSEQUENCES OF DRUG ABUSE

In this chapter it is not possible to review or even mention all of the important consequences of drug abuse; some drug-specific consequences will be covered in later chapters of this report. However, something must be said, albeit in abbreviated form, about two other consequences of drug abuse.

The first consequence concerns the relationship between criminal involvement and drug abuse, principally but not exclusively limited to heroin. A longitudinal study of 243 heroin addicts in Baltimore (Bell et al. 1981, 1982) found that they committed crime(s) on an average of 178 days per year and had committed an average of over 2,000 crimes each since the onset of addiction. When these addicts were using drugs most heavily, on a daily basis, they averaged committing crime(s) during 248 days a year. During periods of abstinence from drugs, the average number of crime-days dropped to 41 per year. Over 90 percent of the crimes committed by these addicts fell into three categories: property theft (38 percent), drug sales (27 percent), and other offenses such as illegal gambling, pimping, and fencing stolen property (26 percent).

The figures presented above are statistical averages. Even so, they are staggering to the imagination. While it is true that more than a few heroin addicts commit crimes to support their habits, most do so at a relatively low rate (Goldstein 1981). However, a relatively small group labeled "violent predators" push the averages up considerably. For example, in one study of over 2,000 inmates in three states (Chaiken and Chaiken 1982), the sample's 10 percent of violent predators who had the highest robbery rates committed over 135 robberies a year. The 10 percent with the highest burglary rates committed over 500 burglaries a year. The 10 percent with the highest drug-dealing rates made over 4,000 drug deals a year. It is clear from these data that this small group contributes disproportionately to the amount of crime experienced in our society. Equally clear is that the violent predators are not just heroin addicts. They are prone to abuse a variety of drugs, more often than not in combination rather than separately. It is also abundantly clear in this and other similar studies that drug abusers commit violent crimes like aggravated assault and armed robbery almost as readily as they commit other crimes.

The violence that permeates the drug-abusing community is becoming increasingly evident. In cities where homicide data are collected at the precinct rather than the city level, many homicides that once would have been classified as unrelated to drugs are now being classified as drug related. This is because police officers and detectives most familiar with the drug and criminal underworld in their part of the city are able to link the homicide victims with the role they play in drug trafficking. Simply put, drugs such as marijuana, heroin, and cocaine are illegal contraband. Their distribution occurs under clandestine conditions for what oftentimes are massive profit margins. As a result, violence is a regular part of the drug-trafficking business. The violence connected with drug abuse threatens the health and safety of our nation.

The second consequence concerns the so-called drug progression or developmental stages hypothesis (Kandel 1975). The underlying assumption is that there are distinct stages of drug use, and that use of drugs at one stage increases the probability of use at a subsequent stage. The stages of drug use are traditionally defined as: (1) beer or wine, (2) cigarettes or hard liquor, (3) marijuana, and (4) illicit drugs other than marijuana, such as heroin and cocaine. Recently, there has been a suggestion that problem drinking (Donovan and Jessor, in press) and use of prescrip-

tion drugs (Yamaguichi and Kandel, unpublished) constitute another stage after use of marijuana.

The principle of the progression hypothesis is not certainty. Obviously, only a subset of those who use marijuana go on to use heroin and cocaine. Therefore, the principle behind the hypothesis is probability: the more extensive the involvement with a drug at a lower stage of development, the greater the likelihood of experimenting with drugs at the next or subsequent stages of development (O'Donnell and Clayton 1982; Clayton and Voss 1983). For example, only 13 percent of male students in the class of 1980 who had never used cigarettes reported having tried marijuana. Among those who had used cigarettes only occasionally, 28 percent had tried marijuana. Sixty-five percent of these students who used cigarettes regularly reported having tried marijuana. The comparable figures for female students in the class of 1980 are 3, 13, and 51 percent. When the relationship between use of marijuana and use of cocaine is reported, only four-tenths of 1 percent of students in the class of 1980 who had never used marijuana report having tried cocaine. The respective percentages reporting having ever used cocaine rise progressively with the number of times a person had used marijuana: 1-2 times marijuana, 2 percent used cocaine; 3-5 times marijuana, 5 percent used cocaine; 6-9 times marijuana, 8 percent used cocaine; 10-19 times marijuana, 12 percent used cocaine; 20-39 times marijuana, 20 percent used cocaine; and for those who had used marijuana 40 times or more, 53 percent report having used cocaine (Clayton and Ritter 1983).

The youth who provided these data were not institutionalized juvenile delinquents, nor were they youth labeled by parents and teachers as troublemakers. In fact, the studies mentioned above do not include high school dropouts or those who were chronically absent (Clayton and Voss 1982). The levels of drug use and the strength of the relationship between marijuana and cocaine use would be even higher and stronger for these groups. The data presented above were provided by mainstream youth; the 75 or 80 percent of the 1963 birth cohort that has not dropped out of school.

The foundation of the progression hypothesis is not pharma-cological. No evidence exists suggesting that some chemical property of drugs at lower stages on the continuum predis-poses someone to use drugs at later stages. Instead, the factors that facilitate progression through the stages of drug use appear to be personal, social, and contextual in nature. At least two of these factors have been identified.

The first seems to be membership in a circle of friends and acquaintances that consists more and more exclusively of drug users. The second is an involvement in selling and distributing drugs (Johnson 1973; Single and Kandel 1978; Clayton and Voss 1983). Using the marijuana-cocaine relationship as an example, the following chain of events plausibly represents what often happens. A young person is offered an opportunity to use marijuana in a social or party setting and receives it free of charge. As his or her use becomes more frequent, often within the same social context and with the same people, the youth offers to pay for his supply of the drug. After a while, that youth begins to provide his or her friends with the drug as part of the social exchange process that has become normative in that group. The supply of marijuana must come from somewhere and someone must pay for it. Before long, the youth's friends offer to pay for their share. The youth has discovered a way to supplement his income while maintaining his own supply of the drug. Eventually, the youth's supplier of marijuana will offer him or her an opportunity to try another drug, such as cocaine, as a reward for being such a good customer. The whole process is not markedly different from the ways things work in other facets of the business world. However, one thing that is different is that the long-term consequences to the health and well-being of the individuals involved are serious.

The scenario described above has occurred time and again, throughout the United States, in the urban ghetto and in the tree-lined streets of practically every suburban neighborhood in our country. Many facets of the problem demand continued policy-related attention at the Federal level. The Department of Health and Human Services will deal with this problem via its initiatives in the area of health promotion and prevention. The Monitoring the Future studies reveal that roughly equal proportions of high school youth believe that regular use of marijuana or cigarettes entails great risk. Efforts to understand the short-term effects and the long-term health and social consequences of all drug use will be a research topic of special interest during the next several years. In addition, efforts to design and deliver effective educational and prevention messages about these consequences will be expanded and constantly updated. While it is an old cliche, the youth of our society are its future. Every effort will be made to provide our youth with the information they need to make healthy decisions about the myriad of behavioral options with which they are faced in this complex society.

CONCLUSIONS

This first triennial report to the United States Congress on drug abuse provides the Department of Health and Human Services with an opportunity to evaluate some of the parameters of drug abuse in the United States. In the recent past, significant advances have been made in what is known about drugs--their chemical composition, how they are chemically transformed by the body, the effects they have on the human organism, how they are used and abused and by whom, and the incredible social and economic effect that use and abuse have on our society. In this first chapter, data have been presented that show that drug use and abuse have penetrated into every part of the population; drug abuse is no respecter of persons. While there are some encouraging signs of changes in the direction of usage patterns, these may be one-time changes or temporary fluctuations instead of permanent trends. Further data are needed before it can be said that there is a trend downward in the prevalence rates. Even if a downward trend is confirmed, the level of drug abuse in the United States is higher than that of any other industrialized country in the world. The magnitude of the problem demands an exceedingly high level of commitment among all segments of the population and by government officials at all levels.

Data have also been presented in this chapter that underscore the seriousness of the problem in terms of medical emergencies and drug-related deaths, automobile accidents in which drug use is implicated, and the effect of drug abuse in the workplace. One thing is certain. There is still a great deal not known about the social and health consequences of drug abuse. However, what little that is known for certain and all there is reason to suspect justify serious national concern.

The chapters that follow will emphasize what is known about specific drugs abused in the United States, and some of the drug-specific effects of that abuse. Each of these drugs and the consequences associated with them are a part of the total problem. The drug abuse problem in the United States is big, complex, and constantly changing. It is a problem that must be dealt with decisively. This triennial report demonstrates some of the ways the Department of Health and Human Services is meeting its responsibilities to the American public in dealing with drug abuse.

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PREVENTION RESEARCH

INTRODUCTION

In view of the difficulties associated with the treatment of
individuals who have already become substance abusers, the
prospect of developing effective prevention strategies holds
a great deal of appeal. For a variety of reasons, however,
the development of effective substance abuse prevention
programs has remained an elusive goal until very recently.
While prevention efforts have only begun, significant prog-
ress in related areas provides preliminary support for the
efficacy of several new substance abuse prevention models.
Although the main purpose of this chapter is to describe
advances in the area of prevention, it would seem appro-
priate to focus briefly on what is known about the etiology
of adolescent substance use and abuse. Such a focus
provides a frame of reference for the rationale behind
various prevention approaches.

UNDERSTANDING THE CAUSES OF SUBSTANCE ABUSE

Age of Onset and Developmental Course

A logical prerequisite for developing effective prevention
strategies involves understanding when and why substance use
begins. For most individuals, initial experimentation and
subsequent, more regular patterns of use typically develop
during adolescence. Since experimentation with a wide vari-
ety of substances is fairly commonplace, multiple use is
frequently viewed by society as normal behavior and perhaps
even as an integral part of the coming of age in America.
Early experimentation is reported to lead to regular use
and, for all too many individuals, to compulsive patterns of
use characterized by psychological and physiological depen-
dence.

The use of most substances tends to be confined initially to
social situations, with solitary use being relatively uncom-
mon. This has led several researchers to speculate that

substance use may provide a major focus for social inter-
action and identity (Beck 1967; Jessor 1976). Although
social and psychological factors appear to be primarily
responsible for the initiation of substance use, as use
becomes more regular, psychopharmacological factors become
increasingly important in reinforcing and maintaining
regular patterns of use (Meyer and Mirin 1979; Ray 1974).
Despite warnings from parents, teachers, and the media, most
adolescent substance users (particularly during the early
stages of use) exhibit a remarkable absence of concern about
consequences related to use of such substances. Moreover,
adolescents tend to overestimate their ability to avoid
personally destructive patterns of use. Adolescent ciga-
rette smokers, for example, typically believe that they can
quit smoking whenever they wish (Botvin 1978). Only when
they have made a serious effort to quit smoking may they
become aware of the extent to which they are psychologically
and physiologically dependent on tobacco.

Experimentation with one substance frequently leads to
experimentation with other psychoactive substances. The
sequence of experimentation and subsequent regular use of
psychoactive substances observed in most individuals sug-
gests what has been referred to as a "substance use hier-
archy" (Hamberg et al. 1975; Kandel 1976). Most individuals
typically begin by using tobacco and alcohol, progressing
later to the use of marijuana. Some individuals may even-
tually progress to the use of depressants, stimulants, and
psychedelics. Typically, the use of opiates and cocaine
appears toward the end of this progression. For this
reason, the use of tobacco and alcohol is viewed by many
experts as gateway behavior for all too many individuals who
go on to use other drugs, e.g., opiates and cocaine.

Factors Promoting Substance Use

Research evidence suggests that a number of factors may
promote and/or facilitate the initiation of substance use
(Blum et al. 1979; Braucht et al. 1973; Jessor 1976;
Wechsler 1976). Individuals from families in which one or
more members (generally parents or older siblings) smoke,
drink, or use drugs are more likely to become substance
users themselves, as are individuals whose friends are
substance users. In addition to these social influences,
the portrayal in the popular media of substance use as
something that is not merely acceptable, but is an important
part of popularity, sex appeal, and good times, appears to
be a subtle and powerful influence for drug use.

Cognitive, attitudinal, and personality characteristics appear to affect individuals' vulnerability to substance use (Millman and Botvin 1983). Psychological characteristics that have been associated with substance abuse include low self-esteem, low self-satisfaction, greater need for social approval, low social confidence, high anxiety, low assertiveness, greater impulsivity, rebelliousness, external locus of control, and impatience to assume adult roles.

Substance users also appear to differ from nonusers along several behavioral dimensions, suggesting different orientations, values, and aspirations. For example, individuals who smoke, drink, or use drugs tend to get lower grades in school, do not participate in organized extracurricular activities such as sports or clubs, and are more likely than nonusers to engage in antisocial behavior such as lying, stealing, and cheating (Demone 1973; Jessor et al. 1972; Wechsler and Thum 1973). Although the causal relationships are not established, evidence from a variety of sources indicates that there are high intercorrelations between the use of various substances so that, for example, adolescents who use opiates are also likely to drink excessively and smoke cigarettes.

In addition to different forms of substance use tending to be highly associated with one another, substance use correlates with other health-related behaviors such as premature sexual activity, truancy, and delinquency. As Jessor (1982) has noted, the association between health-compromising behaviors is perhaps one of the clearest facts to have emerged from the past decade of research, with several types of health-compromising behavior being likely to occur within the same individual. The correlations between these behaviors may be quite substantial and appear to be equally true for males and females. Further, various types of health-compromising behavior "correlate in a similar way with a large number of personality and environmental measures of psychosocial risk" (Jessor 1982, p. 453). This observation suggests that a number of problem behaviors are caused by the same underlying factors. Thus, various forms of health-compromising behavior may more usefully be viewed as a syndrome than as separate or idiosyncratic behaviors. For this reason, it has been proposed that prevention programs be developed to focus on the underlying determinants of several theoretically and empirically related problem behaviors (Botvin 1982; Swisher 1979).

Substance Use and Adolescent Development

The initiation and early stages of substance use among adolescents occurs in the context of great physical and psychological change. As part of the natural process of separating from parents, developing a sense of autonomy, establishing an identity, and acquiring the skills necessary for functioning effectively in an adult world, individuals typically experiment with a wide range of behaviors and life styles. Profound cognitive changes, during the beginning of adolescence, significantly alter the adolescent's view of the world. As Piaget (1932) has observed, the thinking of the preadolescent is rigid, literal, and grounded in the "here and now." Adolescent thought, on the other hand, is more relative, abstract, and hypothetical. In general terms, new hypothetico-deductive modes of thinking enable adolescents to conceive of a wide range of possibilities and logical alternatives, to accept deviation from established rules, and to recognize the frequently irrational and inconsistent nature of adult behavior.

The relative influence of peers and parents also changes. As individuals approach adolescence, there is a gradual but progressive decline in parental influence and a corresponding increase in the influence of peers and other socializing agents (Utech and Hoving 1969). Furthermore, due to what has been characterized as "adolescent egocentrism" (Elkind 1978), adolescents tend to have a heightened sense of self-consciousness concerning their appearance, personal qualities, and abilities.

Developmental changes of this period increase adolescents' risk of yielding to the various direct and indirect pressures to smoke, drink, or use drugs. The combination of adolescent egocentrism and increased reliance on the peer group tends to promote substance use in some individuals. Concurrent cognitive developments can undermine previously acquired knowledge of the potential risk of using these substances, thus increasing vulnerability to substance use influences. For example, the new cognitive orientation may let adolescents see inconsistencies or logical flaws in adults' arguments on the risks of substance use, or may enable adolescents to formulate counter arguments or rationalizations for ignoring these risks. The latter is particularly likely if substance use is perceived to have social or personal benefits. Thus, a recognition of the developmental tasks, issues, changes, and pressures motivating adolescent behavior is necessary to fully understand the etiology of substance use/abuse.

EDUCATIONAL APPROACHES TO PREVENTION

Informatio., Dissemination

Until recently efforts to prevent substance abuse generally
involved the presentation of factual information. Tobacco,
alcohol, and drug education programs were based largely on
the assumption that increased knowledge about these sub-
stances and the consequences of their use would be an effec-
tive deterrent (Goodstadt 1978). For example, smoking
education programs typically provide students with factual
information about the long-term health consequences of
smoking cigarettes (Thompson 1978). Similarly, alcohol and
drug education programs primarily attempt to increase
students' knowledge about the legal, pharmacological, and
medical aspects of using these substances (Goodstadt 1978).

Frequently, such programs use fear arousal messages designed
to scare individuals enough to deter them from smoking,
drinking, or using drugs. However, even when these programs
do not include fear arousal messages, they typically have a
moralistic overtone that suggests well-meaning adults
"preaching" to students about the evils of drug use.
Research results indicate that simply making information
available is not sufficient to positively change attitudes
toward substance use.

Affective Education

In recent years, a variety of other prevention strategies
have been implemented. These programs are categorized as
"humanistic" or "affective" education programs, and gener-
ally attempt to enrich the personal and social development
of students. As Swisher (1979) has observed, the field of
substance abuse prevention has moved toward this type of
program, which is based at least in part on the following
assumptions. First, substance abuse programs should aim to
develop prevention-oriented decisionmaking concerning the
use, by persons of all ages, of any licit or illict drug.
Second, such decisions regarding personal use of drugs
should result in fewer negative consequences for the
individual. And third, the most effective way of achieving
these goals would be via programs to increase self-esteem,
interpersonal skills, and participation in alternatives.

Consistent with these assumptions, the focus of recent
prevention programs has been to increase self-understanding
and acceptance through activities such as values clarifica-
tion and decisionmaking; to improve interpersonal relations

through activities such as communication training, peer counseling, and assertiveness training; and to increase students' abilities to meet their needs through social institutions.

Effectiveness of Educational Approaches

A number of reviews have been published concerning the effectiveness of both types of substance abuse prevention programs (Berberian et al. 1976; Braucht et al. 1973; Dorn and Thompson 1976; Goodstadt 1974; Pyramid 1976; Richards 1969; Schaps et al. 1981; Swisher and Hoffman 1975). The conclusions drawn in each of these reviews are remarkably consistent. First, most substance abuse prevention programs have not contained adequate evaluation components. Many programs that had otherwise sound evaluation designs failed to examine the impact of their prevention programs on actual substance use behavior. For example, of the 127 program evaluations they reviewed, Schaps et al. (1981) found only four relatively well-designed studies that utilized substance use measures. Little positive impact on behavior was demonstrated.

Second, evaluations of programs whose main strategy was providing factual information clearly indicate that increased knowledge has virtually no impact on substance use or on intentions to smoke, drink, or use drugs. Third, although some studies that contain cognitive and affective components have produced at least some positive results (Swisher et al. 1973), in general affective education approaches appear to be more experiential in their orientation and to place too little emphasis on the acquisition of skills necessary to increase personal and social competence, particularly those skills needed to enable students to resist the various interpersonal pressures to begin using one or more substances. Finally, the inescapable conclusion to be drawn from the existing substance abuse prevention literature is that few of these studies have demonstrated any degree of success in terms of actual substance abuse prevention.

In short, traditional educational approaches to substance abuse prevention appear to be inadequate because they are too narrow in their focus. The "affective" or "humanistic" educational approaches, on the other hand, appear to have placed too little emphasis on the acquisition of the kind of skills necessary to increase personal and social competence and enable students to cope with the various interpersonal and intrapersonal pressures to begin using tobacco, alcohol, and drugs.

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PSYCHOSOCIAL APPROACHES TO PREVENTION

Despite the rather unimpressive results of the educational
approaches to substance abuse prevention described above,
there have been sufficiently significant advances in the
field of prevention in recent years to provide cause for
optimism. Most recent advances have been prevention
approaches that combine a strong theoretical foundation with
an emphasis on rigorous research design and evaluation.

Theoretical Foundations

Although theories concerning the etiology of substance abuse
are plentiful (Lettieri et al. 1980), few of these theories
appear to have any direct relevance to the development of
effective prevention strategies. However, despite the vast
array of substance abuse prevention theories and the lack of
a monolithic theory on the initiation of substance use and
abuse, both social learning theory (Bandura 1977) and
problem behavior theory (Jessor and Jessor 1977) provide a
useful conceptual framework for understanding the etiology
of substance use. From this perspective, substance use is
conceptualized as a socially learned, purposive, and func-
tional behavior, resulting from the interplay of diverse
social and personal factors.

Some adolescents may be motivated to engage in drug-taking
behaviors as a way of coping with expected failure or as an
alternative way of achieving some specific desired goal,
e.g., some adolescents may begin to use drugs in response to
the fact that they are not doing well academically and as an
alternative means of achieving popularity, social status, or
self-esteem. The use of tobacco, alcohol, and certain other
drugs may also be an attempt to cope with anxiety, particu-
larly that induced by social situations. Other individuals
may begin smoking, drinking, or using drugs as a result of
what has been referred to as the social influence process.
That is to say, individuals may begin using one or more
substances after repeated exposure either to high-status
models who engage in these behaviors, or to persuasive
appeals made by advertisers or peers.

Differential susceptibility to social influence appears to
be mediated by personality, with individuals who have low
self-esteem, self-confidence, and autonomy being more likely
to succumb to these influences (Bandura 1969; Rotter 1972).
Thus, adolescents may begin smoking, drinking, or using
drugs for a variety of different reasons. This suggests not
one but several different pathways to substance use/abuse.

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Clearly, to be effective, prevention programs must deal successfully with potential motivations to use drugs, and must provide students with the necessary skills to resist pro-use social pressure.

Implications for preventive intervention strategies drawn from these theoretical perspectives provide the basis for several new approaches to substance abuse prevention. All these approaches utilize school-based interventions aimed at junior high school students, and have their roots in social learning theory (Bandura 1977) and problem behavior theory (Jessor and Jessor 1977). They differ on the emphasis of these interventions and their mode of implementation. Some approaches place primary emphasis on increasing students' awareness of prosubstance-use social pressures (referred to as psychological inoculation) and on teaching specific techniques for resisting such pressures; others emphasize the development of more general coping skills and, from a broader perspective, focus on the most significant underlying determinants of tobacco, alcohol, and drug use through personal and social skills training. Such generalized programming may be delivered in the context of comprehensive school health programs.

Psychological Inoculation and Pressure-Resistance Skills

The most significant breakthrough concerning substance abuse prevention occurred with adolescent cigarette smoking. Although several research groups around the country have demonstrated the efficacy of prevention strategies focusing on the social and psychological factors believed to be involved in the initiation of cigarette smoking, Evans and his colleagues at the University of Houston (Evans 1976; Evans et al. 1978) are credited with the pioneer work in the development and testing of a strategy for countering social influences to smoke. In addition to being based on social learning theory, Evans' work was strongly influenced by persuasive communications theory, as formulated by McGuire (1964, 1972). A central feature of the prevention approach utilized by Evans involves showing students films depicting the kind of social pressures to smoke they will encounter as they progress through junior and senior high school, to "inoculate" them against such pressures. These films also demonstrate specific tactics for resisting these pressures to smoke.

Additional intervention components utilized by Evans involve (1) providing students with feedback concerning the rate of smoking among their peers, to correct the perception that

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"everybody smokes," and (2) communicating that cigarette smoking produces immediate physiological effects as well as the long-term effects discussed in most conventional smoking education programs.

Other investigators have elaborated on this model, placing more emphasis on actually training students to deal with both peer and media pressures to smoke, drink, or use drugs. McAlister and his colleagues (McAlister et al. 1979; McAlister et al. 1980; Perry et al. 1980; Telch et al. 1982) use a more intensive approach in applying the concept of psychological inoculation to the prevention of cigarette smoking as well as other behaviors detrimental to health. Two distinctive features of this approach are (1) the use of older peer leaders as the primary agents delivering the prevention program, and (2) the use of role playing and other techniques to enhance the learning of pressure resistance skills. Studies using similar approaches have been conducted in Minnesota (Arkin et al. 1981; Hurd et al. 1983; Luepker et al. in press; Murray et al. 1980), Canada (Flay et al. 1983), and Southern California (Flay et al. in press; Johnson et al. 1981).

