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The International Challenge of Drug Abuse

Editor:

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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The International Challenge of Drug Abuse

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FOREWORD

All over the world, people use drugs outside of medical supervision; this has been true throughout the ages. Such drug use is as unchanging as human physiology and the desire to "feel good." It is as diverse as a ten-year-old street boy sniffing toluene in Mexico City, college students drinking beer or smoking "pot" in Chicago, a young woman "mainlining" heroin in Paris, or an octogenarian smoking his bamboo opium pipe in Burma's Naga Hills. Which drugs and what circumstances of use will be legally and socially acceptable varies widely in different times and places. In the United States, for example, use of caffeine, alcohol, and tobacco is so familiar that it is difficult to think of them as drugs at all.

Often, however, drug use becomes drug abuse in terms of its serious adverse consequences for the individual, such as family disruption, and for the society, as in increases of narcotics-related crime. When this happens, government agencies concerned with public health and safety intervene to try to limit the abuses. Each country directs its limited resources to what are perceived as its own problems of highest priority, seeking to reduce both the supply and demand for drugs.

Not only is the abuse of drugs a global problem and a serious one, it is also growing. This can be understood as the result of such worldwide developments as increased mobility of people and goods, rapid communication of news, greater numbers of young persons concentrated in large cities which provide profitable drug markets, and a general weakening of traditional social controls.

Governments at all levels are recognizing the urgency of their drug abuse problems. More and more there is an awareness that these problems are interrelated. In the demand reduction area, there is increasing recognition of the need to share knowledge about drugs and their effects and about methods of treatment and prevention of drug abuse. These combined efforts will improve the effectiveness and coordination of actions to combat drug problems within each country, between nations, and through international organizations.

An important opportunity for interchange of knowledge about drug abuse took place at the VI World Congress of Psychiatry,

which met in Honolulu, Hawaii, from August 28 to September 3, 1977, bringing together some 4000 psychiatrists. In recognition of the present importance and even greater potential role of psychiatrists in understanding and dealing with demand reduction aspects of drug abuse, a Drug Dependence Section was developed which sponsored a plenary session and several symposia at the Congress. This monograph is comprised of the papers presented at those meetings.

While the United States, Canada, and Western Europe had the largest attendance at the Congress, about one-fourth of those present represented countries of Asia, Africa, and South America. Individuals with major responsibilities in health organizations in their countries and representatives from the United Nations and World Health Organization came together to share their knowledge and their problems in sessions dealing with:

- Drug abuse and actions to deal with it by various countries, the UN, and WHO
- Psychobiology of drug abuse and affective disorders, and mechanisms common to both
- Research on the biological bases of drug abuse
- Treatment of drug abuse, including an overview and detailed reviews on narcotic antagonist therapy and long-acting methadone.

This collection of papers will share the facts and the highly varied perspectives they present with a larger group of professionals around the world who work with various aspects of drug abuse demand reduction. It is offered in the hope that in some small measure it will further our progress and help us better coordinate our efforts to deal with the myriad of problems known collectively as "drug abuse."

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The International Challenge of Drug Abuse

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Chairmen

CHAPTER 1

International Challenge of Drug Abuse: A Perspective From the United States

Robert L. DuPont, M. D.

It is a great pleasure for me to welcome you to this important meeting. With the leadership of my cochairman, Dr. Ling, and the outstanding presentations by members of this panel, we are coming to the end of a unique week-long panoramic view of drug abuse as a key issue in modern psychiatry. The panel members have reflected the global dimensions of this serious, growing problem. We owe all of them our sincere thanks.

Some of the most valuable experiences I have had in the four years since I joined the United States