There is a growing recognition that presenting abstract knowledge about the negative consequences of substance abuse is of marginal value as a prevention strategy, especially if it is the only strategy. Certain types of knowledge, however, concerning the use of tobacco, alcohol, and drugs may be a useful component of substance abuse prevention programs. For example, since observers have noted that adolescents typically overestimate the prevalence of smoking, drinking, and the use of certain drugs (Fishbein 1977), most prevention strategies have attempted to correct normative expectations of high substance use, hoping to reduce the perceived social support for these behaviors. To combat the perceived social benefits of smoking, drinking, or using other drugs, which may override concern for any potential negative consequences (particularly long-term ones), an effort has been made in many prevention strategies to focus on immediate negative consequences of use that may be seen as social liabilities, e.g., nicotine stains on teeth, bad breath, etc. A final component of several studies conducted with this prevention strategy has students make a public commitment to remain a nonsmoker or nondrug user. These programs are implemented using films with teacher-led discussion, older peer leaders, same-age peer leaders, and regular classroom teachers.

Personal and Social Skills Training Approaches

A similar prevention strategy with a broader focus than the social psychological approaches discussed above has been developed and tested over the past few years. While such approaches teach students tactics for resisting peer pressure, the skills are taught within the framework of programs designed to enhance general personal and social competence. Thus, this type of prevention program embodies the broader competence-enhancement philosophy found in affective education.

In addition to demonstrating a strong commitment to research design and evaluation, this type of prevention strategy has a conceptual foundation grounded in social learning theory and employing many of the empirically validated techniques of cognitive-behavior therapy. Although most techniques used in these programs were initially developed for the remediation of existing deficits, they have been widely applied to competence enhancement in recent years (Pentz and Tolan 1983).

Research with this prevention approach is currently being conducted at a number of universities under the sponsorship of the National Institute on Drug Abuse. Despite similarities in the general prevention strategies, these approaches differ with respect to the specific skills incorporated into the intervention program and the extent to which those skills focus on adolescent substance use.

In addition to providing students with general life skills, this prevention strategy applies the skills specifically to the problem of substance abuse. Throughout the program, direct connections are made between the use of general life skills and the issues of smoking, drinking, and drug use. For example, in addition to teaching students general assertive skills, e.g., the use of "no" statements, requests, and the assertive expression of rights, students are taught how to use these skills to resist direct interpersonal pressure to smoke, drink, or use drugs. Thus, students are not only taught a wide range of personal and social skills to improve their general personal competence and reduce their potential motivation to use one or more substances, but also taught the application of these skills to situations in which they may experience prosubstance-use social pressure.

Effectiveness of Psychosocial Approaches

The growing body of research on the recently developed psychosocial prevention programs indicates that both the psychological inoculation/pressure-resistance strategies and the broader personal and social skills training strategies reduce substance use behavior among junior high school students. Both prevention strategies have demonstrated that they are capable of reducing cigarette smoking by approximately 50 percent over a 1-year period (Botvin et al. 1980; Hurd et al. 1980; McAlister et al. 1980). Similar reductions have also been reported for alcohol and marijuana use (Botvin, in press; McAlister et al. 1980).

Followup studies conducted for cigarette smoking indicate that the positive behavioral effects of these prevention approaches are evident for up to 2 years after the conclusion of these programs (Botvin and Eng 1982; Luepker et al. in press; McAlister et al. 1980; Telch et al. 1982). Since, for the most part, studies testing the application of these prevention strategies to other substances, such as alcohol and marijuana, have only recently begun, followup data for these substances are not yet available.

Changes in general interpersonal skills and skills related directly to substance abuse prevention have also been reported as a result of these prevention programs, as have changes on one or more cognitive, attitudinal, or personality-predisposing variables (Botvin et al. 1980; Botvin and Eng 1982; Botvin et al. in press; Pentz 1982a; Pentz 1982b; Schinke and Blythe 1982).

Caveats and Future Directions

Notwithstanding the promising results obtained with the current "generation" of substance abuse prevention approaches, several caveats must be kept in mind. First, the studies referred to have been conducted by highly motivated researchers under well-controlled conditions that may not be representative of most schools or classrooms. It is unclear at this point how effective these prevention strategies will be when implemented under more typical conditions. Second, virtually all the research conducted to date has involved predominantly white, middle-class populations. The extent to which these prevention programs are effective with other populations, e.g., urban minority students, who are likely to be at high risk for becoming substance abusers, has yet to be determined. Third, most studies conducted thus far have focused on cigarette

smoking. The extent to which these prevention programs
effectively reduce the use of other substances has yet to be
determined. Fourth, since these studies have been conducted
with junior high school students, they have been evaluated
in terms of their impact on substance use. Thus, whether or
not these approaches will prove to prevent substance abuse
effectively is still an open question.

In addition, it is possible that these efforts have only
delayed the initiation of substance use. Although several
investigators have conducted followup studies to determine
the long-term effectiveness of these approaches, it is not
yet clear how long the effects of these programs will last,
either with or without active intervention throughout junior
and senior high school. Thus, while recent advances in
prevention have been quite dramatic, future research is
needed to resolve a number of important issues.

SUMMARY AND CONCLUSIONS

The initiation of substance use typically begins during
adolescence and appears to be the result of a complex inter-
play of social, personality, cognitive, attitudinal, behav-
ioral, and developmental factors. Traditional smoking,
alcohol, and drug education programs have attempted to
increase students' knowledge of the risks associated with
using these substances or to create antisubstance-use
attitudes, hoping to deter use. Other programs have
attempted to enrich the personal and social development of
students through what has been referred to as "affective"
education to reduce motivations to use one or more sub-
stances or, in the case of substances such as alcohol, to
encourage more responsible use.

Unfortunately, the inescapable conclusion to be drawn from
the substance abuse prevention literature is that few of
these programs have demonstrated any degree of success in
terms of actual prevention of substance use or abuse.
Traditional educational approaches to substance abuse
prevention appear to be inadequate because they are too
narrow in their focus. The "affective" education
approaches, on the other hand, appear to have placed too
little emphasis on the acquisition of skills that are likely
to increase general personal competence and enable students
to cope with the various interpersonal and intrapersonal
pressures to begin using tobacco, alcohol, and drugs.

The potential effectiveness of a new "generation" of sub-
stance abuse prevention programs, developed and tested in

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the past few years, provides the basis for some degree of optimism. All these approaches are similar, having their roots in social learning theory, but differ in their emphasis and mode of implementation. Substance abuse prevention models have demonstrated, in a number of studies, that they can reduce substance use behavior over short periods of time. Notwithstanding the very promising results of these prevention programs, further research is necessary to determine the applicability of these approaches to a broader range of individuals, implementation situations, and substances.

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TREATMENT RESEARCH

THE EFFICACY OF BASIC DRUG TREATMENT MODALITIES

Historically, there have been four modalities available for
the community-based treatment of drug dependence: detoxifi-
cation, methadone maintenance, residential, and outpatient
drug-free treatment. More recently, opiate antagonists,
such as naltrexone, and opiate agonist/antagonists, such as
buprenorphine, are being tested and developed and hold
promise of becoming new treatment modalities for heroin
addicts.

At the beginning of this decade, researchers were faced with
several basic questions regarding the efficacy of these
treatment modalities. Do patients improve following treat-
ment? Are the improvements confined to drug use or are they
more pervasive? Are these improvements the result of the
treatment process or merely the result of maturation?

Research findings in the past several years have provided
answers to these questions. The development of valid, reli-
able, and comprehensive research instruments contributed to
the investigation. In addition, the application of com-
puters and sophisticated multivariate statistical analyses
in clinical evaluations has made it possible to extract
meaningful information from large-scale studies outside the
traditional laboratory setting (Simpson and Sells 1982).

Several studies have evaluated the effectiveness of drug
abuse treatment modalities with large groups of patients and
in many different treatment programs. The Drug Abuse
Reporting Program (DARP) studied 44,000 treatment admissions
in 52 programs, and conducted followups 4 years after treat-
ment termination on about 10 percent of the admissions
(Simpson and Sells 1982). More recently the Treatment Out-
come Prospective Study (TOPS) followed 11,750 patients in 41
programs scattered throughout the country (Rachal et al.
1983). A third large-scale study evaluated the effective-
ness of 49 VA drug-dependence treatment programs using a

sample of 1,655 patients (Lorei et al. 1978). The design of
all these multiprogram studies called for independent,
unbiased evaluations of patients before, during, and after
treatment. The results were quite similar. Findings from
all three showed substantial client improvements in social
functioning and employment, as well as major reductions in
drug use and criminality, after treatment. These results
applied to patients who had been treated in methadone main-
tenance, residential, and/or outpatient drug-free modal-
ities. Those who dropped out from treatment early showed
little or no improvement, while those who stayed in treat-
ment longer showed more improvement. The findings from the
national studies were consistent with in-depth studies of
individual treatment programs. For example, a study of 742
patients treated in a single methadone program showed a 56
percent reduction in drug use, a 67 percent decrease in
crime, and a 300 percent increase in earned income, 6 months
after treatment (McLellan et al. 1982).

These improvements are not confined to drug use only but
also extend to other aspects of the patient's life. Fur-
ther, there are indications that these improvements are due
primarily to treatment and are not merely the result of
maturation.

Treatment research studies in the drug field do not attempt
to evaluate "cure" rates--rather, overall improvement is
measured. This approach is taken because addiction is now
viewed as a chronic disease, much like cardiovascular or
arthritic diseases. Few patients are "cured" to the extent
that they are no longer at risk for a recurrence of their
illness. Patients tend to follow a relapsing and remitting
course, with successive treatments followed by longer
periods of remission.

THERAPEUTIC COMPONENTS AND THEIR ROLE IN TREATMENT EFFICACY

Given the basic findings, which show that drug abuse treat-
ment is effective, researchers turned to two important
treatment questions. Which treatment modality is "best"?
What treatment factors within the modalities are most
responsible for the observed effectiveness of the modality?

In addressing these questions, clinical researchers have
conducted sophisticated analyses of the specific therapeutic
components of each of the major modalities. This approach
allows selection of a more homogeneous patient sample, in
that patients in comparison groups may be equated on all but
one therapeutic element (the one under study) within the

modality. In turn, this permits the use of random patient assignment without the disadvantage of differential drop-out rates. The results from this approach have led to better understanding of the particular factors associated with patient improvement in each modality.

DETOXIFICATION

As the name implies, the chief goal of detoxification treatment is a planned period of withdrawal from drug dependence, with or without prescribed medication. Detoxification, whether drug free or using chemical aids, is a first step in most treatment programs, but can also legitimately be viewed as a separate treatment modality. The basic goals of detoxification are to provide a safe and relatively painless way to stop opiate use. The approach is based on a pragmatic philosophy, which holds that each day off drugs is a day free from the threats of morbidity, mortality, and criminal activity associated with drug use. An additional goal may be recruitment to a long-term treatment program. If so, detoxification can complement and supplement other modalities of treatment.

Detoxification programs typically serve opiate abusers, but some programs have been designed specifically for polydrug abusers. Detoxification is most often planned to last over a period of 1 to 3 weeks, although some clinics have been using somewhat longer time periods. Senay (1981), for example, evaluated the utility of methadone detoxification in terms of its avowed goals of providing a humane alternative to drug use, while encouraging clients to enter long-term therapy. In comparing two client groups, one on 21-day detoxification followed by a placebo for 69 days and the other on an 84-day detoxification schedule followed by 1 week on placebo, Senay found that the 84-day detoxification group had significantly fewer withdrawal complaints and had significantly better retention in treatment.

Almost all detoxification programs have used chemical aids to minimize or eliminate withdrawal symptoms. A number of drugs have proven effective, but methadone has been the medication of choice in detoxifying heroin addicts (Newman 1979), because it is effective in oral form and remains effective for 24 hours. Clonidine, a drug used for treatment of hypertension, also has been reported to be useful in alleviating withdrawal symptoms. In contrast to hospital or inpatient programs, outpatient detoxification generally

involves daily visits to clinics, where counseling or other services may also be available.

Detoxification programs have been shown to be useful in treating certain addict populations (Newman 1977) that are unwilling or unable to accept long-term treatment. Despite the higher relapse rate among detoxification clients, this short form of treatment provides addicts with a humane means of reducing dependency on heroin, an opportunity to break the cycle of addiction, and a chance to enter longer-term treatment. Data from the Client Oriented Data Acquisition Process (CODAP), a national data system reporting on clients in Federally funded treatment programs (NIDA 1981), show that 13 percent of the clients discharged from detoxification are transferred into or referred to another treatment program.

Gains by a sample of clients receiving detoxification treatment, while less impressive than those receiving longer-term treatment, are still worth noting. Substantial numbers of these clients subsequently entered other treatment modalities, and, therefore, the improvement may partially reflect the influence of that additional treatment. The percent using opioids daily declined by one-third (to 64 percent) in the first posttreatment year and to 37 percent by year three. While 83 percent had been arrested prior to treatment, only 38 percent had been arrested 1 year after treatment, and only 25 percent in the third year after treatment. About half the clients had found gainful employment in the first posttreatment year (Simpson and Sells 1982).

METHADONE MAINTENANCE

The modality that has received the most attention from researchers is methadone maintenance. In this treatment modality the client is given a daily, prescribed dose of methadone, a synthetic and legal narcotic, in order to prevent the craving for heroin. Blocking the craving for heroin makes it possible for the client to escape the competing pressures of the addict lifestyle and thus enables the program to involve the client in rehabilitative activities such as counseling and job training. With relatively little effort, a patient can switch from dependence on street heroin to receiving daily doses of methadone at a clinic. The patient does not have to go through detoxification, nor leave family or job (if employed).

Two major advantages of methadone maintenance are (1) its acceptance, i.e., ability to attract heroin addicts into treatment; and (2) its ability to hold clients in treatment over time. Studies have estimated that as many as 65 to 85 percent of methadone clients remain in treatment for 12 months or more (McLellan, in press). There is now a large body of research indicating that the methadone maintenance modality effectively reduces drug use and crime, and increases employment.

For those treated with methadone maintenance, daily opioid use declined from 100 percent of clients pretreatment to 36 percent during the first year after treatment and continued to decline to 24 percent during the third posttreatment year (Simpson and Sells 1982). Improvement is also evident in the criminal involvement and employment areas. While 88 percent had been arrested prior to treatment, only 27 percent were arrested during the first year posttreatment, with the percentage declining to 20 percent during the third year posttreatment. The percentage employed during at least half the months available for work during the year increased from 33 percent pretreatment to 57 in year one posttreatment.

Many other independent methadone studies have documented favorable outcomes for those who remain in treatment for several months, especially for those who complete the pre-scribed course of treatment. Among methadone maintenance clients at Mt. Sinai Hospital in New York City, for example, 57 percent of the methadone clients who detoxified after completing treatment were drug free during a followup period averaging 31 months (Stimmel 1979).

Other studies show that methadone maintenance dosage prac-tices can influence time and performance in treatment programs. Investigators found that, when methadone dose (or take-home privileges) were individualized, patients were less likely to use street drugs and tranquilizers (Brown et al. 1983).

Studies have shown that psychotherapy and/or pharmacotherapy can be useful in treating drug patients who concurrently suffer from depression. Investigators who conducted con-trolled studies of the effectiveness of psychotherapy found that patients receiving psychotherapy did significantly better than comparison groups. Recent studies have shown that the antidepressant medication, doxepin, produces sig-nificant improvement in depressed methadone-maintained patients. Further, there is evidence that improvement in

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depressive symptoms enhances overall patient performance in rehabilitation programs.

RESIDENTIAL

The primary residential model used in drug treatment is the therapeutic community (TC). TCs emphasize a self-help approach and rely heavily on the use of ex-addicts as peer counselors, administrators, and role models. The atmosphere in the programs is highly structured, especially for newer members. Clients progress through the program in clearly delineated stages. Each succeeding stage carries more responsibility (and, in some programs, more personal freedom) than the previous one. Group counseling or therapy sessions, which are usually confrontational in nature and stress openness and honesty, are a cornerstone of the TC approach to treatment.

Studies (Simpson and Sells 1982) show that daily opioid use declined from 100 percent pretreatment to 39 percent in the first posttreatment year and to 26 percent by the third posttreatment year for those treated in therapeutic community programs. While most of the clients had been arrested prior to treatment, only 33 percent were arrested in the first posttreatment year and 23 percent in year three. Employment also increased after TC treatment, with about two-thirds gainfully employed after treatment.

Therapeutic community programs have been the subject of several independent evaluations. DeLeon et al. (1982) found dramatic improvement in areas of psychological well-being, drug use, employment, and criminality. Outcomes were best for those who completed their TC program, although improvements were also noted for program dropouts. Among those admitted to treatment during 1970-1971, the percentage reporting any use of opioids declined from 84 percent pretreatment to 2 percent for graduates, and from 91 percent to 26 percent for dropouts, at 3 year posttreatment. Full-time employment increased from 3.5 months per year pretreatment to 7.2 months posttreatment for dropouts, and from 2.2 months to 11.1 months for graduates. Arrests declined for graduates (from 53 percent of clients pretreatment to 1 percent at the third year posttreatment) and for dropouts (63 percent to 15 percent). Other recent studies have also documented that patients who remain in TCs longer generally show better results (DeLeon et al. 1982).

OUTPATIENT DRUG FREE

The outpatient drug-free modality subsumes a wide variety of approaches to treatment. Individual programs within this modality may have little in common except that they emphasize counseling in place of medication, and they are not residential.

Outpatient drug free (OPDF) is the most popular modality, accounting for about 48 percent of all clients in treatment. OPDF programs vary widely from drop-in "rap" centers to highly structured programs. Most provide a variety of services, with some form of counseling or psychotherapy as the backbone of treatment. Services for physical and mental health, educational, vocational, legal, and other problems may be provided within the program or through referral to other social services agencies.

For those treated in drug-free outpatient programs (Simpson and Sells 1982), daily opioid use declined from 100 percent pretreatment to 44 percent in the first posttreatment year, and 28 percent in year three. The percent arrested went from 87 percent pretreatment to 34 percent in year one posttreatment, and 22 percent in year three. The percentage employed increased from 24 percent during the pretreatment year to 52 percent during the first posttreatment year and 66 percent in year three.

OTHER TREATMENT METHODS

In addition to psychotherapy, other forms of treatment have proven useful. McAuliffe (1983) recently completed a controlled study that shows that self-help groups can improve treatment outcomes for opiate addicts. This study includes a cross-cultural comparison with addicts treated in Hong Kong.

A survey of 2,010 drug treatment agencies showed that a majority of programs were trying to provide some kind of family service or family-oriented treatment (Coleman and Kaplan 1977). Stanton and Todd (1981) found that a short-term family therapy approach, added to a methadone maintenance regime, was effective in treating addicts. Patients assigned to family therapy stayed in treatment longer and had better treatment outcomes at followup. In

another study conducted by Stanton (1982), involving detoxification of heroin addicts in a family and home context, the highest rate of successful detoxification was reported when the total family of the addict participated in treatment, rather than part of the family or the addict alone.

Other pharmacotherapeutic approaches are under investigation. Levo-alpha-acetyl methadol (LAAM) (a long-acting form of methadone) is now being tested. This is a long-acting maintenance drug which prevents opiate withdrawal for about 3 days. This compound permits maintenance patients to come to the clinic only three times per week and still not take any drugs outside of the clinic. LAAM has been tested in several thousand patients and is currently in Phase III in drug development. Thus far, it has been found to be safe and, for some patients, very effective in reducing dependence on the clinic. This, in turn, allows patients to lead a more normal, nondrug-oriented life.

Buprenorphine is another new drug with potential usefulness in the treatment of opiate dependence. It is already available for the treatment of pain in several other countries and it has been tested in the United States for use in opiate dependence (Mello and Mendelson 1982). Buprenorphine represents a special class of drugs that seem to be able to prevent opiate withdrawal and antagonize the effects of other injected opiates. Buprenorphine also appears to have a much lower abuse potential than methadone or other available opiate replacement treatment drugs. While further research is needed, buprenorphine appears promising for the treatment of opiate dependence.

Narcotic antagonists are nonaddicting drugs that block the effects of opiates. One of the antagonists, naltrexone, has been tested by clinical researchers for the past decade. An oral dose blocks opiate effects for about 3 days. Research indicates that naltrexone may be useful in treating certain groups of patients who have strong motivation to become drug free. For example, it has been effective in detoxifying patients who have been maintained successfully on methadone for a long period but need "insurance" against relapse after going off methadone. Addicted physicians who have access to drugs, and addicts who are highly motivated to rehabilitate themselves, seem to be good candidates for naltrexone treatment.

TREATMENT OF NONOPIATE DRUG ABUSERS

Nonopiate substance abuse is not a new phenomenon.
Researchers have been reporting on the increasing incidence
of nonopiate abuse since the late 1960s (Wesson et al.
1978). Despite early recognition of nonopiate abuse, there
is still a paucity of information available on the kinds of
problems associated with nonopiate abuse, the treatment
services provided to nonopiate abusers, and the effective-
ness of these services.

Most large-scale surveys report on the prevalence of drug
use in single drug categories and do not provide data on
concurrent, sequential or lifetime use by individuals. Yet,
there is growing evidence that multiple drug-use patterns
are increasing.

There has been a steady increase in the percentage of non-
opiate clients admitted to drug abuse treatment programs,
from 33.4 percent of all admissions in 1977 to 54.9 percent
in 1980 (NIDA 1981). Most adolescent clients being treated
for drug dependency are nonopiate abusers; only 1.4 percent
of the clients, 19 years of age and under, reported that
they were primary heroin users.

Based on findings produced by the National Youth Polydrug
Study, youths treated in drug programs across the country
are best characterized as multiple substance abusers.
Adolescent drug abuse clients, on the average, report using
six different drugs prior to coming into treatment (Beschner
and Friedman 1979).

Yet, one cannot understand the nonopiate drug abuse phenom-
enon by studying clients in drug treatment programs alone.
Researchers have found large numbers of nonopiate drug
abusers among clients in many other settings, e.g., hospital
emergency rooms, community mental health centers, schools,
and juvenile delinquency facilities.

Shader and Anglin (1982) reported that a large percentage of
the clients treated in hospital emergency rooms for
sedative/hypnotic overdoses have drug dependency problems
but are rarely treated for these problems. More than one-
third (33.4 percent) had been using prescribed medications
daily for more than 1 year.

Community mental health centers provide treatment to a
significant number of clients who are nonopiate abusers
(Safer and Sands 1979). In some areas, school settings have

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been modified so that services could be provided to the increasing number of adolescent nonopiate abusers being identified (Gottheil et al. 1977). A recent survey of juvenile delinquency facilities shows that more than half of the delinquent youngsters treated in residential group care facilities are substance abusers (Papperfort et al. 1983).

Up to this point, there has been little effort to evaluate the treatment programs designed specifically for nonopiate abusers. Study findings show that traditional drug treatment programs are, at best, only moderately successful in treating nonopiate abusers (Brown 1982).

Using composite measures of program success, DeLeon (1982) found that nonopiate abusers treated in a therapeutic community (TC) had a success rate of 37 percent compared to 54.4 percent for opiate residents. In assessing outcomes at 1 year posttreatment, Simpson et al. (1980) reported that 47 percent of the nonopiate clients treated in TCs were drug free and showed "little or no criminality." The outcomes for nonopiate clients were somewhat better than the outcomes for opiate clients studied. Based on a study of multiple substance abusers, Avery et al. (1978) produced findings showing that 90 percent continued to use illicit drugs 5 months after being admitted to treatment.

Tennant (1979) reported that it was difficult to retain nonopiate abusers in treatment--only 28.3 percent of the nonopiate clients remained in treatment beyond 90 days. On the other hand, Friedman (1982) found that adolescent clients (predominantly nonopiate abusers) stayed in treatment as long as clients who had abused opiates.

What makes this a particularly difficult area of research is the fact that there are so many different drug-use patterns. Nonopiate drug abuse involves heterogeneous populations using different drugs in a variety of ways and for a variety of reasons.

There is obviously a need for tightly controlled studies designed to evaluate and compare the effectiveness of different treatment approaches for different nonopiate abusers. Since nonopiate abusers are seen in many different settings, special efforts must also be made to evaluate the impact that these settings have on these clients and their drug abusing behavior.

DIAGNOSTIC TOOLS

It has become clear that drug abuse is a multidimensional condition which cannot be adequately understood by measures taken in only one domain. This realization has led to the development and advancement of new diagnostic tools/instruments for use by clinicians and researchers. The use of structured diagnostic interviews and application of diagnostic criteria, e.g., Research Diagnostic Criteria, DSM III, has improved client assessment, and, thereby, gives promise of improving treatment planning and referral strategies. The Addiction Severity Index (ASI), developed by a group of clinical researchers in Philadelphia (McLellan et al. 1980), has proven to be a useful research/clinical tool for evaluating and categorizing patients and measuring change over time.

The importance of good client diagnostic instruments has been demonstrated in a number of NIDA-supported studies. Investigators have been able to identify client subgroups that benefit most and least from particular treatment methods. For example, Woody et al. (1983) produced some evidence to suggest that psychotherapy may be useful in treating drug abusers under certain conditions. They found that drug clients with serious psychiatric problems can benefit significantly from psychotherapy. On the other hand, clients with few psychiatric symptoms showed improvement whether they received professional psychotherapy or counseling alone.

In evaluating the effectiveness of psychotherapy on a wide cross section of drug abusers, Rounsaville, et al. (1983) concluded that 1-hour weekly interpersonal psychotherapy sessions were no more effective than 20 minute monthly psychotherapy sessions. Findings from these studies point to the usefulness of psychodiagnostic and assessment strategies in subclassifying drug clients and exploring more appropriate client-treatment matching.

FUTURE DIRECTIONS

As pointed out earlier, large followup studies and most of the controlled studies have found that the treatment of drug abuse produces substantial positive results. However, more work is needed in determining which patient groups (based on better classifications) do best in particular treatment modalities. Correct matching between patient type and treatment modality can result in great improvement, whereas the wrong combination results in no improvement or even

worsening of treatment outcome, often at great cost to the patient and the treatment facility. Future studies of substance abuse treatment will also result in the development of better diagnostic tools.

Future treatment research is needed to evaluate the effect of conditioning in addictive disorders. Certain conditioned responses occur in human addicts, similar to those reported by Pavlov in dogs almost a century ago. For example, when certain environmental stimuli, such as a neighborhood or a street corner, are repeatedly paired with drug withdrawal, a detoxified former addict can experience withdrawal symptoms and craving whenever he/she returns to that area. Recent studies indicate that at least one-third of the patients on methadone maintenance show significant conditioned responses when exposed to drug-related stimuli (Childress et al. 1983). Researchers are currently investigating ways in which these conditioned responses can be extinguished, as part of an overall treatment program.

The system for delivering treatment to Americans who are involved in substance abuse has matured greatly over the past decade. At present, there are several distinct and effective modalities widely available to people from all walks of life. The development of these existing modalities and the large number of treatment methods that are in the process of being tested are, to a large extent, a direct result of the investments made in treatment research.

Clinicians have responded to new problems by developing new techniques. But treatment advances are not accomplished by creative clinicians working alone. Modern treatment advances are accomplished by teams of researchers and clinicians studying homogeneous samples of patients, defined by specific diagnostic criteria, and then randomly assigned to competing treatments or to a placebo-control group. Such modern research design is required to assess the fluctuations in the natural course of an illness, and the influence of nonspecific factors such as maturation. Given the improvements in therapeutic techniques for treating drug dependence, the advances in research methodology for evaluating these treatments, and continued support of both these efforts, it seems reasonable to expect continued progress on this important sociomedical problem.

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MARIJUANA AND CANNABINOIDS

Marijuana consists of the dried upper leaves and flowering
tops of Cannabis sativa (Indian Hemp). The identification
of the chemical constituents in marijuana has been partially
completed. Some 421 separate chemical entities have been
isolated (Turner 1980), and it is expected that over a
thousand will eventually be identified. Delta-9-tetrahydro-
cannabinol (THC) is the major psychoactive component,
although over 60 other cannabinoids (chemicals related to
THC) are known. Marijuana is by far the most frequently
used illicit substance.

During the past 15 years a planned program of marijuana
research by the National Institute on Drug Abuse (NIDA) has
uncovered significant new insights about the drug and its
contents. Some of the major earlier findings are listed
first so that the more recent investigations can be under-
stood within the context of the previous studies. The
following statements about marijuana are confirmed or have
strong scientific support.

CHEMISTRY

- Delta-9-tetrahydrocannabinol is the principal psycho-
  active ingredient in cannabis. It has been isolated,
  identified, and synthesized in pure form (Mechoulam and
  Gaoni 1967).

- THC is relatively insoluble in water but soluble in vola-
  tile solvents. It gradually decomposes in light, heat,
  or exposure to air. Considerations for its use as a
  therapeutic agent must include careful handling and
  storage to maintain potency.

- Although, in earlier years, confiscated marijuana rarely
  averaged above 0.5 percent THC, more recent samples grown
  in this country and abroad average above 4 percent, with
  some exceeding 10 percent. "Hash oil," a black market
  extract of marijuana, has been assayed at 15 to 30

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percent THC (Turner 1980). Such a quantum increase in potency makes some of the earlier investigations with cannabis inapplicable to our present situation and underestimates earlier assessments of adverse reactions.

PHARMACOLOGY

- The long half-life (the length of time required to reduce by half the amount in the blood) of THC and its metabolites (about 50 hours) can lead to accumulation in frequent users (Jones 1980). It is lipophilic (an affinity for fatty tissues) and it binds strongly to plasma proteins, characteristics which contribute to its long residence in the body.

- It is believed that the lipophilic characteristics of the cannabinoids have secondary effects upon fatty acid, cholesterol, phospholipid, triglyceride, steroid, and prostaglandin metabolism.

- The two most regularly observed physiologic effects of smoked or eaten marijuana are a substantial increase in heart rate (up to 50 percent or more for a short time) and a dilation of the conjunctival vessels (red eye). The acceleration of the heart rate would place a burden on an impaired cardiovascular system and would reduce maximal exercise tolerance (Shapiro et al. 1976). Other physiologic changes sometimes encountered include postural hypotension, increased appetite, diarrhea, and drowsiness.

- Dilation of the bronchial tubes occurs with marijuana use. However, this effect is reversed on continued smoking, due to the irritant effect of the smoke, which results in bronchoconstriction (Tashkin and Cohen 1976). When bits of animal lung tissue were exposed to condensed marijuana smoke, alterations in the structure and growth of the cells were observed (Leuchtenberger et al. 1973).

- Tolerance to many of the effects of marijuana and THC, including euphoria and heart rate acceleration, occurs in chronic users (Nowlan and Cohen 1977). A mild physical withdrawal syndrome has been documented (Arif and Archibald 1981).

- Some cannabinoids or their metabolites enter the placenta and are secreted in human milk. They can also be found in the lipid tissues of most organs, including the brain and gonads.

ACUTE EFFECTS

• Several studies have shown that marijuana intoxication impairs driving, flying, and other complex skilled activities. Many elements of effective psychomotor performance are worsened by the drug because of decrements in recent memory, tracking performance, glare recovery, motor coordination, depth perception, time sense, and peripheral vision (Moskowitz and Petersen 1982). Complex reaction time, attention, and signal detection are worsened. Moskowitz et al. (1981) reported that the impairment of needed driving skills persists for 10 hours after smoking, with a gradual return to baseline performance. The diminished ability to function at skilled tasks, therefore, would last long after the subjective "high" has waned.

• Learning ability during marijuana intoxication is diminished because of the perceptual and memorial difficulties mentioned above. In addition, motivation and cognition may be altered making the acquisition of new information difficult (Ferraro 1980).

• Euphoria is the most common mood state associated with marijuana intoxication. Infrequently, anxiety, panic, paranoid reactions, and brief psychotic episodes have occurred.

• The interaction between marijuana smoking and drinking alcoholic beverages is additive, that is, the effects of combined use produce an incremental impairment on a series of psychomotor tasks (Moskowitz and Petersen 1982).

LONG-TERM EFFECTS

• Marijuana has a moderate depressant action on sperm production and motility in humans (Hembree et al. 1979). It has been shown to suppress ovulation in monkeys and to induce irregular menstrual cycles (Bauman et al. 1979). Over several months, developing tolerance reverses these effects (Smith et al. 1983).

• Regular smokers may experience upper airway inflammation (bronchitis and pharyngitis). Analyses of cannabis smoke reveal that irritants, tumor initiators, carcinogens, and co-carcinogens are present in amounts often exceeding their concentration in tobacco smoke (Hoffman et al. 1975). The presence of premalignant bronchial changes in

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heavy cannabis smokers has been reported from biopsy specimens (Tennant et al. 1980). Marijuana tar, like tobacco tar, produces tumors when painted on the skin of mice (Hoffman et al. 1975).

● A chronic cannabis syndrome sometimes follows heavy daily use, particularly in adolescents and young adults. It consists of a gradual loss of energy, apathy, loss of drive and motivation, some depression, and a passive withdrawal from prior interests. Such lethargy and loss of goal directedness persists during the interval between intoxications with marijuana and is generally reversible after months of abstinence. This subject has recently been reviewed (Marijuana and Youth 1982).

● There is suggestive, but inconclusive, evidence of an adverse effect of cannabis on immune system function. It remains to be seen whether the lowering of immunologic responses found in vitro and in animals is relevant to humans.

THERAPEUTIC POTENTIAL

● Several studies have shown that THC provides some pro-tection against the nausea and vomiting of cancer chemo-therapy. It is superior to a placebo and as effective as other available antiemetics. This literature has been reviewed by Ungerleider et al. (1982a). In certain instances THC has been found to be helpful after other antiemetics did not provide relief and vice versa.

● Neither THC nor cannabis is recommended for the treatment of asthma despite its acute dilation of the bronchial passages. The irritant effects of both the smoked or aerosolized materials may worsen and prolong an asthmatic attack (Tashkin et al. 1977).

· ● Both marijuana and THC reduce eyeball pressure, which makes them potentially helpful in the management of certain kinds of glaucoma. Glaucoma treatment would require lifetime use of the material, and the chronic adverse effects must be considered. Elderly patients and those with no prior marijuana experience tend to object to the intoxicating effects of marijuana and THC. Efforts to produce an effective eyedrop preparation have met with limited success but are continuing (Green 1979).

- Preliminary clinical reports indicate that marijuana or THC may play a role in the treatment of muscle spasticity (Petro 1980).

- Cannabidiol, a nonpsychoactive constituent of marijuana, is undergoing animal and human testing as an anti-convulsant (Karler and Turkanis 1976).

- Synthetic analogues of THC (nabilone, for example) may be more satisfactory than marijuana or THC for therapeutic purposes because of their greater stability and efficacy (Milne et at. 1980).

RECENT RESEARCH

Many recent research efforts have been devoted to replica-tion of earlier studies. Selected areas of research in which progress has been made include the following.

Analysis of Cannabinoids in Biological Fluids

Recent advances in the development of analytical methods for cannabinoids have proceeded along two lines of emphasis. More sensitive and specific quantitative assays have evolved for applications in basic research studies on marijuana. Other methods have evolved that are directed at the problems of marijuana-component detection in body fluids. While there is overlap between these two areas of research, each manifests unique needs and problems. Many of these tech-niques and related issues are the subject of a recent NIDA Monograph on cannabinoid assays (Hawks 1982).

Basic research in the areas of pharmacokinetics, pharmacol-ogy, and toxicology demands highly sensitive and specific assays for THC and its metabolites. While many techniques have evolved for cannabinoid assays in serum and other fluids, those which have proven most useful to the broadest experimental audience have been the radioimmunoassay (RIA) and gas chromatography/mass spectrometry (GC/MS).

RIA assays have been developed that can be used for the quantitative analysis of THC and two of its principal metab-olites in blood and serum to levels of 2 ng/ml (2 parts in a billion). These assays can be applied both to serum and whole blood. They are provided by NIDA to investigators to support a variety of drug abuse research.

The GC/MS assay has been the primary quantitative reference method for cannabinoids and other drugs for several years.

Recent advances in the development of this methodology include the use of capillary column gas chromatography and negative ion detection systems in the mass spectrometer. These instrumental improvements have enabled quantitative analysis of THC and two of its metabolites in serum to levels of 100 picograms per milliliter or less (100 parts per trillion) (Foltz et al. 1983).

Another type of mass spectrometer system developed in recent years is called MS/MS and refers to a system of two mass spectrometer instruments configured in a tandem arrangement. This system has been used recently for THC studies in the rabbit and has been capable of quantitatively detecting THC for 7 days after a single dose at a sensitivity limit of 5 picograms per ml of serum (Harvey et al. 1982).

During the past 2 years, there has been a significant increase in research emphasis on developing forensic detection methods for marijuana components. The basic reason for this new emphasis on forensic analytical research has been the concern about the use of marijuana, by segments of our population, that might be particularly dangerous to individuals or to those around them. While research has attempted to define the extent of this risk to individuals and society, there has been a parallel effort to eliminate the risk by developing ways to identify users or those intoxicated.

Particular impetus to the new forensic emphasis in cannabinoid assay development resulted from the commercial introduction of the EMIT system of screening for cannabinoids by SYVA Company in 1980. The EMIT system's relatively simple method created a rapidly growing interest in such screening by organizations that consider marijuana use a cause for administrative measures. These organizations include the Department of Defense, police departments, and certain industrial companies.

The EMIT test detects metabolites of THC in urine several days after a smoking incident. The method is relatively inexpensive and simple to use, although not sufficiently foolproof to be used without laboratory confirmation of positive results when punitive measures could follow detection.

A similar urine test based on the technique of radioimmunoassay has been marketed recently by Roche Diagnostics and is also designed for the detection of THC metabolites in urine for up to several days after smoking. This and the EMIT

test are the primary commercially available cannabinoid
assays for urine screening.

Because of the requirement for a separate, nonimmunoassay
method to be used as a confirmation of urinalysis in foren-
sic cases, there has been much new work done on gas liquid
chromatography (GLC). One published method has become the
standard confirmation method used in the armed forces, and
others are pending (El Sohly et al. submitted for publica-
tion). These are methods capable of detecting the primary
metabolite of THC (9-carboxy-THC) in urine at levels of
25-100 ng/ml.

New research emphasis on high performance thin layer chroma-
tography (HPTLC) has resulted from the rapidly growing
interest in drug screening in both the military and private
industry. Preliminary tests indicate a potential for
HPTLC's use as a confirmation method competitive with GLC
techniques when it is desired to examine urine for a variety
of drugs.

The best confirmation method for urinalysis screens remains
the GC/MS method, since it provides both the retention time
of the GLC and the specificity resulting from the ability to
monitor ion fragments characteristic of the molecule to be
detected.

Since neither blood nor urine assays have a direct relation-
ship to the degree of intoxication, other body components
have been studied. Research in the use of breath as an
alternative to urine for marijuana screening indicates very
limited potential due to the very small amount of THC pres-
ent in such a sample. Saliva, however, contains a rela-
tively larger concentration of THC and holds more promise as
a less invasive screening sample than urine or blood. In
breath or saliva, the THC analyzed is that deposited in the
mucous membranes at the time of smoking, and does not come
from the blood, as in alcohol breath tests.

Reproductive Effects

Second to the issue of the mental changes produced by mari-
juana, the questions about reproductive changes are matters
of considerable social concern. A number of studies have
attempted to evaluate changes in plasma testosterone in
humans and other species. Variable results have been
obtained. In some recent investigations, Dalterio et al.
(1981) and Gilbeau et al. (1981) have found that dose levels
of THC relevant to human consumption produced an initial

increase, then temporary depressions of testosterone in mice. This biphasic effect may explain some of the conflicting results hitherto obtained.

Significant decreases in the levels of the female sex hormones have also been observed. Decrements in follicle stimulating and leutinizing hormones, progesterone, and prolactin have all been reported. Burstein et al. (1980) explain these alterations as an inhibition of gonadal esterases, enzymes necessary for hormonal production. THC and certain nonpsychoactive cannabinoids inhibit these sex hormone enzymes. When adult male mice are exposed to THC, cannabinol and cannabidiol (the latter two compounds occur in marijuana but have no psychoactive effects), a significant reduction in fertility and evidence of considerable chromosomal abnormalities are found. These effects are noted, not only in the treated mice, but also in their untreated male offspring (Dalterio et al. 1982).

Smith (1981) reported some inhibition of male and female hormones that control sexual development, fertility, and sexual functioning. Much of this effect appears to be mediated via the pituitary gland, although direct effects on the ovaries and testes may occur. These effects are reversible in sexually mature primates. During primate adolescence and puberty, the neuroendocrine mechanisms necessary for normal fertility may be vulnerable to marijuana's effects. In rhesus monkeys, THC treatment has also been reported to be associated with fetal deaths, stillbirths, and neonatal deaths. Birth weight of the male infants of treated monkeys was significantly less than that of the controls (Sassenrath 1979). Marijuana's effects upon the fetus might be explained by means of interference with placental function. The nonspecific and variable nature of these effects, however, would be difficult to document in relation to marijuana use in a human population.

Teratogenic Effects

At Boston City Hospital, 1,690 mother-child pairs were examined to determine the impact of alcohol or marijuana on fetal development. It was found that maternal marijuana use during pregnancy was associated with a significantly decreased fetal growth. The infants were five times more likely to have features compatible with the fetal alcohol syndrome than were those mothered by marijuana nonusers. The decreased fetal weight was directly related to the total consumption of marijuana smoked, and was greater than the weight decrease found in infants from alcohol-using mothers.

In fact, the features associated with what is called the fetal alcohol syndrome were more closely related to the amount of marijuana used than to the amount of alcohol consumed (Hingston et al. 1982).

Psychological Effects

In a 5 to 6 year followup survey of regular marijuana users, it was found that the continued use of the drug was associated with a decrease in certain pleasurable effects (Weller and Halikas 1983). Feelings of relaxation, peacefulness, enhanced sensitivity, floating sensations, self-confidence, subjective feelings of heightened mental powers, and other sought-after effects had diminished significantly. This loss of enjoyment over time has also been commented upon in the underground press. Undesirable effects persisted essentially unchanged. The lessened pleasure did not necessarily lead to a discontinuance of use of cannabis. The persistence of a well-established habit without particular positive rewards is seen with many other drugs like tobacco, phencyclidine, and heroin.

Negrete (Arif and Archibald 1981) has reviewed the effects of marijuana on preexisting serious psychiatric conditions like schizophrenia. Sufficient clinical information is available to recommend abstinence for schizophrenics in remission, because of the danger of relapse. Although infrequent, other psychiatric problems occasionally arise. An acute toxic cannabis psychosis of brief duration occurs and seems to affect heavy users. Acute paranoid states will also occur at times, even in experienced smokers who have previously used the drug without apparent untoward reactions.

A shift in cerebral hemispheric dominance was postulated because of the musing, imagistic, nonlogical type of thought induced by cannabis. It was suspected that the shift would be from predominantly left to a right hemispheric processing of cognitive activities. This hypothesis was tested and found to be correct. The shift was due to impaired left hemispheric functioning, with no change in right hemispheric performance (Hecht 1980).

Pulmonary

The current status of the effects of chronic cannabis smoking on the respiratory tract has been summarized as follows.

- Chronic tobacco use is associated with obstructive pul-
monary disease and pulmonary carcinoma. Since the smoke
of tobacco and marijuana is similar, it can be antici-
pated that the increasing use of the latter drug will
produce similar morbidity and mortality. When both
plants are inhaled by the same person, the effects can be
expected to be more intense than the use of either alone.

- The noxious effects of smoking cannabis have been demon-
strated in cellular, animal, and human studies. Human
lung cancer due to marijuana has not yet been seen, but
the latent period for development of this condition
extends over decades. Physicians are also unlikely to
inquire into marijuana smoking habits when confronted by
a patient with a pulmonary malignancy.

- For reasons described (probably greater irritant effect,
greater degree of upper airway involvement, different
smoking techniques involving deeper and longer inhala-
tions, etc.), it appears that marijuana may be more
pathogenic than tobacco, although this possibility
requires further study (Tashkin and Cohen 1981, p. 34).

Physicians treating pulmonary disease are less likely to ask
about marijuana use if they know their patient uses tobacco
heavily.

Other Effects Found During Research Studies

Occasionally an infection has been related to marijuana use.
Eighty-five cases of salmonella infection, a dysentery-
producing disorder, were traced to contaminated marijuana by
Taylor et al. (1982). Ungerleider et al. (1982b) cultured
marijuana, supplied by NIDA for research purposes, prior to
administering it to young patients with acute lymphomas to
ameliorate the nausea and vomiting of whole body irradia-
tion. Such patients are known to have a minimal resistance
to infection. Aspergillus fungi, Klebsiella bacteria, and
other microorganisms were identified. It is possible to
sterilize marijuana without loss of potency with ethylene
dioxide or irradiation. It must be assumed that pathogens
probably exist in marijuana from all sources. It is not
known whether the smoking process destroys fungi and
bacteria. A few cases of aspergillus pneumonia in marijuana
smokers have been reported.

In addition to the development of tolerance to the euphoria
and the increased heart rate that marijuana initially pro-
duces, tolerance to other effects is identifiable. The skin

temperature decrease, the orthostatic hypotension, the reduction in intraocular pressure, the decreased rapid eye movement during dreaming sleep, and the diminution in salivary flow all were partially or completely reversed after about 10 days of continuous use. The tachycardia may even become a bradycardia with persistent dosing. Dependence, manifested by withdrawal symptoms after as little as 7 days of heavy THC administration, is characterized by irritability, restlessness, insomnia, anorexia, nausea, sweating, salivation, increased body temperature, altered EEG, tremors, and weight loss. The withdrawal syndrome was reminiscent of the sedative withdrawal state, although milder (Arif and Archibald 1981).

The issue of the morbidity of paraquat-sprayed marijuana has been recently reviewed (Marijuana and Health 1982; Landrigan et al. 1983). About 21 percent of the marijuana confiscated at the Mexican border was found to be contaminated with paraquat. To date, no toxic effects attributable to paraquat have been demonstrated in smokers of paraquat-sprayed marijuana. A minute amount of paraquat survives the heat of the smoking process. In a very heavy smoker of paraquat-contaminated material, it may be possible to obtain a toxic amount. While it can be stated that the acute hazards of paraquat-marijuana inhalation are negligible, no assurances can be made about the chronic use of the contaminated material. The final evaluation of paraquat toxicity is complicated by intrinsic cannabis toxicity to the lungs.

FUTURE DIRECTIONS FOR RESEARCH

A review of current research findings on the subject suggests the following future research:

● Prospective studies of adolescents who use marijuana frequently in order to determine their vulnerability to the psychological effects of the drug, and whether significant residuals occur during the drug-free intervals.

● Scrutiny of a large series of children born of mothers who have used marijuana during pregnancy.

● Serial studies of pre-teenagers who use marijuana. This is a small, but growing, population of marijuana users, and their vulnerability to certain undesired effects of the drug should be evaluated.

- Prospective studies of the pulmonary effects of persistent cannabis or cannabis-tobacco use.

- Further studies of endocrine, reproductive, teratogenic, and immunosuppressive data to clarify human effects.

- Additional work to determine whether gross or microscopic structural brain changes occur as the result of chronic, heavy use of cannabis.

- Examination of specifically designed synthetic analogues of THC for their therapeutic potential as antiemetics, anticonvulsants, antiepileptics, and muscle relaxants.

- Determination of the biologic significance of the persistence of marijuana in the body (long half-life).

- Studies to provide more precise knowledge of the mechanism of action of the cannabinoids.

- Extended cannabis research with women.

- Studies of the quantitative effects of marijuana, alone or in combination with alcohol, on psychomotor performance over time.

SUMMARY

Marijuana, the most frequently used illicit drug, has received sufficient scientific attention during the recent past to allow a broad conclusion. In general, an analysis of the research findings indicates that persuasive evidence supports the statement that consistent heavy use of this drug poses hazards to personal and public health. In addition, acute intoxication impairs functioning to the point that operation of industrial machines and motor vehicles is hazardous.

It is difficult to disagree with the final statement of a recent Institute of Medicine report:

> Our major conclusion is that what little we know for certain about the effects of marijuana on human health, and all that we have reason to suspect, justifies serious national concern. Of no less concern is the extent of our ignorance about most of the basic and important questions about the drug (Marijuana and Health 1982, p. 5).

A World Health Organization report prepared by the Addiction Research Foundation of Toronto, Canada, comes to a similar conclusion after examining the toxicity of cannabis on the various organ systems in experimental animals and in humans (Arif and Archibald 1981).

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TOBACCO

INTRODUCTION

The persistence of tobacco use, in spite of repeated health
warnings from the Surgeon General, is quite remarkable if
tobacco use is simply a voluntary behavior. Most smokers
believe that smoking is harmful to their health, and most
say they would like to quit. What, then, are the mechanisms
underlying the use of tobacco? The role of nicotine in
smoking behavior has been the primary focus of tobacco-
related research by the National Institute on Drug Abuse.
This section will discuss the pharmacological aspects of
compulsive tobacco use but will not attempt to examine the
interaction of other complex psychological, social, and
environmental factors that have been implicated in smoking
behavior.

Much has been learned about tobacco use in recent years: it
may now be convincingly argued that tobacco ingestion is an
orderly form of drug self-administration in which nicotine
plays a critical role. Three lines of evidence for such a
conclusion will be summarized in this review. First, some
commonalities between cigarette smoking and drug abuse are
described. Second, studies are reviewed in which amounts of
nicotine are manipulated to assess the extent to which there
are compensatory changes in smoking. Third, recent studies
are described in which the abuse potential of nicotine is
directly compared to that of prototypic drugs of abuse.

COMMONALITIES BETWEEN TOBACCO USE AND DRUG DEPENDENCE

Historical. The most obvious commonality between the use of
tobacco and drugs of abuse is the extent to which all have
been surrounded by controversy; on one hand, use of tobacco
and other substances has been advocated for medicinal pur-
poses, while, on the other hand, tobacco and drug use has
been denounced as an indicant of moral decay. For example,

in 1885, the New York Times editorialized: "The decadence of Spain began when the Spaniards adopted cigarettes and if this pernicious habit obtains among adult Americans the ruin of the Republic is close in hand" (Brooks 1952). Attempts to eliminate tobacco use from any culture into which it has been introduced have been unsuccessful. Between 1895 and 1921, 14 states completely banned the use of cigarettes and the remaining states (except Texas) had laws that regulated the use of cigarettes and their possession by minors (Austin 1978).

Acquisition and Maintenance. Most cigarette smokers begin smoking at an early age, smoke for some period, attempt to quit, but then relapse. This sequence is similar to that for drugs of abuse. For example, both the opium and tobacco habits develop quite rapidly. Cocteau's dictum, regarding opium smoking, that "he who has smoked will smoke," is equally true for tobacco smoking (Russell 1976). In both cases, simple exposure to the substance ("experimentation") usually leads to repeated and then chronic use (Bejerot and Bererot 1978). To the extent that experimentation leads to chronic use, tobacco appears to have an "addictive potential" similar to that of opium.

Social Factors. Social pressure from peers and family members is also critical in initiating the use of tobacco and abused drugs (Reeder 1977; Kozlowski 1979; Nurco 1979). Adolescents who smoke are more likely to have friends who smoke, other siblings who smoke, and parents who smoke (Evans and Raines 1982). The social acceptability of tobacco use may also be a major factor in its initial use (Haertzen, personal communication).

Personality and Psychosocial Factors. Kellam and his coworkers (1982) assessed social adaptation, psychological well-being, learning problems, and aggressiveness in first-grade children, and then reinterviewed the children 10 years later. Children who were rated high on shyness or aggression scales exhibited the highest rates of cigarette and marijuana use 10 years later, indicating a relationship between personality factors and substance abuse.

Relapse. Hunt and his coworkers (Hunt et al. 1971; Hunt and Bespalec 1974) found striking similarities between cigarette smoking, alcoholism, and opioid dependence, with regard to patterns of relapse. For all three substances, relapse rates were highest during the first few months after quitting, then gradually tapered off to about 75 percent at 6 months. Another parallel was found in the types of situa-

tions in which relapse occurs. Marlatt and Gordon (1980) examined the situational and contextual factors present during the relapse episodes of alcoholics, tobacco smokers, and heroin dependents. The types of situations in which relapse occurred were similar across substances (Shiffman 1982).

Tolerance. With some drugs of abuse (most notably, the opioids), tolerance and physiological dependence are thought to be instrumental in the pattern of drug abuse. The phenomenon of nicotine and tobacco smoke tolerance has been extensively studied (Gilman et al. 1980). Following several hours of deprivation, e.g., overnight sleep, tolerance to nicotine is diminished and smokers are sensitive to its effects (Jones et al. 1978). Consequently, the first couple of cigarettes of the day, or the first few of a series of nicotine injections, have the strongest and most pleasurable effects (Henningfield et al. 1982a).

Physiological Dependence. Abstinence from cigarette smoking may be accompanied by mild physiological changes such as increased heart rate, hand tremor, and skin temperature (Gilbert and Pope 1982), and subjective changes such as increased desire to smoke and irritability (Gilbert and Pope 1982; Shiffman and Jarvik 1976). Preliminary findings suggest that nicotine is critical to these effects, since administration of a nicotine-delivering chewing gum reduces abstinence-associated discomfort and desire to smoke (Fagerstrom 1982). Nevertheless, an invariate "withdrawal syndrome" analogous to that associated with opiates has not been described, and the character of the postnicotine use period more closely resembles that of other stimulant drugs.

Patterns of Drug Self-Administration. One characteristic of drug dependence is that orderly patterns of administration develop that transcend individual, and even species, differences. Tobacco use is no exception. When relatively unrestricted, people (Griffiths and Henningfield 1982a) and nonhuman primates (Ando and Yanagita 1981) smoke in orderly patterns from day to day. Interestingly, these patterns resemble those found in animals which are free to self-inject cocaine (see figure 1).

Another characteristic of drugs of abuse is that deprivation increases the tendency for the substance to be ingested. A laboratory study of smoking, using volunteers, showed that the tendency to smoke is directly related to the amount of time that the subjects are deprived of cigarettes (Henningfield and Griffiths 1979). Another study showed that pat
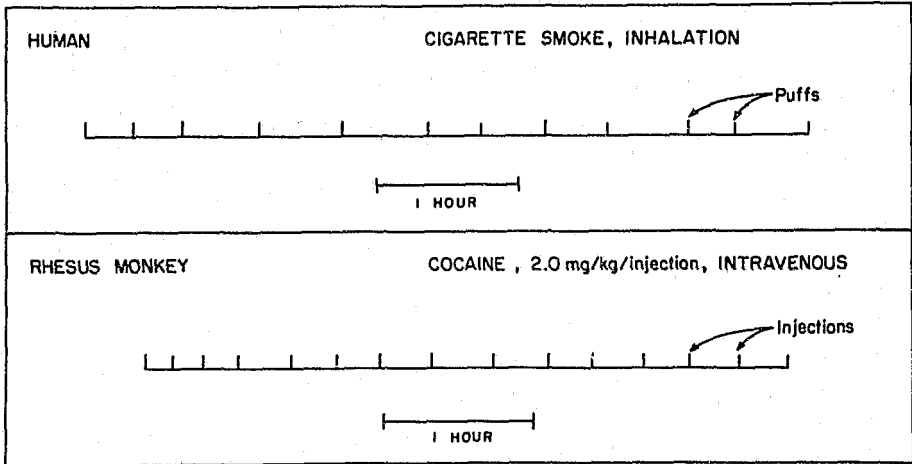
FIGURE 1. *Similar patterns of iv cocaine self-adminis-
tration by rhesus monkeys and cigarette smoking by volun-
teers, when each substance was freely available (JAI
Press, Inc. Griffiths et al. 1980. Reprinted with permis-
sion).*

terns of smoking following a night of sleep are regular from
day to day in that the time between each cigarette increases
with each cigarette smoked (Burling et al. in preparation).
This pattern is similar to the "loading up" pattern seen
when alcohol or sedatives are presented to animals following
a period of overnight abstinence (Meisch et al. 1981). Pre-
cise analysis of the specific features of behavior, inclu-
ding patterns of puffing and inhaling, showed the behavior
to be remarkably orderly. For instance, the interval be-
tween puffs increases, while the duration of each puff de-
creases, from the first to the last puff of a cigarette
(Griffiths and Henningfield 1982a; Chait and Griffiths
1982).

Implications of Commonalities. The commonalities among
phenomena associated with use of tobacco and drugs of abuse
provide compelling, albeit circumstantial, evidence that
tobacco use is an orderly and addictive form of behavior
(Jaffe and Kanzler 1979; Henningfield et al. 1981a; Levison
et al. 1983). These studies do not indicate, however, which
elements of tobacco smoke are critical to the maintenance of
tobacco use. The conceptual leap from habitual behavior to
drug abuse can only be made on the basis of evidence impli-
cating a specific psychoactive drug as critical to the
behavior. The next two sections will address this issue.

STUDIES ON THE REGULATION OF NICOTINE INTAKE

Among the many constituents of tobacco, nicotine appears to be the dependence-producing drug that maintains the behavior of smoking (Griffiths and Henningfield 1982b). Via its action on the central nervous system, nicotine is reponsible for many of the physiological effects of tobacco (Russell 1976). Furthermore, only nicotine, not the tar, gases, nor particulate matter, is delivered when noncombustible forms of tobacco are used, e.g., snuff. Evaluation of nicotine's role, and the extent to which smokers regulate its intake, has been a major focus of recent research.

Assessment of the role of nicotine in smoking behavior is hindered by various difficulties. With most other forms of drug use, it is relatively simple to study the suspected factors. For instance, the amount of morphine per injection, of ethanol per drink, or of amphetamine per tablet, can be precisely specified and measured. However, as shown in figure 2, the nature and quantity of constituents in any given puff is a function of multiple factors, including cigarette constitution and inhalation parameters. Frequently, experiments designed to assess the role of nicotine are confounded by the other substances in the smoke (McMorrow and Foxx 1983; Moss and Prue 1982).

Manipulation of Nicotine Delivery of Cigarettes. The most common paradigm used to assess nicotine regulation has been to alter the nicotine delivery of the cigarette, and then to determine if there are compensatory changes in cigarette smoking behavior. Compensation is typically measured by (a) changes in the number of cigarettes smoked, (b) changes in patterns of puffing and inhaling, or (c) changes in various biochemical measures of smoke intake, i.e., expired air carbon monoxide, saliva thiocyanate, plasma continine (Benowitz in press). These studies are important because (a) they help reveal the extent to which nicotine controls smoking behavior, and (b) they help evaluate the assumption on which a trend toward the production and sale of cigarettes with lower tar and nicotine deliveries (USPHS 1981) has been based: that such cigarettes are less harmful (Gori 1976; Gori and Lynch 1978; Hoffman et al. 1980; Ross 1976). A health-related issue is that if people make compensatory changes in their smoking behavior when nicotine levels of cigarettes are decreased, they may increase the hazards (Kozlowski 1982; Kozlowski and Herman in press).
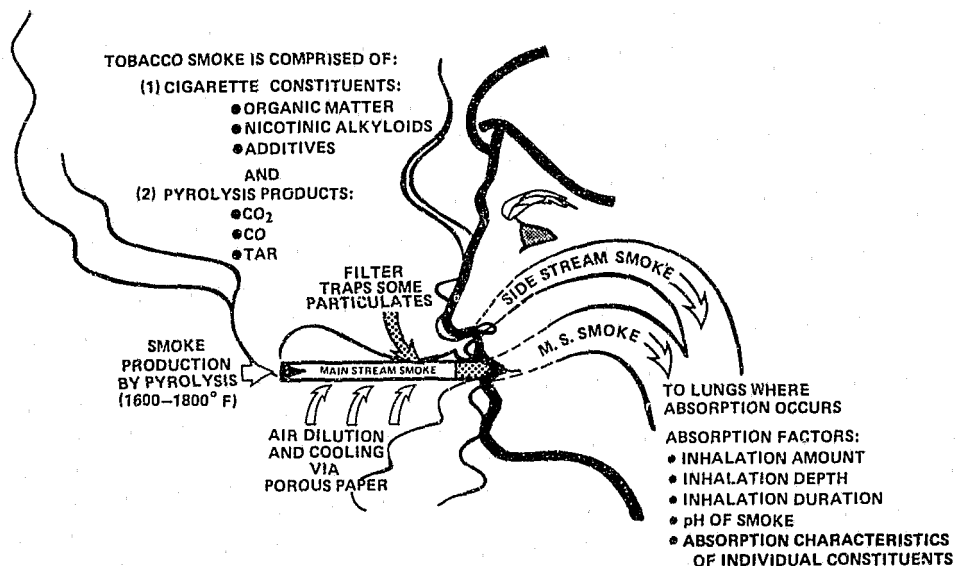
FIGURE 2. *Variable quantities of substances are present in cigarettes, are modified by the combustion process, and are variably inhaled. Certain factors of possible import, e.g., tar, CO, are not present in unburned tobacco (Henningfield 1983).*

Three exhaustive reviews of studies on nicotine regulation have been published in the last 3 years (Gritz 1980; Moss and Prue 1982; McMorrow and Foxx 1983). Gritz concluded, "Almost all of the studies demonstrate some increase in smoking as cigarette nicotine content falls below accustomed levels, and a decrease in smoking when cigarette nicotine content is unusually high" (Gritz 1980, pp. 91-158). Moss and Prue, and McMorrow and Foxx, concluded that whereas behavioral measures of cigarette smoking generally imply that compensation occurs, physiological measures, e.g., plasma nicotine level, are quite variable and seldom reflect clear compensation. Clearly, problems remain in the actual measurement of cigarette smoking behavior, and these problems impair resolution of some critical issues (Grabowski and Bell in press). Foremost is the extent to which changes in smoking behavior produce corresponding changes in actual intake of nicotine. Furthermore, many studies have employed commercially available cigarettes (brand-switching) which differ from each other in a number of ways, e.g., tar delivery, taste, besides nicotine level. It is not always clear, in these studies, the extent to

which nicotine is responsible for the observed changes in smoking. This issue is partially resolved by the use of cigarettes that vary delivery of nicotine but not of other constituents (Gust and Pickens 1982; Herning et al. 1981).

Nicotine Preloading Studies. In experimental settings in which cigarette smoking is relatively free to occur, both oral and intravenous nicotine administration decrease subsequent cigarette smoking (Henningfield et al. 1983a; Herman 1974; Kozlowski et al. 1975; Kumar et al. 1977; Lucchesi et al. 1967). In cigarette smoking treatment programs, administration of nicotine-delivering chewing gum results in reduced cigarette-smoking rates of numbers of cigarettes smoked (Jarvis et al. 1982).

Antagonist Studies. Like the opioids, nicotine has a specific cellular site of action (viz., nicotine receptors). At least a partial blockade of nicotine's effects can be achieved by administration of nicotine antagonists. When mecamylamine (a centrally-acting nicotinic blocker) was given to smokers who were not trying to quit smoking (and were presumably trying to maintain their usual nicotine intake), the subjects increased their smoking rates (Stolerman et al. 1973; Henningfield and Jasinski 1983).

Summary of Studies on the Regulation of Nicotine Intake. The data reviewed suggest that nicotine is one of the major functional constituents in tobacco smoke. Additionally, the results of these studies are comparable to those obtained in similarly conducted studies with other drugs. For instance, when drug dose is increased for either animals or humans that are free to self-administer the drug, there are compensatory reductions in number of doses taken, although actual drug intake tends to increase somewhat; opposite results are obtained when drug dose is decreased (Griffiths et al. 1980).

ABUSE LIABILITY OF NICOTINE[1]

The preceding sections characterize tobacco use as a prototypic form of drug dependence, and provide evidence that nicotine plays a functional role in tobacco use. However, if nicotine's role is similar to that of central-nervous-system-affecting agents that are present in substances of abuse, e.g., the cocaine in coca leaves, then nicotine should prove to be a reinforcing and abusable substance, even in the absence of the multitude of stimuli surrounding tobacco use. That is, self-administration must be shown to occur when nicotine is the only major stimulus

component. Methods for assessing the abuse liability of nicotine are available (Henningfield and Jasinski 1983): they are objective and are accepted by the World Health Organization (Jasinski et al. submitted for publication).

Two kinds of studies are critical in the assessment of the abuse potential of a substance: (1) single dose (human) or drug discrimination (animal) studies in which the stimulus effects of the drug are compared to those produced by proto-typic abused drugs; and (2) self-administration studies in which the drug is evaluated for its potential to serve as a reinforcer. Conducting the studies in both animal and human subjects establishes validity in the species with which we are ultimately concerned (namely human), while providing a means of establishing the biological generality of the phenomenon without the possible confounding influence of per-sonality, special, or cultural variables. Close concordance between findings from animal and human studies has been shown over a wide range of drugs (Griffiths et al. 1980).

Animal Studies of the Stimulus Properties of Nicotine (Drug Discrimination). The general procedure in these studies is to train the animal to press one lever when the test drug, e.g., nicotine, is injected, and to press another lever when placebo or a different drug, e.g., a sedative if stimulants are being studied, is injected (Winter 1978). After train-ing, other drugs may be injected to determine which lever the animal will press. Preliminary findings suggest that nicotine has amphetamine-like stimulus effects. For example, rats trained to discriminate amphetamine (a stimu-lant) from pentobarbital (a depressant) pressed the ampheta-mine lever after nicotine injections (Schechter 1981). Similarly, animals trained to discriminate phenobarbital (sedative) from saline, pressed relatively little on the phenobarbital lever when nicotine, cocaine, and several other nondepressants were tested (Overton 1982). Recently, Stolerman and his coworkers (in press) reported that nico-tine stimulus effects in animals are blocked by pretreatment with mecamylamine.

Animal Studies of Nicotine as a Reinforcer (Self-Adminis-tration). These studies arrange for some arbitrary response, e.g., lever press, to result in an automatic in-jection of the substance (Johanson 1978). More than a dozen animal studies of nicotine self-administration have been published in the last 3 years. In brief, the findings are as follows: (1) nicotine serves as a positive reinforcer for several species; (2) nicotine serves as a reinforcer under a variety of conditions of access; (3) nicotine, like

drugs of established abuse potential, is a more efficacious reinforcer when the animals are hungry; (4) nicotine has moderate cocaine-like reinforcing effects; (5) the effects of nicotine on receptors in the brain are critical for nicotine to serve as a reinforcer; (6) nicotine, like cocaine, exerts either positive or negative reinforcing properties depending on the dose and schedule of availability; (7) nicotine differs from cocaine in that its abuse potential is limited to a considerably smaller range of conditions; and (8) nicotine's strength as a reinforcer is augmented by ancillary environmental stimuli (analogous to stimuli that occur when nicotine is taken by humans in the form of tobacco) (Deneau and Inoki 1967; Lang et al. 1977; Singer et al. 1978; Hanson et al. 1979; Smith and Lang 1980; Latiff et al. 1980; Ator and Griffiths 1981; Goldberg et al. 1981; Goldberg and Spealman 1982; Singer et al. 1982). Taken together, these results show that nicotine has actions in the brain that are sufficient to account for its self-administration, and that, like other drugs, its effectiveness can be enhanced by a variety of factors.

Human Studies of Nicotine's Subjective Effects (Single Dose Studies). These studies give a range of doses of the test compound and placebo to volunteers with histories of drug abuse. Such subjects accurately discriminate compounds with a potential for abuse and can compare the effects of the compounds to those of abused drugs (Jasinski et al. submitted for publication). In a study at the Addiction Research Center, nicotine was given both intravenously and via tobacco smoke to eight subjects with histories of drug abuse (Henningfield et al. 1981b). Both routes produced a similar profile of effects across a variety of measures. In addition, nicotine was shown to be a euphoriant as defined by elevations in scores on the Morphine-Benzedrine Group (MBG) scale of the Addiction Research Center Inventory, and the drug-liking scale of the Single Dose Questionnaire (see figure 3). When subjects were asked to identify intravenous nicotine from a list of commonly used drugs, the most common identification was "cocaine," followed by "morphine." This finding is comparable to those obtained in the animal drug discrimination studies described above. Similar effects of nicotine, given by both routes, were also obtained on several physiological measures, including pupil diameter, blood pressure, and skin temperature. These similarities in subjective and physiologic responses to nicotine given as either tobacco smoke or intravenous nicotine confirm that nicotine is the critical pharmacologic compound that accounts for these effects of tobacco smoke. A subsequent study showed that both nicotine's subjective and physiologic

effects could be blocked by oral pretreatment with mecamyla-
mine (Henningfield et al. 1983). Taken together, data
collected on the various psychometric instruments confirm
that nicotine is psychoactive, is a euphoriant, and is
appropriately categorized as a drug with potential to pro-
duce abuse or addictive behavior.
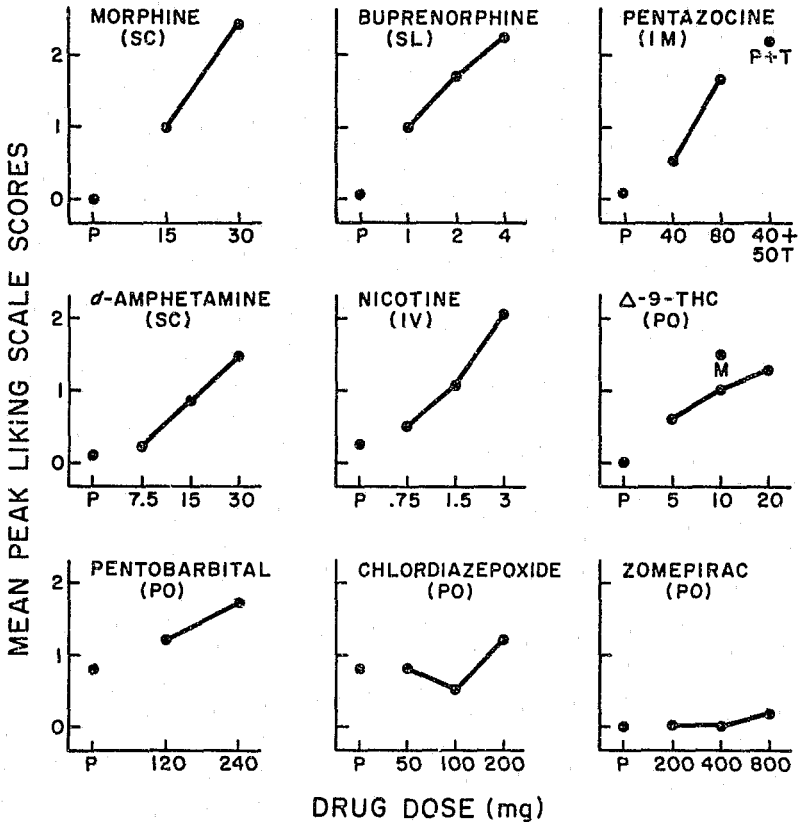
FIGURE 3. *Scores on a liking scale by subjects with his-*
tories of drug abuse are shown. Nicotine, like drugs
known to be abused, produced dose-related increases in the
liking scale scores (Jasinski et al. submitted for
publication).

**Human Studies of Nicotine as a Reinforcer (Self-Adminis-
tration).** The general strategy is to use methods originally
developed with animals to assess the ability of a drug to
maintain its self-administration (drug-seeking behavior).
This strategy produces results consistent with predictions
from animal studies and from the single dose human studies
(Johnson et al. submitted for publication; Jasinski et al.
submitted for publication). More specifically, it is a

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direct way to determine if nicotine can substitute for tobacco smoke and can serve as a reinforcer in its own right. In one study, volunteers were given the opportunity to press a lever that resulted in either nicotine or a placebo injection (Henningfield et al. in press). All six subjects self-administered nicotine in patterns that were similar to those observed when human subjects smoke cigarettes and when rhesus monkeys take intravenous cocaine injections (see figure 2). When subjects were given access to both nicotine and placebo at the same time (by pressing alternate levers), they chose nicotine, confirming that nicotine had come to serve as a positive reinforcer. The results of the self-administration studies are similar to those obtained when squirrel monkeys have been similarly tested (Henningfield et al. 1982b), indicating that biological actions of nicotine in the central nervous system are sufficient for nicotine to serve as a reinforcer.

Self-Quitting. Since the publication of the first Surgeon General's Report on the Health Consequences of Cigarette Smoking, there are currently 33 million ex-smokers (alive) in the United States. It has been estimated that 95 percent of those who have stopped smoking have done so without the aid of organized smoking cessation programs (SGR 1982). In addition, most current smokers indicate a preference for quitting with a procedure they may use on their own.

Unfortunately, most self-help interventions for smoking have not been systematically evaluated. Existing studies have not identified strategies or informal approaches which are more efficacious than others. In addition, little is known about which types of self-help materials are most effective with smokers during different stages of change, e.g., pre-quitting decisionmaking, quitting, and maintenance. Recent research efforts are directed at understanding the self-help process with the intent of providing more targeted strategies. Some of these include the use of minimal contact groups, informal peer lead programs, and the development of mass media messages which contain specific cues for motivating self-quitting and maintenance of nonsmoking behavior.

Cigarette Smoking Cessation Strategies. Although environmental and psychological factors play a significant part in the initiation of smoking, subsequent drug dependency interacts to maintain smoking behavior. This combination of factors creates a well-reinforced habit that is resistant to change. To further complicate this situation, researchers have found that smoking behavior differs across individuals, making cessation efforts even more difficult.

Unfortunately, after many decades of research, cigarette smoking remains one of the most resistant problems to modify. Current research is guided by a small number of theoretical constructs, e.g., behavioral modification and social learning principles. Findings from this research indicate that composite behaviorally-based programs ensure only a moderate level of success. At the present time, there exists no dependable program to treat this behavior. Although recent findings in the area of pharmacology may lead to more effective treatment strategies, present cessation research programs are reporting 15 to 40 percent success rates one year post-intervention (SGR 1979).

Pharmacological Adjuncts. The recent development of a nicotine chewing gum may aid in the cessation and maintenance of nonsmoking behavior. Clearly, nicotine gum poses fewer risks than cigarette smoking and other forms of tobacco use. As an adjunct to physician-supervised cessation strategies, the brief use of such gum may serve to reduce withdrawal symptoms, nicotine cravings, and other discomforts frequently experienced by those attempting to overcome a complex series of behavioral, environmental, and pharmacological interactions.

Patterns of Use. Although 53 million people continue to smoke cigarettes, important changes in smoking trends have occurred in the United States. During the past 15 years, the proportion of smokers declined from 53 to 37 percent among males and from 33 to 29 percent among females (Holbrook 1982). Recent survey data indicate that the number of teenagers and older females initiating smoking continues to decline. During the period, however, per capita consumption of cigarettes among current regular smokers appears to be increasing. This phenomenon may be partially due to compensation on the part of smokers who have switched to low-yield cigarettes.

Etiology of Disease. Cigarette smoking has been recognized as one of the Nation's leading preventable causes of disease, disability, and death. Research has established the causal link between cigarette smoking and cancer and has associated this habit with increased incidence of other serious and often fatal health consequences, e.g., coronary heart disease and arteriosclerotic and peripheral vascular disease. Epidemiological data indicate that smoking and tobacco use may be responsible for some 350,000 excess deaths per year.

IMPLICATIONS

In answer to the question, "What are the mechanisms that underlie the compulsive use of tobacco?", the National Institute on Drug Abuse is in agreement with other organizations, e.g., the American Psychiatric Association and the World Health Organization, that tobacco use can be an addictive form of behavior (USDHHS 1983). In addition to this conclusion, an appraisal of data collected by NIDA's intramural and extramural research programs indicates that the behavior is a form of drug abuse, or drug addiction, in which nicotine is critical. Specifically, it is evident that the role of nicotine in cigarette smoking is similar to the role of cocaine in coca use, of THC in marijuana smoking, and of ethanol in alcoholic beverage consumption. This conclusion provides a rational basis for the treatment of cigarette smoking by approaches developed to treat other forms of drug abuse. For instance, promising behavioral approaches developed in studies of narcotic and sedative abuse are already being applied to control cigarette smoking (Stitzer and Bigelow 1982). Additionally, two pharmacotherapeutic approaches have shown promise in initial clinical trials. One is a drug substitution approach in which the abused drug (nicotine) is replaced with a safer and more manageable form of the drug, namely a nicotine-delivering chewing gum (Fagerstrom 1982; Jarvis et al. 1982). The other is a blockade approach in which the dependence producing effects of a drug are blocked by pretreatment with another drug, namely mecamylamine (Henningfield et al. in press; Tennant et al. in press).

FOOTNOTE

1. A concept central to many discussions of drug abuse is that the substance produces "damage" or "debilitation." This aspect of cigarette smoking will not be addressed here as there are extensive data indicating (1) the actual toxicity of tobacco, and (2) the widespread perception by smokers that their habit is harmful (USDHEW 1979).

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COCAINE AND STIMULANTS

Some historical perspective is necessary to understand the
great appeal of stimulant drugs. During the past few years,
cocaine has been in the limelight, but cocaine represents
only one of a large class of drugs. Some of the oldest
psychoactive drugs are plants containing central nervous
system stimulants. The use of coca (cocaine) in South
America and kaht (cathine) in Africa are examples of stimu-
lants used extensively for hundreds of years. The plant
tobacco (nicotine) acts primarily as a central nervous
system stimulant. Coffee, and its psychoactive ingredient
caffeine, is the most commonly consumed drug in the world.
In the world marketplace, the dollar value of coffee is
second only to oil, by far exceeding the wildest estimates
of illicit coca and cocaine commerce.

Thus, long before the availability of synthetics like the
amphetamines (in the early thirties), stimulants were
commonly used in large amounts by enormous numbers of people
and were of great commercial and trade importance. Kaht
chewing was described as a widespread, socially accepted
habit in writings dating back to the 12th century. The
first written reports of coca chewing appeared coincident
with the discovery of the New World. Late 16th century
manuscripts described the value of coca chewing for increas-
ing endurance, enhancing work output under adverse condi-
tions, and generally elevating mood. It's curious that
despite the recognition of coca's stimulant effects it never
became important in the European culture in the way that
tobacco and coffee did in the 16th century.

The increased research activity in recent years on the
chemistry and pharmacology of caffeine, cocaine, nicotine,
and the host of synthetically derived stimulant drugs like
the amphetamines has aided understanding of their effects
and some mechanisms, and initial puzzling through the neuro-
chemistry of brain function. Although chemically quite
different and also different in mechanisms of action, all
stimulant drugs have much in common. When trying to

understand general principles controlling drug use and attitudes towards drug use, much can be learned from considering society's dependence on stimulants. Results from recent experiments in controlled laboratory settings illustrate how a drug can be used widely for 400 years or more (for example, cocaine), yet fundamental aspects of drug effects, mechanisms, and consequences of use can remain unrecognized. Whenever it is claimed that we know all about a drug and therefore can make rational decisions and predictions about it, some consideration of the history of stimulant use might temper confidence in that claim.

Significant "breakthroughs" in scientific research are rare. Scientific discovery usually proceeds in small stepwise advances, with periods where very little progress is evident to the casual observer who has not followed a line of research over time. Thus, it should not be surprising that in the past 3 to 5 years no new fundamental concepts or discoveries have revolutionized our understanding of stimulant drugs. However, for a number of the stimulant drugs bits of new information have the cumulative effect of clarifying some major issues, and providing links between understanding of drug effects and phenomena studied by other disciplines, i.e., the neurophysiology of pleasure and pain and the effects of reward and punishment on behavior.

Research with stimulant drugs during the past few years has begun to clarify and broaden traditional concepts of drug dependence, tolerance and addiction. Use of operant behavior techniques to study drug self-administration by experimental animals clearly demonstrates that drugs themselves have primary reinforcing properties. Recent studies of cocaine self-administration in humans demonstrate that these animal models have significant validity when compared with human drug self-administration (Fischman and Schuster 1982). The use of operant techniques has helped to clarify how factors such as social reinforcement allow weak reinforcers, e.g., alcohol, to become more effective reinforcers when paired with strong primary reinforcers (Woolverton and Schuster 1978).

As clinical observations accumulate, the existence of a true withdrawal syndrome following stimulant drug use seems likely. Although not completely fitting the model of opiate or alcohol/sedative withdrawal, the depression, social withdrawal, craving, tremor, muscle pain, sleep and eating disturbance, electroencephalographic changes, and changes in sleep patterns are more than simply the consequence of what has usually been termed psychological dependence. Clearly,

tolerance, that is, decreased effect with repeated dose, develops to all stimulant drugs. The tolerance appears to be dose related with higher and more frequent doses producing more rapid tolerance.

Research with stimulants has contributed to understanding the nature of reinforcement itself (Woolverton and Schuster 1978; Fischman and Schuster 1982). The "reward system" in the brain has been under study for some years in a host of neurophysiological and neuropharmacological studies. But the mechanisms by which the reward system turns on the reinforcement process and just how drugs bring the reward-reinforcement system into play are still poorly understood, though the complexity of the system has become more apparent. Although, to the nonspecialist, self-injection and micro-injection studies of cocaine or amphetamine isomers into rodent brains may seem a long way from the practical problems of stimulant and other abuse, rational and specific therapeutic interventions that might block the reinforcing properties of drugs without interfering with other aspects of human functioning are not likely to develop until the nature of the reward system is better understood.

COCAINE

During the past few years, cocaine use has increasingly been viewed with concern by the scientific community. Evidence that the drug is addictive and extremely reinforcing, together with clinical reports of the considerable health hazards of chronic high-dose use, indicate the need for greater attention to scientific and therapeutic issues surrounding cocaine abuse. This view can be further strengthened by concerns regarding the hazards of new forms of use, for example, coca paste smoking, that may emerge on the drug abuse scene.

Although cocaine has been used extensivey in medical practice for over 80 years as a local anesthetic and vasoconstrictor, a reassessment of the medical and psychological implications of modern day use only began in 1975 when NIDA funded a series of research contracts studying the pharmacology of cocaine in humans. Those studies and others that evolved from them have provided detailed and accurate descriptions of the acute, short-term cocaine effects in humans. They have provided new information on the relationship between dose and route of administration, and between blood levels of the drug and physiologic or psychologic effects (Fischman et al. 1976; Resnick et al. 1977; Van Dyke et al. 1978; Fischman and

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Schuster 1980a,b; Van Dyke et al. 1982; Fischman et al. 1983). However, very little more is known about the chronic, long-term effects of cocaine than was recognized by Sigmund Freud and other investigators at the beginning of this century (Freud 1974; Van Dyke and Byck 1982).

The health implications of differing routes of adminis-tration: sniffing, smoking, chewing, injecting, or swallow-ing; the importance of frequency of use; the expectations of the user; and circumstances in which cocaine is used (Paly et al. 1979; Paly et al. 1982; Siegel 1982) are beginning to be understood. In laboratory experiments with humans, a few doses of chemically pure cocaine, when given at doses commonly used in illicit settings, are relatively nontoxic when judged by behavioral toxicity or magnitude and duration of physiologic change. The increases in heart rate and blood pressure, decreases in skin temperature, increased mild tremor, presence of euphoric mood, relief of fatigue and boredom, mild increase in body temperature, and slight dilatation of pupils of the eye, were all recognized by investigators like Sigmund Freud, William Halsted, and others almost 100 years ago. Under controlled conditions, very rapid tolerance develops to most of the effects, both physiological and psychological. A variable degree of dysphoria and mild depression follows even single doses. Perhaps such mood changes are the laboratory correlate of a depressed and dysphoric state (often severe) that follows periods of sustained high doses of cocaine taken in non-laboratory settings (Siegel 1982). In concert, the results indicate the danger which can clearly emerge in the uncontrolled use of cocaine, although the mechanisms by which the problems evolve have not been thoroughly delineated.

It is clear from studies and observations over the past few years that cocaine is a drug that is addictive. Tolerance develops rapidly to cocaine, so that repeating the same dose causes a progressively diminished response (Fischman and Schuster 1981). Although the phenomenon has not been docu-mented under controlled conditions, clinical observations suggest that physical dependence develops to the point that repeated doses are required to prevent the onset of a with-drawal syndrome (Siegel 1982). Perhaps the most important element in defining a drug as addictive is that obtaining the drug becomes an all-important activity in the user's life. Although controlled studies in humans that would clearly document these attributes have not been carried out, the weight of the data from the short-term controlled laboratory studies with humans and animals, when considered

together with clinical observation, indicates cocaine is an addictive drug.

The availability of sensitive biochemical assays to measure tissue levels of cocaine, coupled with some understanding of its metabolism, now allow researchers to assess the significance of clinical data better and, for the first time, to design rigorous research studies properly (Jatlow and Bailey 1975; Chinn et al. 1980; Lindgren 1981; Ambre et al. 1982). For example, single doses of cocaine given intravenously, nasally, or orally can all produce blood levels of cocaine that are well tolerated in short-term experiments but appear to be behaviorally toxic with sustained, repeated use under some conditions (Foltin et al. 1981). Great variability of blood levels in different people getting the same dose suggests unrecognized differences in metabolic processes (Javaid et al. 1978).

Accurate measures of cocaine in the blood have produced some puzzles. The blood levels of cocaine in Quechua Indians and others who commonly chew coca leaf in the Peruvian Andes are similar to blood levels that are sometimes encountered in people sniffing cocaine in the United States (Paly et al. 1979). Yet the euphoria, the "high," and other effects valued in the United States are neither reported nor evident in the Quechua Indians (Negrete 1978; Allen 1981; Weil 1981). There are reasons to assume that the pharmacology of cocaine found when the natural plant is chewed may differ from that found when the purified cocaine is sniffed or injected (Bedford et al. 1982). However, such issues as cultural differences, the importance of different expectations, and in general the socialization or domestication of a drug are probably important. Certainly different effects from sustained moderate doses of cocaine and episodic high doses are likely and, when fully understood, may teach us much about how society or a group of people learn to handle certain psychoactive drugs. Whenever a new drug is introduced into a society without a well developed and functioning belief and support system, problems may be expected to arise. For our society, cocaine is a relatively new drug even though to the Quechua it may be a very old one.

Cocaine is an exceedingly reinforcing drug (Post et al. 1976; Woolverton and Schuster 1978). That is, animals and, under some conditions, humans will repeatedly take the drug as long as it is available. Laboratory studies in recent years have well documented what was suspected: low doses of cocaine taken not too frequently are relatively nontoxic, compared to other psychoactive drugs, and certainly quite

pleasurable. Cocaine's rapid metabolism and apparent lack
of active metabolites would contribute to this (Wilkinson
et al. 1980; Barnett et al. 1981; Zahler et al. 1982).
However, animal studies and clinical observations indicate
that repeated higher doses produce a predictable, severe
behavioral and physiologic toxic state (Post et al. 1976;
Epstein and Altshuler 1978; Foltin et al. 1981; Stripling
and Hendricks 1981; Branch and Dearing 1982; Siegel 1982).

Whether the toxicity is predictable and inevitable in all
people who use cocaine if they use it long enough and often
enough is not established. Such research is complex and
more expensive than short-term experiments. There probably
will be individual differences in susceptibility to toxic
effects, as is the case with every psychoactive drug. The
controlled laboratory studies demonstrate great individual
variation in both the metabolism of cocaine and its effects
compared to other psychoactive drugs. The variability is
not clearly attributable to prior experience with cocaine or
other drugs, genetic differences, health status, or other
easily identified factors.

The relatively low toxicity of cocaine at low and infrequent
doses is well known to users and potential users, and this
knowledge contributes to cocaine use. The relative lack of
toxicity at low doses leads to problems as cocaine's availa-
bility increases. What is not well appreciated is the quite
different spectrum of effects and consequences at higher and
more frequent doses. Until that is fully accepted and
understood by potential users, one might expect increasing
popularity of use. Even when it is fully appreciated by
potential users, there will be the natural inclination of
some people to think such things cannot happen to them
because they will not increase the dose to a potentially
toxic level.

The very intense cocaine effects that the smoker of the so-
called cocaine "free base" (that is, cocaine base rather
than its salt) experiences probably reflects the fact that
smoking any drug is a very efficient way of delivering it in
a very concentrated form to the brain (Perez-Reyes et al.
1982). That the intense, pleasurable and, hence, rein-
forcing effects lead to frequent, compulsive, repeated use
should not be unexpected. The reinforcing effects of nico-
tine for the tobacco smoker may be similarly explained. In
addition, the metabolism of cocaine at high dose levels has
not been studied and might well be different. Techniques
developed in tobacco and marijuana smoking research have
much relevance to cocaine smoking. The toxicity that

develops with smoked high-dose use or, for that matter, with high-dose use by any route of administration, is not well understood in terms of mechanisms (Siegel 1982). The problems which may evolve if smoking cocaine becomes more widespread are substantial. Of still greater concern would be the consequence if coca paste (an intermediate product with numerous toxic impurities) were to become widely available.

Treatment of the irritable, hypervigilant, paranoid, suspicious state associated with prolonged high-dose cocaine use is as yet empirical rather than rational. Many techniques are being used, but proper evaluation of outcome from any of them has not been done (Siegel 1982). Organ (brain, liver, etc.) toxicity has not been noted in humans. However, a number of studies with rodents have found evidence of liver damage, presumably from a cocaine metabolite (Freeman and Harbison 1981; Rauckman et al. 1982). Whether this is likely or even possible in humans, or whether it is simply a phenomenon seen in rodents because of some metabolic difference, is unknown.

Many questions remain. The psychoses seen after sustained amphetamine use and after cocaine use are similar and have been thought to be a useful model in the study of naturally occurring schizophrenic psychoses (Post et al. 1976). Whether people with a genetic predisposition for schizophrenia are more at risk to cocaine-induced psychoses has not been determined. Animal studies indicate that coca leaf contains constituents other than cocaine that contribute to toxic effects (Bedford et al. 1982). Identification of these substances in the coca leaf would be of relevance to the 4 million or so people who regularly chew coca leaf. The interactions between cocaine and other drugs, that is, other drugs taken therapeutically or illicitly, or even the many substances used as additives to cocaine when sold on the illicit market, have not been studied in animals or in humans. The relative absence of reports of clinical phenomena consistent with "kindling," that is, enhanced sensitivity and responsivity of various neural and other systems (Post et al. 1976; Post et al. 1981; Stripling and Hendricks 1981), is puzzling. Perhaps such phenomena are evident in long-term, frequent cocaine users, but such populations have not yet been studied systematically.

AMPHETAMINES

Amphetamines are similar to substituted phenethylamines, that is, catecholamines. Thus, similarities to naturally

occurring compounds in the body make the study of amphetamines important since understanding their pharmacology may help understand brain function. Hundreds of amphetamine analogues have been synthesized. Many have been used in medical practice and many other analogues have appeared on the illicit market. A vast and diverse literature makes simple summary statements potentially misleading (Angrist and Sudilovsky 1978).

It is important to note, however, that currently, in the United States, there are only three indications for which amphetamines may be prescribed legally by physicians: narcolepsy, hyperkinetic behavior in children, and obesity. Until relatively recently amphetamines were commonly used to treat mild depression, parkinsonism, or to relieve fatigue. Earlier (up to the 1940s), they were prescribed for such diverse clinical entities as schizophrenia, Meniere's disease, irritable colon, night blindness, and hypotension among others. In well-controlled, clinical studies, however, amphetamines were shown to be effective treatment for only two indications: narcolepsy and hyperkinetic behavior in children. The treatment of obesity, accounting for the overwhelming majority of amphetamine prescriptions, was no doubt a principal contributor for the majority of addictions to this drug. But the clinical studies showed that while amphetamines did help some individuals curb their appetite for short periods, the long-term results were as good with diet alone. Weight reduction is no longer a justifiable indication for amphetamines. Their use by sportsmen, truck drivers, and others, to improve performance and decrease fatigue, is also not acceptable.

All the above medical considerations as well as the need of society to cope with the growing spread of amphetamine abuse have led the government to impose tighter controls and regulations. As a result, in 1971 amphetamines were placed in Schedule II of the Controlled Substances Act which carries severe restrictions on prescription and manufacturing of this drug (Spotts and Spotts, 1980).

Biochemical research with amphetamines has resulted in some interesting observations. In humans, amphetamine, like cocaine, can lead to schizophrenic-like behavior. Stimulant effects are partially mediated by dopaminergic neurons in the brain. Anti-psychotic drugs, useful in the treatment of schizophrenia, produce dopamine receptor blockade. Thus, it seemed reasonable to consider amphetamine-induced psychoses as useful models of schizophrenia (Post et al. 1981). In retrospect, the hypothesis seems a little simplistic. But

the testing of that model led to a better understanding of brain neurochemistry and function. The amphetamines will continue to be potent research tools for trying to understand the pathogenesis of schizophrenia and other psychotic states.

Perhaps the most important recent observation has been that changes induced by single doses or short-term administration of amphetamine are quite different from consequences of long-term administration, raising the question of whether the serotonin hypothesis for schizophrenic-like psychoses was prematurely cast out in favor of the dopamine hypothesis (Trulson and Jacobs 1979; Beninger and Hahn 1983). However, good research involving prolonged administration of drugs is more complex and expensive. It tends to be neglected in favor of acute experiments that are easier to do but are not as relevant to clinical problems. Research with amphetamines illustrates the utility of nontargeted research activities in the sense that studies of amphetamine undertaken from a mental health perspective often provide important data relevant to the abuse of that class of drugs. Understanding amphetamine actions and mechanisms is relevant to understanding cocaine (Leith and Barrett 1981). Studies of a class of amphetamines usually referred to as substituted amphetamines, of interest because of their hallucinogenic properties and the fact that relative ease of synthesis leads them to appear frequently on the illicit market, have led to a better appreciation of commonalities among hallucinogens, stimulants, and naturally occurring mental disorders.

In recent years there has been a move away from human studies with the amphetamines and related stimulant/hallucinogens in favor of biochemical and behavioral studies in animals. Although animal toxicology must be understood and certain metabolic and neurochemical data can be obtained only in animal studies, many effects of amphetamine, particularly the novel hallucinogenic amphetamines, can be measured only in humans.

CAFFEINE

Caffeine, like cocaine, is an alkaloid, but it occurs in coffee plant seeds and in tea leaves. Caffeine is most commonly consumed in coffee and tea, but also is present in substantial amounts in cocoa, chocolate, cola drinks, and many nonprescription medicines, including some of the so-called look-alike drugs. Caffeine is commonly ingested to increase wakefulness and for its mood arousing and

stimulatory effects, although many caffeine users, for example drinkers of cola drinks, do not usually attribute the good feelings following the drink to the ingestion of the drug caffeine. In the United States, over 1 billion kilograms of coffee are consumed yearly. One average cup of brewed coffee contains about 100 to 150 mg of caffeine. Instant coffee contains much less. Tea contains about half as much as a cup of coffee, and cola drinks, about a third as much per bottle. About 3 percent of the adults in North America consume 600 mg or more of caffeine daily. The daily dose is higher in many other parts of the world.

Caffeine is a potent drug affecting many bodily systems, particularly the central nervous system, cardiovascular system, and gastrointestinal system (Lancet 1981; Curatolo and Robertson 1983). At high doses it produces effects that mimic anxiety disorders (White et al. 1980). Its other health consequences have been endlessly debated (Lancet 1981; Curatolo and Robertson 1983). Caffeine is rapidly and completely absorbed with the peak blood levels at about 30 minutes after an oral dose (Blanchard and Sawers 1983). The rate at which it is eliminated varies greatly between people, with half-lives varying from 2.7 to 9.9 hours (mean = 2.5 hours). That is faster than amphetamine and slower than cocaine. Caffeine metabolism is complex, with probable interactions between the processes of distribution, metabolism, and excretion of the many metabolites (Tang-Liu et al. 1983).

Recently, evidence has been accumulating that the behavioral, and perhaps many other, effects of caffeine and other methylxanthines involve the receptors for adenosine (Boulenger et al. 1983; Glowa and Spealman 1983; Von Borstel et al. 1983). This is possibly important because adenosine is involved in many bodily processes. For example, adenosine constricts bronchi, inhibits platelet aggregation, and dilates coronary and other blood vessels. In the central nervous system, adenosine may function as a neuromodulator, thus interacting with many neurotransmitters. It has roles in nucleic acid formation, ATP synthesis, and in the intermediary metabolism of a number of intracellular substances. Caffeine and other methylxanthines antagonize the effects of adenosine. Adenosine is a potent depressant. It inhibits the release of excitatory neurotransmitters. Thus, adenosine antagonism by caffeine would be consistent with the increased arousal, anxiety, hypervigilance, and agitation associated, for some people, with frequent and high-dose caffeine use.

Tolerance and dependence on caffeine is reflected not only in symptoms and behavior evident in heavy caffeine users when deprived, but also in animal studies where adreno-receptor activity is decreased, along with a parallel rise in circulating catecholamines, for some days after caffeine withdrawal (Mackenzie et al. 1981). Caffeine withdrawal may be a useful model with which to study the biochemical correlates of tolerance and dependence.

Caffeine also stimulates the release of immunoreactive beta endorphin by mechanisms possibly involving opiate receptors (Arnold et al. 1982). The investigators speculated that the popularity of caffeine may be related to its endorphin releasing activity. An even more speculative recent study found that coffee contained material that in vitro acted like an opiate-receptor antagonist (Boublik et al. 1983; Iverson 1983). The material is clearly different from caffeine. It is a low molecular weight, dialysable, heat stable, ether-extractable material and is not present in tea. The amount of this unidentified material in the average cup of coffee (either regular or decaffeinated) is about five times the dose needed to see effects in the in vitro experiments. How such activity might affect a coffee drinker is unknown. The activity might be only at the level of gut opiate receptors, but could get into the general circulation as well. Although the chemical identity remains to be established, from the receptor binding and the guinea pig ileum bioassay studies, coffee clearly contains a substance whose activity is opiate-receptor mediated and, so far, specific to coffee. The health significance of such findings, of course, is uncertain.

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SEDATIVES AND ANTI-ANXIETY AGENTS

Widespread use of sedative-hypnotics has been a cause for concern virtually since the introduction of barbiturates into medical practice almost 80 years ago. Since then, a number of new sedative-hypnotics of the nonbarbiturate type, such as glutethimide (Doriden), ethchlorvynol (Placidyl), ethinamate (Valmid), and meprobamate, as well as a legion of benzodiazepine derivatives exemplified by chlordiazepoxide (Librium) and diazepam (Valium) have at various times eroded the popularity of barbiturates. The use of barbiturates and so-called nonbarbiturate sedative-hypnotics has markedly decreased during the past two decades, while the use of benzodiazepines has risen dramatically and remains high. Figure 1 indicates the trend in prescriptions for anti-anxiety drugs, another name for sedatives. The recent decline in number of prescriptions has now leveled off.
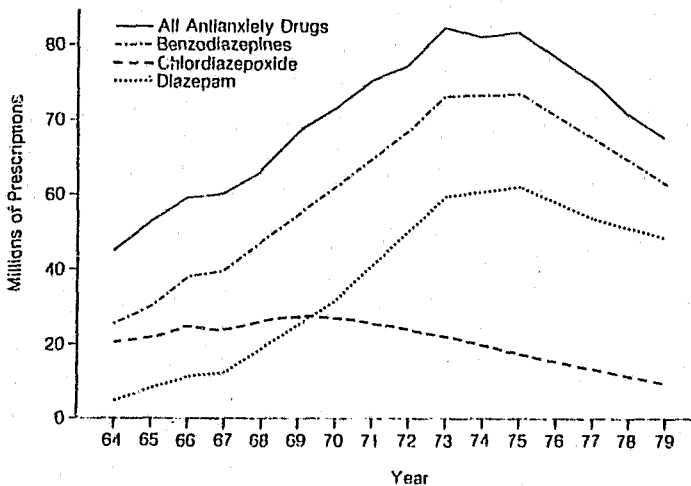
FIGURE 1. *Trends in prescribing sedatives 1964-1979 (from National Drug Prescription Audit, 1980.)*

Sedative-hypnotics have legitimate medical uses, which accounts for the great number of prescriptions for them. Anxiety and insomnia are common and disturbing symptoms for which these drugs provide easy relief. It is the ease with which they provide relief that has been disquieting. Many fear that it predisposes to misuse and possibly to abuse of these drugs.

DEFINITION OF TERMS

It might be well to clarify the terminology used in this report. Sedatives (usually employed for relief of anxiety) will not be distinguished from hypnotics (usually employed for relief of insomnia). The traditional hyphenated term, "sedative-hypnotic," to describe drugs of this class is well justified. Depending on the dose and its frequency, virtually any of the drugs in this class could be used interchangeably for either medical indication. The artificial distinction is based primarily on pharmaceutical marketing strategy rather than on pharmacological differences.

"Misuse" will describe ill-advised patterns of prescribing by physicians or use by patients within the context of medical treatment. "Abuse" will refer to a pattern of use of these drugs by patients for psychic effects beyond those for which the drugs are normally prescribed, that is, for non-medical use.

Patterns of abuse may arise from supplies of drugs obtained licitly by prescription as well as those obtained through illicit sources on the street. It is difficult to know precisely how much of sedative-hypnotic abuse is fueled by each potential source.

HAZARDS OF SEDATIVE-HYPNOTICS IN MEDICAL USE

Not only do these drugs provide effective and prompt symptomatic relief, but they do so with a high degree of safety when properly used. Adverse effects on major organ systems (liver, kidneys, heart, lungs, blood, gastrointestinal tract) are extremely rare. The principal areas of concern relate to their actions on the central nervous system.

Psychomotor Impairment

This problem is probably the most frequent. Some patients treated with these drugs may develop a degree of intoxication resembling that from alcohol. The extent to which such an intoxication develops is a function of the dose and

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dosage schedules, the pharmacokinetic parameters of the specific drug (how readily it is eliminated from the body), and the variable individual responses of patients to comparable concentrations of these drugs.

Despite the fact that a diligent search has been made for several years to detect the contribution of these drugs to fatal automobile accidents, alcohol remains overwhelmingly the major contributor. Experimental studies of driving skills (either in a robot or in an actual vehicle) have demonstrated impairment when single doses of sedative-hypnotic drugs are given to volunteer subjects. A rather typical study of this sort was published recently based on a study done in Holland. Nine male police officers from 24 to 34 years of age were given a single 10 mg dose of diazepam and 1 hour later their night driving was monitored. Two of them veered into an adjacent lane and onto the shoulder of the road. Average lateral variability (the side to side movement of the car) was significantly higher in all the men after the 10 mg dose than after a 5 mg dose, or a placebo, or taking nothing (O'Hanlon et al. 1982).

Contrived situations such as this differ vastly from that of the troubled patient who takes these drugs chronically and may have developed tolerance to the sedation they produce. One might even argue that anxious, preoccupied patients are more dangerous when driving a car with untreated symptoms than they would be if they had been treated with a sedative-hypnotic, even were the drug to produce some degree of impairment (Hollister 1974).

Epidemiological studies usually estimate a greater risk of road accidents for persons chronically taking sedatives. The relative risk estimate in one study was 4.9 among persons taking drugs, relative to a matched group not taking drugs (Skegg et al. 1979). Some of the cases counted as contributing to a higher risk were dubious. For instance, one person fell from her bicycle when a car door opened unexpectedly. Any experienced bicycle rider knows that this risk is usual, whether or not one is taking drugs.

A similar concern revolves about the residual effects of hypnotics. These drugs are usually taken only at night, but active concentrations may still be present in the body the following day. Long-acting drugs, such as flurazepam (Dalmane), have been thought to contribute to a daytime hangover that might significantly impair function. On the other hand, short-acting hypnotics, such as temazepam (Restoril) or triazolam (Halcion), have been thought to be

associated with "rebound" insomnia and anxiety (Nicholson 1980). One can control the residual effects to some extent by simply reducing the dose.

Medical overdoses of these drugs represent a classic instance of misuse. The situation is totally avoidable if both physician and patient pay close attention to the doses prescribed, the frequency with which they are taken, and the patient's reactions to them.

Dependence and Withdrawal

Some people become so enamored of the tension-relieving action of these drugs that they take them continually, another form of misuse. They become physically dependent. Psychic dependence usually precedes development of physical dependence but does not lead inevitably to it. Physical dependence is manifested by the appearance of symptoms and signs, generally opposite to the actions of the drug taken, when the drug is suddenly stopped.

Rather surprisingly, it was only in 1950 that withdrawal from pentobarbital sodium (Nembutal) was shown experimentally to be due to the abrupt cessation of drug-taking of larger than customary doses. The syndrome resembled, in most respects, the syndrome seen following alcohol withdrawal, including a delirium tremens-like state (Isbell 1950). Physical dependence on benzodiazepines was first produced experimentally in 1961, not long after chlordiazepoxide was marketed. Ten of eleven patients treated for several weeks or months with daily doses of 300 to 600 mg, 8 to 20 times the usual therapeutic dose, experienced an abstinence syndrome after being abruptly switched to placebos without their knowledge. Two patients had seizures, one at 7 days after withdrawal, the other at 8 days. The estimated plasma disappearance half-life of chlordiazepoxide and its metabolites was 48 hours, consistent with the late onset of seizures. The difference between the withdrawal syndrome from chlordiazepoxide as compared with that from short-acting barbiturates, or drugs such as meprobamate, was that it was both milder and more attenuated than the acute explosive withdrawal reaction seen with short-acting drugs (Hollister et al. 1983). A similar withdrawal syndrome was observed in a group of schizophrenic patients treated with diazepam. Clinical signs of withdrawal reaction were seen in 6 of 13 patients abruptly switched to placebos after daily doses of 120 mg, or about eight times the usual therapeutic dose. One patient had a major seizure on the 8th day

of withdrawal (Hollister et al. 1983). The diazepam
withdrawal reaction was also mild and attenuated.

Since these early experimental studies in man, a number of
clinical reports of spontaneous dependence on benzodiaze-
pines have appeared. As might be expected from the use
pattern of chlordiazepoxide and diazepam, the majority of
the clinical reports concerned these two drugs. The reports
in the literature through most of 1978 have been reviewed
(Marks 1978). Slightly more than 400 individual patients
have been reported to be dependent on benzodiazepines. The
majority of these patients were dependent in the context of
concurrent abuse of alcohol and other drugs. Only 56 cases
of physical dependence were specifically noted, the vast
majority of patients being assumed to have only psychic
dependence.

No one is sure how often patients chronically treated with
sedatives increase their dose to counter the effects of
tolerance. Among 108 neurosurgical patients who had taken
diazepam (usual daily dose 15 mg) for one month to 16 years
(median 5 years), no definite evidence of dose augmentation
could be discovered from measurement of plasma concentra-
tions of the drug. One-third of the patients seemed to be
using less than the prescribed amounts as judged by low
plasma concentrations (Hollister et al. 1981). Whether this
experience can be extrapolated to that of psychiatric
patients is uncertain.

During the last several years, a new phenomenon has been
described that may be far more common and far more ominous
in its implications. So-called "therapeutic-dose depen-
dence" on benzodiazepines has been noted with doses within
the acceptable therapeutic limits, but which have been
continued for months or years. Initial reports of this
syndrome were scattered, but the number has greatly
increased since an experimental study in 1973 (Covi et al.
1973).

The symptoms of this kind of dependence resemble those for
which the patient was originally treated (anxiety, sleep
disturbance, tremor, depression, irritability, loss of
energy) which makes the distinction between a true with-
drawal syndrome and recrudescence of symptoms difficult.
Weight loss, headache, and perceptual changes are symptoms
that seem to be much more common in the true withdrawal
syndrome from therapeutic doses (Petursson and Lader 1981;
Schopf 1983).

Perhaps to avoid such symptoms, patients on long-term treatment with benzodiazepines are often loath to stop the drug. In a sense, they are "hooked." Several studies in which patients have been withdrawn from long-term therapeutic use of benzodiazepines without their knowledge (by substituting a placebo unbeknownst to the patient) have sometimes failed to demonstrate this withdrawal syndrome (Bowden and Fisher 1980; Laughren et al. 1982). On the other hand, some authorities argue that a substantial number of persons on long-term treatment with these drugs are at risk, which in the United States might represent several million people.

The discovery in 1977 of specific receptors for benzodiazepines in the brain suggests a possible mechanism for this new phenomenon. Drug receptors may change during chronic treatment to accommodate the effects of the drugs. Thus, when the drug is suddenly withdrawn, a form of "receptor rebound" may occur, similar to what has been described for the beta-adrenoreceptor blocking drugs so useful for treating patients with angina and hypertension (Cowen and Nutt 1982). The phenomenon of "therapeutic-dose dependence" deserves the highest priority for study, as it is new, controversial, and of potentially great importance.

Overdoses

Sedative-hypnotics have been a popular way to commit suicide for many years. The life-support system treatment introduced in the early 1960s resulted in much more successful management of barbiturate overdoses. Nonetheless, completed suicides from overdoses of these drugs remained high. The gradual displacement of barbiturates by the much safer group of benzodiazepines has diminished the number of successful suicides from overdoses of sedative-hypnotics.

The benzodiazepines are remarkably safe when overdoses are taken. An extensive survey of 27 medical examiner or coroner offices in the United States and Canada was conducted during the latter part of 1976. The combined jurisdictional population of these sites was 79.2 million people. Diazepam was found to be present on toxicological analysis in 1,239 cases of death. Drugs alone caused death in 914 cases; the remaining 375 fatalities were due to other causes. Only two patients died after having taken diazepam alone (Finkle et al. 1979). Considering that one is always at some risk of death whenever one is comatose and treatment

is delayed, this number of deaths is probably the irreducible minimum for drug overdoses.

Questionable Problems

Paradoxical excitement, rage, and hostility have been reported occasionally from benzodiazepines. Data on these reactions indicate that they are rare (6 of 2,086 patients treated with chlordiazepoxide and 4 of 2,623 patients treated with diazepam). Such reactions are probably idiosyncratic, occurring mainly in patients with poor impulse control or with aggressive, destructive behavioral tendencies that are released by the drugs (Greenblatt 1976). Such reactions have also been reported following use of barbiturates, phenothiazine, and antidepressants, and are notoriously common following alcohol.

Some patients become depressed when treated with sedative-hypnotics. As depression is usually accompanied by anxiety and insomnia, symptoms that could be relieved by these drugs, sedative-hypnotics may be misprescribed for depressed patients. The known pharmacology of this class of drugs makes it unlikely that they are truly "depressogenic."

HAZARDS OF SEDATIVE-HYPNOTICS IN NONMEDICAL USE

Abuse of these drugs is frequently in the context of abuse of other agents, especially alcohol. Considering the pharmacological similarities exhibited by alcohol and sedative-hypnotic drugs, it is not surprising that many persons attracted to alcohol are also attracted to sedative-hypnotics. Because of this proclivity, it is relatively easy to convert an abuser of alcohol to an abuser of sedatives. Although the latter drugs are highly useful in treating alcohol withdrawal, they have no place in the long-term management of alcoholics because of possible abuse.

A substantial number (two-thirds) of users of "hard" drugs, such as opiates, also use barbiturates, with overt clinical signs of barbiturate intoxication in a third of those using both (Aylett 1978). An earlier survey found that 62 of 65 heroin addicts also abused barbiturates (Mitcheson et al. 1970). Pharmacologically, sedative-hypnotics have little in common with opiates, yet heroin users will turn to sedatives if the supplies of heroin decrease or the expense of the habit becomes too high. The combined use of these drugs prolongs the consciousness-altering effect of the opiates.

Formerly, barbiturates were often alternated with
amphetamines or other stimulants. This practice is not as
widespread among current users of cocaine, possibly because
cocaine stimulation is relatively short-lived and does not
need to be countered with a sedative.

The majority of cases of sedative abuse is either in the
context of polydrug use or past drug abuse. Some persons
have abused only sedatives, but they are rare. Virtually
all will have started to abuse sedatives that were initially
prescribed for medical purposes.

Patterns of Abuse

The clinical patterns of sedative abuse have not changed
much over the past 30 years. Oral doses are almost always
the rule, seldom exceeding the equivalent of 1,000 to 2,000
mg daily of secobarbital sodium (Seconal). Use tends to be
in a "spree" fashion rather than continual. Primarily, the
effect sought from these excessive doses is a drunken state
akin to alcohol intoxication, with relief of tension,
euphoria, and, later, sleepiness. By titrating the dose,
users can maintain a constantly intoxicated state during the
day, but sleep it off at night. Tolerance rapidly develops
if barbiturates are used, so that the dose must be
repeatedly raised to attain the same effects. Many such
tolerant individuals can take ordinarily-lethal doses with
impunity.

Those who abuse sedatives do so to obtain a rapid but fairly
brief state of intoxication, comparable to that caused by
alcohol. It would be expected, therefore, that the drugs
most likely to be abused would be rapidly absorbed and have
a short span of action. These requirements are well met by
secobarbital, pentobarbital, or amobarbital among the
barbiturates, and by meprobamate, methaqualone, or glutethi-
mide among other classes. Drugs which are longer-lasting,
such as phenobarbital and some benzodiazepines, do not lend
themselves well to repeated bouts of intoxication. Thus,
the biological half-life of the drug seems to have an
important bearing on its potential for abuse. For a variety
of reasons, including easier availability and cheaper price,
secobarbital sodium is the preferred street drug. However,
periodically one or another short-acting drug becomes the
fad of the moment. Thus, at various times glutethimide,
meprobamate, ethchlorvynol, diazepam, and methaqualone have
been favored.

Methaqualone

The case of the short-acting sedative-hypnotic, methaqualone (Quaalude) is instructive. This drug was introduced into the United States in 1965, even though it had been documented that it was widely abused in Europe and Australia in a preparation called "Mandrax," consisting of 250 mg of methaqualone and 25 mg of diphenhydramine. It had also been abused in Japan. This history of abuse on three continents prior to admission to the United States should have provided a warning of what to expect. Its reputation on the street as a drug to enhance sexual pleasure led to a rapidly evolving pattern of abuse (Inaba et al. 1973). Sources included various "street clinics," which purported to use the drug medically, as well as abundant suppliers of illegal methaqualone from South America. Between 1978 and 1980, hospital emergency room logs showed that methaqualone-related fatal overdoses rose 154 percent from 2,389 to 6,091.

In January 1984, the United States manufacturer of methaqualone ceased production of the drug. In addition, the People's Republic of China, a major source of the illegal methaqualone diverted to this country through Colombia, stopped manufacturing and shipping the drug. As a result of these actions, the supply of methaqualone in this country has been nearly completely curtailed.

In retrospect, a major error may have been made in allowing this drug to be used medically in this country. Still, it is highly likely that methaqualone would have gained entry illegally, as is the case with many other abused drugs that have no medical use.

HEALTH HAZARDS OF SEDATIVE-HYPNOTIC ABUSE

The major health hazards of abuse of sedative-hypnotics are fatal overdose, accidents, and withdrawal reactions. These adverse consequences are similar to those from alcohol abuse. The major difference is that alcohol has directly toxic effects on the brain, liver, heart, gastrointestinal tract, blood, and other major organ systems. In addition, as alcohol is a food that provides only "empty" calories, its chronic use is associated with a variety of nutritional deficiencies. On the basis of present knowledge, one must conclude that abuse of sedative-hypnotics has fewer adverse consequences on health than comparable degrees of alcohol abuse.

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Overdoses

Fatal overdoses ensue because of errors in judgment regarding different degrees of tolerance to the pharmacological actions of sedatives. Tolerance develops rather quickly to the sedative actions of these drugs, resulting in the augmentation of doses. Tolerance to the respiratory depressant actions of these drugs does not develop at the same rate. Thus, at the high doses often used, respiration may be markedly impaired. The addition of an extra amount of drug or of alcohol may be lethal. Some fatalities may be due to errors in dose. Many of the illicit preparations available on the streets contain amounts of drug far in excess of their labelling. Such a risk is inherent in any use of illicit drugs.

Accidents

The role of sedatives in accidents is unclear, as alcohol is often present simultaneously. Epidemiological data concerning accidents reflect the greater prevalence of alcohol abuse over sedative abuse. The involvement of sedative abuse with accidents seems most certain for methaqualone. Users of this drug apparently do not know how impaired they really are. Consequently, they operate vehicles or boats without appreciating the danger (Wetli 1983). This kind of poor judgment is probably not unique to methaqualone but seems to be less common with other sedatives.

Withdrawal Reactions

Physical dependence on sedative-hypnotics can develop with prolonged use or daily doses four to six times the usual dose, that is, about 400 to 600 mg daily of pentobarbital sodium. Because abusers of sedatives generally consume much higher daily doses, they are at constant risk for withdrawal reactions if their supply of drug is interrupted.

The clinical manifestations of physical dependence on these drugs resemble those of alcohol dependence and are termed withdrawal reactions of the "alcohol-barbiturate type" (Eddy et al. 1965). They consist of alterations of consciousness (delirium), neuromuscular irritability (tremors and seizures), and autonomic nervous system disturbances (vomiting, sweating, rapid heart rate). Uncontrolled seizures may lead to death. The onset of these symptoms following abrupt cessation of drug-taking may be hours, in the case of short-acting drugs, or days, in the case of long-acting drugs. As might be expected, the duration and intensity of the syn-

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drome are related to the length of time it takes for the
drug to be eliminated from the body. The more rapidly the
decline from high to low or absent blood concentrations of
the drug, the more severe the symptoms. Thus, slowly
eliminated drugs tend to produce a milder but more pro-
tracted withdrawal syndrome. The relationship between
plasma half-life of a sedative and the abruptness and
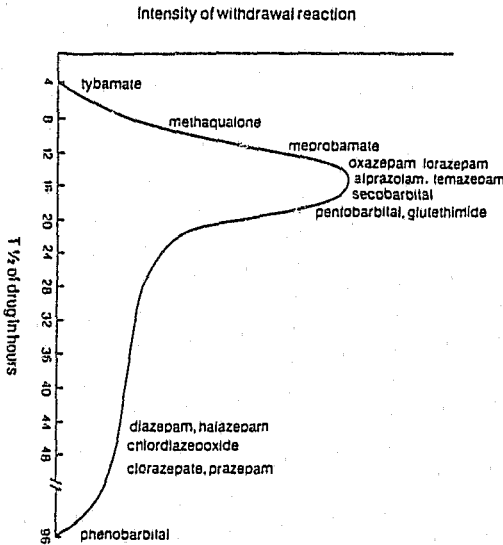severity of the withdrawal reaction is shown in figure 2.

FIGURE 2. *Hypothetical relationship between plasma half-
life and the abruptness of onset and severity of with-
drawal reaction.*

TREATMENT OF SEDATIVE-HYPNOTIC ABUSE

Perhaps because sedative-hypnotic abuse occurs so often in
the context of polydrug abuse, no specific treatment
programs have been devised for it. Rather, treatment is
usually directed at the most important other drug being
used, such as alcohol or opiates. One might assume that,
since the drugs share so many other factors, programs geared
for treating alcoholics might suitably treat the minority of
persons who abuse sedative-hypnotics only.

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SUMMARY

Abuse of sedative-hypnotics has occurred during most of this century. These drugs are widely prescribed in medical practice, where deliberate abuse is probably infrequent. On the other hand, inadvertent dependence may develop if these drugs are used constantly over long periods of time. This phenomenon of "therapeutic-dose dependence" is relatively new. Neither the parameters of dose and duration of treatment nor the pharmacological mechanism of "therapeutic-dose dependence" is completely understood. Nonmedical use of sedatives is the major pattern of abuse, supplies being obtained either from unscrupulous physicians or from drugs smuggled into the country. More often than not, abuse of sedative-hypnotics is part of a pattern of polydrug abuse, the most commonly associated drugs being alcohol and opiates. The hazards of abuse of sedatives are similar to those of alcohol, although the former drugs do not have the direct toxicity on many organ systems that alcohol has. Specific treatment programs are not available for chronic abuse, nor does it seem necessary to devise any. Treatment might best be directed at the more important associated drugs or follow the mode of alcohol treatment programs, i.e., treat the withdrawal syndrome.

The phenomenon of therapeutic-dose dependence with benzodiazepines raises serious questions. Top priority should be given to research efforts to define its parameters, its mechanisms, and possible approaches to its prevention.

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HALLUCINOGENS AND INHALANTS

OVERVIEW

Hallucinogens and inhalants are a diverse group, some occurring naturally, most the products of synthetic chemistry. Although current interest is in the consequences of misuse, some of these substances are useful for legitimate research on the neurochemical mechanisms of brain function. The use of hallucinogens and inhalants in experimental psychiatry is presently almost nonexistent because of the ethical, legal, moral, and sociological aspects of inducing "temporary insanity" in normal volunteers and in mentally ill subjects. Therapeutic application of the hallucinogens at present is nonexistent. However, specific antidotes to the hallucinogens offer promising new approaches to the therapy of mental illness. Such an idea is very old but, as yet, no specific antidotes have been developed. In fact, relatively negligible research is being done to develop antidotes to hallucinogens. Such substances, at the very least, might be of value in the treatment of subjects who overdose themselves.

Little research has been done on inhalants (other than general anesthetics). Perhaps the most significant development has been the use of animal models for self-administration of inhalants. Speculation regarding the mechanism of action of inhalants relates to their actions on membranes of many cells, including those in the brain. No antidotes are known for these agents.

HALLUCINATIONS VERSUS ILLUSIONS

Many chemical substances can alter central nervous system function and result in confusion and delirium, with and without memory loss. Distorted sensory input results in illusions. Illusions are altered sensory perceptions of actual objects in the environment. General anesthetic agents, volatile organic solvents, and many other substances such as heavy metals in large doses cause significant

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generalized metabolic disruptions of the brain and can result in illusions. In contrast to illusions, hallucinations represent sensory experiences presumably experienced within the person's brain, for which there is no object in the external environment. A person given a general anesthetic like nitrous oxide may have an illusion, but seldom a hallucination. In contrast, a person taking LSD-25 has hallucinations, particularly visual, involving colored geometric patterns. Thus, LSD-25 is a hallucinogen, but nitrous oxide is not. Organic solvents involved as inhalants usually produce illusions, not hallucinations. Some substances, such as phencyclidine (PCP), have general anesthetic properties and, like general anesthetics, produce illusions more frequently than hallucinations. However, PCP has a unique effect of reducing sensation from the entire body, and thus producing numbness like that of a local anesthetic, except that it is over the entire body. A person under the influence of PCP may state that he or she has no arms or legs, is floating, is in outer space, or is dead. PCP, in particular, is considered to be an excellent drug model of schizophrenia in contrast to substances like LSD-25.

TYPES OF HALLUCINOGENS

Chemical derivatives of at least six major chemical structures produce hallucinations. These include: (1) lysergic acid-based compounds, of which the prototypic substance is LSD-25, the twenty-fifth lysergic acid structure to be synthesized as a possible therapeutic agent; (2) phenethylamine derivatives, of which mescaline and related amphetamine derivatives are best known; (3) indolealkylamine derivatives, of which psilocybin and dimethyltryptamine (DMT) are prototypes; (4) several naturally occurring and synthetic compounds, similar to atropine and Ditran; (5) arylcyclohexylamines similar to phencyclidine (PCP); and (6) opioid derivatives, including mixed agonist-antagonists such as nalorphine, cyclazocine, and N-allylnormetazocine. Substances with a number of other complex heterocyclic structures also produce hallucinations. These include constituents of nutmeg, harmine, and ibogaine alkaloids, etc. The lysergic acid, phenethylamine, and indolealkylamine derivatives produce somewhat similar effects clinically in humans, although there are certain differences. Many experts view these as one broadly similar group of substances. Atropine-like hallucinogens are seldom abused because these substances produce significant memory deficits during the period of intoxication so the abuser does not recall his or her "trip." This is in sharp contrast to the LSD and PCP-

like substances. Animal behavioral pharmacology has made many important contributions to our knowledge of hallucin- ogens, especially with regard to their unique characteris- tics as discriminative stimuli (Seiden and Dykstra 1977). Two major symposia on the discriminative properties of drugs in general have been published describing important informa- tion on the hallucinogens (Colpaert and Rosecrans 1978; Colpaert and Slanger 1982).

LSD-LIKE HALLUCINOGENS

Knowledge of the site and mechanism of action of LSD-25 and related hallucinogens has been slowly increasing. In the 1960s and 1970s a great deal of research effort was expended on LSD-25 and related hallucinogens, and has been summarized extensively (Brawley and Duffield 1972; Cohen 1971; Freedman 1969; Hollister 1968; Hofmann 1979; Sankar 1975; Stillman and Willette 1978). For many years numerous investigators have pointed out the structural similarities between the chemical messengers (neurotransmitters) 5-hydroxytryptamine, 5-HT (or serotonin), LSD-25, and dopamine (DA) shown below.

5-HT   LSD-25   DA
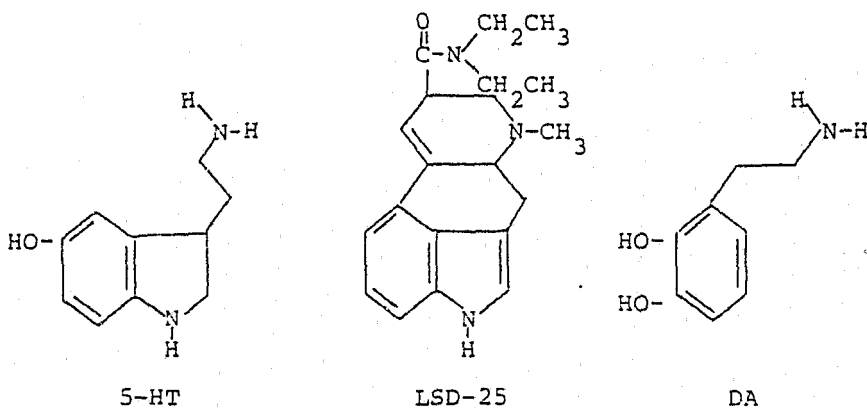
It can be seen that an indole structure is common to both 5- HT and LSD-25. However, a phenethylamine structure is also common to LSD-25 and another chemical messenger in the brain, DA. The molecular relationships of LSD-25 have been extensively described. Such studies have provided evidence for the fact that LSD-25 can react with both 5-HT and DA receptors. Thus, a dual pharmacology of LSD-25 is to be

expected in which this hallucinogen acts on at least these two chemical messenger systems. Physiological evidence, obtained primarily in animals such as the rat, documents this interaction with both 5-HT and DA throughout the body, but especially in the brain. A special group of 5-HT neurons in the raphe nuclei in the brainstem stop firing after the administration of LSD-like substances (Aghajanian et al. 1968). These 5-HT neurons are involved in sleep, so that when they stop firing the subject stays awake. Radio-labeled LSD-25, in particular, has been important in defining multiple 5-HT and DA receptors in the brain (Fillion 1983). Radioactive LSD-25 labels a subset of 5-HT receptors. It also labels a subset of DA receptors. This has important implications in the possible discovery of novel LSD-25 antagonists or antidotes.

Several leads have been developed regarding possible LSD-25 antidotes. One approach involves the opiates, including morphine, methadone, and some of the synthetic peptides related to endogenous enkephalins present in the brain. These narcotic agonists markedly reduce the effects of LSD-25 and DMT in rats, while narcotic antagonists such as naloxone potentiate their effects (Domino and Ruffing 1982; Ruffing et al. 1979; Ruffing and Domino 1980, 1981, in press). It is not yet known if these leads for antidotes, based on animal research, will apply to humans.

Current treatment of LSD-like hallucinogens is a symptomatic approach. "Talking the patient down" in a quiet environment during a "bad trip" appears to be most effective. The use of various neuroleptic or antipsychotic drugs is generally not indicated during the actual period of intoxication, but may be used secondarily. Treatment of LSD-induced flash-backs (which are relatively rare and poorly understood) is symptomatic and generally not very satisfactory. It appears that prevention through avoidance of use is the best approach.

PCP-LIKE PSYCHOTOMIMETICS

As described earlier, PCP-like drugs can produce hallucina-tions, but such hallucinations are much less common than the vividly colored geometric-design hallucinations produced by LSD-like substances. PCP-like agents produce a mental state more similar to acute schizophrenia. Hence, "psychotomime-tic" seems to be a better term for PCP-like substances. A number of reviews on the multiplicity of PCP actions have appeared (Petersen and Stillman 1978; Linder et al. 1981). Two volumes on PCP and related arylcyclohexylamines have

been published (Domino 1981; Kamenka et al. 1983). The Phencyclidine Abuse Manual by McAdams et al. (1980) is quite a valuable, practical source book for substance abuse workers. PCP-like substances are unique among psychotomime-tics for many reasons. Although LSD- and atropine-like substances are not self-administered by animals (Pickens et al. 1978), humans readily self-administer all of these substances.

An overview of the complex actions of PCP and derivatives has been summarized in a recent French-United States seminar (Domino et al. 1983). One of the most exciting new develop-ments is discovery of the existence of PCP receptors as well as endogenous PCP-like peptides (one called "angeldustine" by the discoverers) in the brain. Perhaps such knowledge will stimulate further research for a PCP antagonist that might be useful, not only to block the actions of PCP in patients who take an overdose, but also in the treatment of mental disease. Especially interesting is that sigma type opioid agents like N-allylnormetazocine are really PCP-like substances that act on PCP receptors. The ultimate question still remaining is why are PCP receptors and related endoge-nous peptides present in the brain? For what purpose? Are they there to produce a dissociated mental state following severe trauma or stress? Can the release of "angeldustine" explain the "floating" experiences outside of the body described by persons who are dying? Perhaps one of the major dilemmas as far as drug abuse is concerned is why would anyone wish to take substances like PCP? Why do these agents produce drug-seeking behavior?

Treatment of PCP overdosage is not very satisfactory. No specific antidotes are known. In general, a symptomatic approach is used. Urine acidification does enhance PCP excretion in the urine, but animal studies suggest that the amounts excreted are negligible compared to those that intoxicate. Following the initial period of PCP intoxi-cation, the psychotic states have been treated with neuro-leptics but their beneficial effects are questionable.

INHALANTS

The number of substances inhaled to obtain mental aberration is surprisingly large. Most are volatile organic solvents that are found in common household products. Inhalant types include: spray paint, glue, toluene, amyl nitrite, lighter fluid, gasoline, liquid paper, thinner, refrigerant gas, sprays of various types, fingernail polish remover, spray deodorant, nitrous oxide, cleaning fluid, sealer, and shoe

polish. The common characteristics of most of these sub-
stances are various organic solvents or substances like
nitrous oxide that act on the brain as general anesthetics.
Not only are some of these substances toxic to the brain,
but also to the liver and other body organs. Substances
like the nitrites and nitrates act to lower blood pressure
and thus reduce the amount of blood reaching the brain to
produce relative oxygen lack. Amyl and butyl nitrite have
been used by some individuals to affect sexual responses,
presumably through their vasodilator actions on the sex
organs. No scientific studies have been done on this
phenomenon. Inhalers as a group tend to use spray paint,
glue, toluene, and lighter fluid most frequently, although
prevalence figures vary markedly with the subpopulation of
substance abusers studied.

Sharp and Korman (1980) have reviewed the abuse aspects of
volatile substances. While everyone likes to smell pleasant
odors, the volatile-substance abuser seeks to alter his or
her state of consciousness, frequently at a severe price of
systemic toxicity. Peripheral nerve damage and toxicity to
the liver, kidneys, or bone marrow have been reported. More
recently, evidence has accumulated for a growing incidence
of brain toxicity. For example, chronic toluene inhalers
show cerebellar, cortical, and functional brain impairment.
Not only can the original substance be toxic, but also its
biotransformed metabolites. For example, solvents contain-
ing n-hexane and/or methyl-n-butyl ketone produce a neuro-
toxic syndrome in part due to a neurotoxic metabolite, 2,5-
hexanedione (Howd et al. 1982). Rats exposed to high
concentrations of hexane in a pattern resembling human
solvent abuse show significant plasma levels of its neuro-
toxic metabolite. This is true despite rapid elimination of
the parent compound, hexane. Neurotoxic effects in rats
include decreased hind-limb grip strength, foot-dragging,
and, with prolonged exposure, hind-limb paralysis. To date,
there are no antagonists to the effects of organic solvents
used as inhalants. Especially interesting is that animals
such as the monkey voluntarily inhale substances that are
abused by humans. About 13 years ago, Yanagita et al.
(1970) in Japan reported the voluntary inhalation of various
volatile anesthetics and organic solvents by monkeys.
Subsequently, Wood et al. (1977; Wood 1978) have confirmed
and extended these findings. Inhaled substances can modify
behavior in a variety of ways including: (1) a direct toxic
action; (2) acting as discriminable stimuli; (3) supporting
behavior; (4) suppressing behavior; (5) eliciting uncondi-
tioned reflexes; (6) acting as negative reinforcers; and
(7) as positive reinforcers.

CONCLUSIONS

We have a long way to go before significant progress will be
made in hallucinogen and inhalant abuse. There is a need to
develop specific antidotes, important in the treatment of
overdosage. While the neural mechanisms of LSD-like
substances are perhaps best understood, our neurobiologic
knowledge of the action of other substances such as PCP and
the inhalants is, at best, still quite primitive.

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HEROIN AND NARCOTICS

HISTORY AND PERSPECTIVE

The abuse of narcotic analgesics (opiates) such as heroin and morphine has remained a significant problem in the United States from the 1920s to the present. Although the size of the problem waxes and wanes, there are several reasons for believing that their abuse is still a serious and unsolved problem. Heroin and related drugs such as morphine and methadone are very potent respiratory depressants, and the death rate among heroin abusers is still large compared to that among users of other groups of drugs. Narcotics also produce a high degree of tolerance and physical dependence when used repeatedly, and the abstinence syndrome that results when dependent patients are withdrawn creates a drug need that takes precedence over other body needs and induces drug-seeking behavior. Because of this property, heroin abuse gives rise to conditioning processes that strengthen dependency and make withdrawal and abstinence difficult.

The United States has led the world in efforts to minimize and control the heroin problem, although the prevalence of abuse may not be greater in the United States than it is in other countries. The availability of heroin, and, to a lesser extent, other narcotic analgesics, is much restricted in the United States. The commerce of these drugs is closely controlled, and rigid prescribing practices are mandated. The penalties for possession and sale of narcotic analgesics are severe.

The pharmaceutical industry and others have made major commitments to developing new analgesic drugs that will relieve severe pain effectively but safely, have a lower abuse potentiality, and be less addicting (dependence producing) than heroin and morphine. Heroin occupies a unique niche in both medicine and drug abuse. Although heroin continues to be the most widely abused of all narcotic analgesics, many physicians and laity feel that it is endowed with properties

that are especially useful in the treatment of terminal
chronic pain. Heroin was studied intensely in the 1950s and
early 1960s and has been reinvestigated recently (Kaiko et
al. 1981; Martin and Fraser 1961; Martin et al. 1976; Smith
and Beecher 1962). The findings continue to indicate that
heroin is more soluble in both water and tissues than mor-
phine and is capable of entering the central nervous system
following administration somewhat more rapidly than mor-
phine. It is rapidly metabolized first to an intermediate
and finally to morphine, which in turn is changed into a
water soluble form (by glucuronidation) for excretion (Way
and Adler 1962). Pharmacologic studies have indicated that,
in man, heroin may have a somewhat more rapid onset of
action than morphine and has the same or a slightly shorter
duration of action, probably because it enters the brain
more rapidly than morphine (Way and Adler 1962; Martin and
Fraser 1961). Heroin appears to be between two and three
times stronger than morphine on a gram weight basis, but
when heroin and morphine are administered in equally potent
doses they produce the same pharmacologic effects (Reichle
et al. 1962; Martin and Fraser 1961; Kaiko et al. 1981).
Thus, there appears to be no pharmacologic reason for the
preference of addicts for heroin nor a medical basis for
believing that it is more effective for treating pain,
except that it may have a more rapid onset of actions and be
more potent.

OPIOID RECEPTORS AND NEUROTRANSMITTERS

It is known that morphine-like drugs and drugs that are
related to morphine interact with several types of opioid
receptors. These different types of opioid receptors are
located in different parts of the brain and on different
nerve cells (Martin et al. 1976). It is for this reason
that some of the analgesics which have been discovered
during the last 10 to 15 years are safer and less addicting
than morphine or heroin. They interact with different types
of opioid receptors than morphine does and produce different
kinds of analgesia as well as other effects. At least nine
opioid receptors have been identified, in one species of
animal or another, that interact with opioid-type peptides
(Martin in press). The number of these receptors present in
man is not known. There is clear evidence that at least
three types of opioid receptors are present in the human
brain (Martin et al. 1976). Identification of the different
opioid receptors has been made possible by studying the
pharmacology of newly developed and unique analgesics as
well as by studying the effects of opioid peptides. Finding
opioid peptides in the brain that mimic the actions of

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opioid analgesics was a major and exciting observation. It is now known that the brain has several types of opioid peptides which interact with different opioid receptors (Wu et al. in press). These brain peptides may decrease as well as increase sensitivity to pain. Because it is reasonably certain that people do not become dependent on their own opioid peptides, it seems possible to develop new opioid analgesics that will be devoid of dependency properties (Jasinski et al. 1967). Further, it is known that these opioid peptides and opioid receptors are involved in many physiologic processes, such as respiratory, endocrine, cardiovascular, and gastrointestinal functions (Jaffe and Martin 1980). The understanding of opioid receptors has led to observations that may have immediate and practical implications for the development of safer analgesics. These important observations indicate that it is entirely feasible to identify new drugs that will be devoid of morphine's adverse effects such as lethal respiratory depression. For example, a receptor has been identified, in the mouse, that is responsible for the analgesic action of morphine, and another closely related receptor has been identified that is responsible for its respiratory depressant actions (Wolozin and Pasternak 1981). If these two receptors are present in man and serve the same role, it should be possible to find a pain-relieving drug that would be devoid of respiratory depressant effects.

Chemistry

The chemistry of pain-relieving drugs has become enormously sophisticated. Virtually hundreds of drugs are synthesized each year that have the potential for being useful analgesics. Thus, there are many drugs and chemical syntheses that could, if the need arose, provide analgesic drugs that would not depend on the production of opium. Nevertheless, morphine and codeine continue to be the drugs that many doctors use skillfully, are familiar with, and regard as essential to medical practice. Further, the cultivation of the opium poppy from which morphine and codeine are obtained is an important part of the economy of certain opium-producing countries. Important basic research is being conducted, however, to develop economic and practical ways of synthesizing morphine and codeine. Basic synthetic efforts have not only given rise to analgesics with safer properties, but have produced analgesics and drugs with unique and useful properties. For example, through manipulation of the chemical structure of analgesic drugs it has been possible to obtain analgesics of very short or very long durations of actions (Jaffe et al. 1970). One of

these, L-alpha-acetylmethadol (LAAM), is a very long-acting morphine-like drug used for treating narcotics addicts. It need be given only every other day in maintenance therapy, thus saving both the treatment facility and the patient money.

Opioid drugs have also been developed that occupy opioid receptors but do not produce any effect. These drugs are called opioid antagonists and are useful for the treatment of morphine-type overdose and for replacement therapy of heroin addicts (Martin 1977). Again, through chemical manipulation of the morphine molecule, it has been possible to obtain an antagonist, "naltrexone," which has a long duration of action. A newer example of a unique drug is "buprenorphine," which is both an agonist and an antagonist. It produces morphine-like effects but only to a limited degree. It is a safe analgesic and may be especially useful in maintenance therapy of heroin addicts (Jasinski et al. 1978).

Modern receptor theory suggests that parts of the opioid receptor are not involved in the activity of the drug but contribute to the tightness with which the drug fits the receptor. It has been possible to synthesize drugs that interact with the morphine receptor in an irreversible manner (Portoghese et al. 1979; Archer et al. submitted for publication). The implications of these drugs in treatment will be discussed subsequently. These irreversible binders have also provided a unique tool for identifying different types of opioid receptors and binding sites. To illustrate, it has been possible to administer irreversibly acting opioids in combination with opioid-like drugs that bind specifically to certain receptors. When such a mixture of drugs is added to the isolated opioid binding sites, the irreversible drug cannot get on the receptor that is protected by the specific drugs but can occupy all of the other types of receptors. This technology should eventually allow a more clear-cut understanding of the role different opioid receptor subtypes play in brain functions and in moods and feeling states.

Highly reactive analgesics are also being used to isolate and separate opioid receptors using a technique called affinity chromatography. This technique attaches reactive opioid molecules to much larger molecules and exposes solu-bilized receptors to these complex molecules. The receptor recognizes the opioid attached to the large molecule and binds to it. The nonopioid material can be washed away, and the purified receptor can be dislodged from the complex

opioid molecule. Using this technique, researchers have
identified several opioid binding sites.

Analgesia

The discovery of opioid antagonists that occupy opioid
receptors but do not exert any pharmacologic action is one
of the important discoveries of the last 20 years. This
discovery helped unravel the nature of the brain's capacity
to reduce the painfulness of injurious stimuli. In the
central part of the brain are areas that can be activated by
a variety of stimuli and that reduce the response of
organisms to painful stimuli. It is thought that these
centers provide the basis for reduction of pain by acupunc-
ture. Some of the analgesia that can be evoked by stimula-
tion of these centers can be blocked by the narcotic antago-
nist, naloxone, whereas some of the analgesia cannot (Akil
et al. 1976). These observations have been interpreted as
indicating that the endogenous opioid peptides in the brain
mediate the naloxone-antagonizable analgesia, whereas a
nonopioid mechanism (nonmorphine-like) is involved in the
analgesic response that is not antagonized by naloxone.

Pharmacologic experiments performed by many investigators
have shown that there are a variety of other brain neuro-
transmitters that modify the perception of painful stimuli
and the actions of morphine-like drugs (Han and Terenius
1982). These brain transmitters, which are thought to be
important in brain function, include agents such as acetyl-
choline, serotonin, norepinephrine, and epinephrine; the
opioid peptides dynorphine, leucine, and methionine-enke-
phalin; and the endorphins. Thus, the brain probably has
many ways of modifying perception of pain. These all pro-
vide opportunities for developing strong new analgesics that
do not have the adverse effects of those currently avail-
able. It is entirely possible that, in the future, resear-
chers will develop analgesic mixtures containing drugs
related to the above mentioned neurotransmitters as well as
to the opiates.

The study of narcotic antagonists has also shown that
individuals differ with regard to susceptibility to pain,
and thus provides a partial explanation of why some individ-
uals can accept pain while others react vigorously to minor
discomfort. Some valuable research shows that the narcotic
antagonist, naloxone, will relieve pain in some individuals
and make it worse in others (Levine et al. 1979). Related
to this are findings that the brain may very well have both
analgesic and hyperalgesic systems, mediated by different

opioid receptors and different opioid transmitters. Recent
findings reveal that an opioid (a kappa agonist), when
administered to the medullary region, produces hyperalgesia
or the worsening of pain (Wu et al. in press). It is
further known that dynorphin may have predominantly kappa
activity. On the other hand, when morphine or related drugs
are injected into the periaqueductal gray, a region in the
center of the brain, analgesia is produced (Chavkin et al.
1982). It is thus possible that the balance of both hyper-
algesic and analgesic systems in the brain could vary from
one individual to another and that this balance may be
related to how they react to pain.

The Way Opioid Analgesics Work

The important role of opioids in the functioning of the body
and brain, as well as their relationship to tolerance and
dependence, has stimulated research on their basic mechan-
isms of action at both a cellular and molecular level. When
opiates are applied directly on nerve cells that are respon-
sive to them, they most often depress nerve function.
Studies of two types of nerve cells indicate that this
depression may be due to changes in ion conductance of nerve
membranes, so that they become more stable and less easily
excited (Morita and North 1982). The identification of the
opioid receptor is an important area of research in which
exciting progress has been made recently. It is now thought
that the opioid receptor probably has two parts; one part
consists of a lipid and the other part a protein. Abood and
Takeda (1976) have identified at least two lipids that may
be part of the opioid receptors cerebrosidesulfate and
phosphatydlserine. The material identified using affinity
chromatography is probably a protein (Loh et al. 1975).

Tolerance and Dependence

The ability of most opioid drugs to induce tolerance and
dependence when administered repeatedly is well known. Both
of these phenomena are extremely complex; however, they both
have practical significance. The ability of the opioids to
induce tolerance seriously affects treatment of pain, for it
is necessary to increase the dose of these drugs to attain
the desired therapeutic effect. As patients become increas-
ingly tolerant, the amount of drug that is required can
increase enormously. Physical dependence for some opioids
is associated with an unpleasant and sometimes health-
threatening abstinence syndrome when the drug is withdrawn
or withheld. Not only is there a complex physiologic
syndrome that commonly makes the patient sick, but this

abstinence syndrome is associated with a perceived need for the drug of dependence. This withdrawal illness makes it difficult to terminate the use of narcotics after they have been given for a long time at high doses (Martin and Sloan 1977). Therefore, these two phenomena continue to occupy the interest of scientists not only from a theoretical point of view, but because of their practical importance.

It is known that some types of tolerance and dependence can be induced rapidly while other types require the drug to be administered for a longer time and in higher doses. Basic research has shown that opiates inhibit the activation of a basic enzyme, adenylate cyclase, that is involved in nerve function and perhaps in memory. When morphine is administered chronically, this effect is decreased; when it is removed, the adenylate cyclase activity is increased. The administration of morphine chronically to animals results in an increased phosphorylation of certain proteins that are in the nuclei of nerve cells (Sharma et al. 1975). These changes, as well as changes in adenylate cyclase, may produce long-term changes in the functioning of the brain. Animals which have been dependent and withdrawn can be made dependent again even after a single dose of narcotic. This dependence can be revealed by a dose of a narcotic antagonist which precipitates a moderately severe abstinence syndrome. Such observations are providing a basis for diagnosing protracted abstinence (Martin and Jasinski 1969). Patients are given a dose of morphine followed by a dose of an antagonist. If abstinence is precipitated the patient may be in protracted abstinence (Brase et al. 1976).

TREATMENT

The treatment of heroin and morphine dependence has evolved markedly over the last two decades. The introduction of methadone maintenance therapy and the demonstration that it decreased criminal behavior have encouraged other chemotherapeutic approaches (Martin 1977). Although methadone is a relatively long-acting drug, it is necessary for patients to take it daily lest they go into withdrawal. LAAM is a drug with pharmacologic properties similar to those of methadone except that its duration of action is much longer. It has been shown that it can be administered every other day or every third day without patients going into withdrawal (Jaffe et al. 1970). The effects of methadone and LAAM on animals and animal fetuses is being studied to understand the drugs' effects on fetuses of pregnant women in maintenance therapy.

The narcotic antagonist naltrexone has also been introduced into therapy (Martin et al. 1973). Naltrexone prevents the effects of opiates from becoming manifest by blocking their effects at the receptor level. This treatment modality has proved very efficacious in some patients, but relatively few addicts will accept it. More recently, buprenorphine, which has limited morphine-like activity and will block the effects of large doses of heroin, has been introduced experimentally into therapy. At this time, it appears that patients' acceptance of this drug is good (Jasinski et al. 1978). It is a safe drug, produces only a minimal degree of physical dependence, and appears to be promising for maintenance therapy.

SUMMARY

Research on narcotics and addiction has extended our concepts of the disease. New and safer analgesics have been developed, and it is anticipated that even safer ones with lower addiction liability will be forthcoming. As the population of the world becomes older, the need for analgesics will become greater because of degenerative and neoplastic diseases. The understanding of pain mechanisms that has stemmed from the development of the neurosciences may allow the development of entirely new therapeutic modalities for treatment of pain and suffering. Further understanding of the addiction process has provided a basis for developing new and innovative therapies. The finding that there are multiple opioid receptors and multiple opioid transmitter substances in the brain has been a major chapter in understanding pathophysiologic processes.

The work in addiction has had many important spin-offs. It is now known that certain pituitary hormones are under the control of opioid-like hormones and transmitters (Meites and Sonntag 1981). The opioid hormones definitely affect the nervous system, which regulates cardiovascular and respiratory function. The narcotic antagonist, naloxone, and its longer-acting sister drug, natrexone, can reverse neurogenic, hemorrhagic, and toxic shock, so may help severely brain-damaged patients, those who have lost large quantities of blood, or those who have severe infections to survive (Holaday and Faden 1981). Endogenous opioid peptides are also present in the intestine; certain types of constipation may be due to excessive quantities of these substances. These disorders can be treated with the narcotic antagonists, naloxone and naltrexone (Kreek et al. 1983). Recent evidence suggests that the narcotic antagonists may have an appetite inhibitory effect, permitting their use in the

treatment of obesity. Finally, it has been shown that some of the agonist-antagonist opioid analgesics interact with the receptor that causes a type of insanity (Watson et al. 1978; Emrich et al. 1979). This receptor may provide further insight into mental illness.

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BASIC RESEARCH ON ENDORPHINS AND ENKEPHALINS

INTRODUCTION

Basic research on drug abuse over the past 3 years has
focused on the endorphins, the large family of substances
made within the body that act like morphine, and on the cell
systems of the central and peripheral nervous system that
make, secrete and respond to these substances. When they
were first discovered, there was great enthusiasm for the
possibility that the existence of natural morphine-like
substances and the specific molecular recognition sites that
permit selected cells to recognize and respond to these
substances might permit far better insight into the mecha-
nisms responsible for addiction to opiate drugs, and the
possible individual biological differences in susceptibility
to addiction. Based on other biological hypotheses of
transmitter-based behavioral disorders (Snyder 1982; Bloom
1982), the imposition of experimental opiate addiction might
be expected to affect or be affected by concentrations of
the natural endorphins, or the number of cellular sites
capable of responding to opiate drugs. No such simple
relationships were discerned under a wide variety of test
cases (Bloom 1983).

Thus, research strategies have recently adopted a more
fundamental approach, searching for important molecular
differences among endogenous substances that exhibit
morphine-like actions, on their unique sites of cellular
production and release, and on the mechanisms by which each
of these substances can influence the cell types that
recognize them. Given such information, the changes that
occur during experimental addiction may be more readily
revealed, and examination of the possible unique biological
factors predisposing certain individuals to opiate addiction
may again be feasible.

A little background may help place the recent advances and
approaches in this field in perspective. Three major types

of basic research have greatly accelerated progress pertinent to drug abuse considerations. Primary among these advances are highly refined methods of circuit tracing, which permit better understanding of the general organization of the brain. Circuit tracing provides a means to determine which neuronal systems are crucial to exhibition of drug-abuse phenomena, e.g., opiate dependence, tolerance, withdrawal, and reinforcement behaviors. These neuronal systems may then be related to the cellular systems of the nervous system which use one of the endorphins as a communicating molecular messenger (Bloom 1983; Cuello 1982).

A second advance in basic research has developed highly sensitive chemical methods, using molecular genetics, immunology, and synthetic and analytical chemistry to reveal differences between endorphin molecules (Bloom 1983). These methods permit rapid preparation of large amounts of newly recognized natural molecules, as well as their chemical analogs, for tests as improved versions of the natural materials (termed agonists), or as drugs that prevent cells from responding to the natural materials (termed antagonists). These methods have clarified, very rapidly, the relationships between the many different endorphin molecules, and have led to several important molecular questions: which of the many potential natural endorphin agonists are normally used by specific nerve cells to communicate neuronal messages? Can this system of chemical production be altered by natural regulatory processes? Can such processes provide insight into drug abuse phenomena?

Finally, very sensitive methods of characterizing the response sites and response mechanisms of cells that recognize one or more of the many natural agonists have been developed (Paterson et al. 1982; North 1979; Nicoll et al. 1980; Siggins and Zieglgansberger 1981). These methods permit discrimination of the functions of the different natural agonists and determination of their relevance to opiate dependence and susceptibility. They also may suggest therapies with which to interrupt the addictive process. Although many aspects of the field contain controversial scientific questions, the rate of progress is encouraging.

ENDORPHINS

The term "endorphin" (for endogenous morphine) includes all those substances produced by animal cells (largely nerve cells and certain glandular cells) that exhibit morphine-like actions. Such actions generally include the ability to

depress excitability of certain isolated smooth-muscle systems (such as the muscles of the intestine or genital tracts) or to compete with morphine-like drugs for binding to specific opiate recognition sites in brain membranes (the "receptor displacement" assays). The actions of the endorphins are prevented by the same drugs that selectively antagonize morphine, such as naloxone or naltrexone. When endorphins are adminstered chronically into the nervous system, animals generally exhibit tolerance to the morphine-like actions, and may show withdrawal signs when challenged with an antagonist drug. When animals are addicted to morphine, they will accept the natural endorphins as substitutes for intravenous self-administration (Khazan et al. in press). Thus, endorphins would appear to be the natural chemical substances that account for the existence of receptors for the cellular actions of morphine drugs, because these same receptors were already able to respond to one or another of the natural endorphins.

All known animal endorphins are peptides, that is, chains of linked amino acids whose sequences include a specific 5-amino-acid segment (tyrosine-glycine-glycine-phenylalanine in the first four positions, and either methionine or leucine in the fifth position. This pair of 5-amino-acid sequences were the first endorphins purified from brain extracts for their ability to prevent contraction of genital smooth muscle strips, and were given the names Met[5] and Leu[5] enkephalin by their discoverers (Hughes et al. 1975). Current biochemical parlance refers to the structural similarities among the several different endorphin molecules as a structural "family" (see table 1).

In general, the final peptide product secreted by a nerve or gland is made from a much larger precursor propeptide, from which the active product is cut by special enzymes. If the larger form is also biologically active without further cutting it may be considered as an independent agonist. Frequently the potential cleavage sites within a propeptide are pairs of basic amino acids (arginine or lysine). Intrinsic peptide cleaving enzymes or peptidases can both destroy active species and generate them from inactive precursors (Schwartz et al. 1978; Hersh et al. 1980; Fricker and Snyder in press). Molecular genetic methods now make it possible to determine more directly the sequence of the relevant endorphin propeptides from specific endorphin-producing cells.

However, the mere existence of these peptides cannot accurately specify which segments of the propeptide are "the" active ones. In fact, many of the endorphin propeptides appear to be capable of generating several potential active products which frequently show varying degrees of potency.

The recognition of so many potential endorphin molecules indicates that there are at least three major branches of the super-family endorphin: (1) the pro-opiomelanocortin (POMC) family (Nakanishi et al. 1979; Roberts and Herbert 1977; Roberts et al. 1979); (2) the proenkephalin family (Gubler et al. 1982; Noda et al. 1982; Comb et al. 1982); and (3) the prodynorphin family (Goldstein et al. 1981; Kangawa et al. 1981; Nakao et al. in press).

The major endorphin agonist derived from POMC is beta endorphin; the brain's content of beta endorphin arises exclusively from a single cluster of brain neurons (Zakarian and Smyth 1982; Rossier and Bloom 1982).

The second branch of the endorphin family centers on the "original" enkephalins (Goldstein 1976; Simon and Hiller 1978; Terenius 1978; Beaumont and Hughes 1979). The precursor of this series, the proenkephalin (Gubler et al. 1982; Noda et al. 1982; Comb et al. 1982) contains a 6:1 ratio of Met^5-enkephalin to Leu^5-enkephalin, separated by other cleavage-sensitive sequences. This enkephalin prohormone is independent of the POMC and other branches of the endorphin family tree (Zakarian and Smyth 1982; Rossier and Bloom 1982; Hokfelt et al. 1980; Bloom and McGinty 1981).

The third branch of the family, prodynorphin, consists of the C-terminally extended Leu^5-enkephalin peptides, dynorphin (Goldstein et al. 1981; Tachibana et al. 1982), alpha neoendorphin (Kangawa et al. 1981; Weber et al. 1981, 1982), and beta neoendorphin (Minamino et al. 1981) all of which contain a N-terminal Leu^5-enkephalin sequence followed by further C-terminal sequence extensions of different lengths. All three are potent agonists in bioassays without cleavage to the Leu^5-enkephalin pentapeptide. Mapping studies (Chavkin et al. 1982; Weber et al. 1982; Minamino et al. 1982) suggest that these longer Leu-enkephalins may coexist within certain central nervous system (CNS) circuits originally thought to contain classical enkephalins (Bloom and McGinty 1981; Sar et al. 1978; McGinty et al. 1982b; Gall et al. 1981). The prodynorphin-derived natural agonists also share effects at a similar class of opiate receptors (Chavkin et al. 1982; Wuster et al. 1981; Bloom 1983).

This impressive array of natural substances, all sharing some properties of opiate agonists, makes it difficult to recall that the idea of an endogenous morphine-like factor was once considered rank speculation. There may be still more substances not yet well characterized.

MORPHOLOGICAL DISTINCTIONS BETWEEN PRO-OPIOMELANCORTIN AND PROENKEPHALIN NEURONS

The neurons containing beta endorphin and enkephalin have distinct morphological features which may be of functional significance. Enkephalin immunoreactive (IR) cells are, in general, small short axon cells with fine axons, groups of which are widespread throughout the nervous system. POMC neurons comprise a single relatively homogeneous larger cell type, with one elongated series of periventricular targets (Bloom 1983). Thus, it seems reasonable to include the POMC neuronal system as a component of the more general endocrine peptidergic network in the periventricular hypothalamus (Bloom and McGinty 1981). The neuroanatomy and hetero-geneous morphology of enkephalin neurons suggest that enkephalin may mediate synaptic events of significance to many diverse areas and functions of the nervous system.

DISTRIBUTION OF PRODYNORPHIN PEPTIDES

Although much less is known about the detailed anatomical locations of these peptides, it appears they are independent of the POMC or proenkephalin neurons, by content and immuno-histochemical mapping (Watson et al. 1981; Weber et al. 1981; Goldstein and Ghazarossian 1980; Watson et al. 1982). The prodynorphin neurons may coexist, in cells of the magno-cellular hypothalamic nuclei, and may also coexist with the vasopressin-IR neurons (Watson et al. 1982). They may parallel a separate enkephalin-IR projection (Rossier et al. 1979; Vanderhaegen et al. in press). The intrahippocampal mossy fiber pathway shows dynorphin and alpha neoendorphin-IR (Weber et al. 1982; McGinty et al. 1982a,b), which are visualizable directly; this may explain the conflicts in previous reports of enkephalin-IR elements of the rat hippo-campus (Sar et al. 1978, McGinty et al. 1982a). The generally weak enkephalin-IR of cerebral cortex (McGinty et al. 1982b), like that of hippocampus (Sar et al. 1978; McGinty et al. 1982a; Gall et al. 1981), may be interpreted retrospectively as cross-reactivity with dynorphin-containing cells. Thus, the independent but overlapping existence of enkephalin circuits and dynorphin-alpha neoendorphin circuits in spinal cord, hypothalamus,

hippocampus, and presumably other regions will continue to be a source of confusion until some means are found to examine the functions of these systems separately.

RECEPTOR MAPS AND CIRCUIT MAPS

Several methods are now available for discrimination of the several classes of opiate receptors, those molecular recognition sites at which opiate alkaloids or opioid peptides combine with intact tissue preparations to initiate a biological response (Chang and Cuatrecasas, 1981). In addition to the physiological responses of isolated organs, receptor subgroups have been characterized by whole animal behaviors such as the chronic spinal-transected dog preparation employed by Martin (1981) and by discriminative behavioral responses of experimental animals (Zukin and Zukin 1981). In addition, electrophysiological actions have been employed in vivo and in vitro (Bloom 1983). The most recent thrusts in this field have emphasized the localization of binding sites in slide-mounted brain sections, combining sensitive chemical detection with a much higher degree of structural resolution (Goodman et al. 1980; Herkenham and Pert 1980; Lewis et al. 1981).

These approaches fully support the concept that there are multiple opiate receptor subtypes, of which some (the mu, kappa, and delta sites) can be assessed by both functional responses and binding assays. However, the present structural evidence obtained on receptor distributions does reveal patterns that directly correlate the anatomy of the specific branches of endorphin peptides with one or another receptor type. There may be reasons for such discrepancies. The lack of precise matching between ligand binding and peptide circuits may indicate that other relevant peptide circuits are still to be identified. Alternatively, neurons may manifest opiate receptors more diffusely on their cell surface rather than on just the synaptic regions at which they are contacted by fibers of one or another opioid peptide system. Such noninnervated receptors might permit responses to systemically administered drugs but have no direct function in terms of the endogenous peptide circuits.

The best concordance between receptor subclasses and opioid peptide systems has come from the work on prodynorphin-derived peptides. Goldstein and Chavkin (Chavkin et al. 1982) and others (Oka et al. 1982; Wuster et al. 1981) have demonstrated convincingly that this peptide appears to act primarily as a kappa agonist, both centrally and in the

guinea pig ileum preparation. Alpha neoendorphin (Oka et al. 1982; Wuster et al. 1981) and so-called dynorphin B (Morre et al. in press; Corbett et al. in press) may have similar selective actions. If these findings exclude the kappa sites from receptors for beta endorphin or the cleavage products of the proenkephalin series (which would include Met[5]-enkephalin, Leu[5]-enkephalin, and the Met enkephalin arg[6]-phe[7]) then these two peptide groups might be considered to share the mu and delta sites. Target cells bearing coexisting receptor subclasses may be difficult to detect in vivo in the absence of selective antagonists. However, the use of selective synthetic agonists, with ligand-displacing properties that are selective among the subclasses of receptors, may discriminate the cellular responses associated with these receptors (Chang and Cuatrecasas 1981; Williams and Zieglgansberger 1981; Egan and North 1981) and related to the specific neural circuitry from which the peptide agonists must be released.

CONCLUSIONS

The initial interest in endorphins was motivated by their presumed relationship to opiate analgesia (Goldstein 1976; Simon and Hiller 1978; Terenius 1978; Beaumont and Hughes 1979; Snyder and Childers 1979; Watkins and Mayer 1982) and hence to opiate addiction. While there has been some recent success in defining the nature of the receptor adaptation that occurs during the development of opiate tolerance (Maurer et al. in press; Nishimura and Pasternak in press; Chang et al. in press; Lenoir et al. in press; Maneckjee et al. in press) this remains an open issue in need of methods that can dissociate the phenomena of molecular and cellular tolerance from those of the whole behaving animal. Behavioral tolerance has not yet been associated with a change in either ligand binding, endogenous peptide content, or processing.

Efforts to develop therapeutic agents that could modify endorphin function have focused on synthetic peptide agonists with potency as analgesics (Beaumont and Hughes 1979; Snyder and Childers 1979; Watkins and Mayer 1982; Chang and Cuatrecasas 1981) and inhibitors of the enzymes that break down the active agonist forms (Schwartz et al. 1978), thus improving the analgesic potency of the substances released endogenously. There is some indication that novel species of enkephalinases may be amenable to selective antagonism (Schwartz et al. 1978; Hersh et al. 1980; Fricker and Snyder in press).

An important open issue is whether plasma-borne endorphins are functional in terms of opiate receptor actions. Either blood-borne endorphins do or do not enter the CNS (Bloom 1983). If they do, then a large number of potential CNS phenomena are open to mischievous manipulations of peripheral (i.e., hormonal) endorphin fluctuations. If they do not, as the body of available evidence indicates, then blood-borne peptides must act at peripheral receptors. As indicated above, this could occur either through direct peripheral actions (Knepel et al. 1982) or through actions on parts of the CNS which are not guarded by the blood/brain barrier.

At the present time, the field of basic research on drug abuse is one of the most exciting and intensely followed fields of biological research. Fundamental questions can now be framed to permit direct testing of biological mechanisms of drug addiction and dependence: how many endorphins are there, which ones are the ones released physiologically (Chavkin et al. in press); which ones act naturally to suppress pain, and which ones, acting at which brain sites, may account for the addictive actions of morphine-related drugs? If neither the content nor the specific endorphins nor their absolute number of receptors is changed by continuous exposure to opiate drugs (Chang et al. in press; Lenoir et al. in press) as occurs during addiction, could the functional changes lie in more subtle aspects of receptor mechanisms, such as the as yet unclear steps by which the occupied receptor is coupled to other membrane molecules to initiate cellular actions (Wuster et al. in press; Parenti et al. in press). Awareness of the broad distribution of endorphin-containing nerve circuits has led to the employment of the opiate-antagonist drug naloxone as an important adjunct in the treatment of hemorrhagic shock (Holaday and D'Amato in press). Thus endorphin research may well be expected to contribute important insights into other biomedical questions as well as insights relevant to drug abuse.

TABLE I. Peptides of the super-family endorphin

I.   Peptides of the Pro-Opiomelanocortin Series

    A. Opioid Peptides

        β-endorphin   YGGFMTSEKSQTPLVTLFKNAIIKNAH (KKGQ)
        α-endorphin   YGGFMTSEKSQTPLVT
        γ-endorphin   YGGFMTSEKSQTPLVTL

    B. Non-Opioids

        γMSH   ...SYSMEHFRWGKPV
        βMSH   DSGPYKMEHFRWGSPPRD
        γMSH_3 .... YVMGHFRWDRPGRRNGSSSSGVGGAAQ

II.   Enkephalins

    Met^5-enkephalin   YGGFM
    Leu^5-enkephalin   YGGFL
    Met^5-Arg^6-Phe^7 Enkephalin   YGGFMRF

III. C-terminally Extended Enkephalins

    Dynorphin   YGGFLRRIRPKLKWDNQ
    αneo endorphin   YGGFLRKYPK
    β-neo endorphin YGGFLRKYP

Each letter stands as the symbol for a single amino acid
(Bloom 1983).

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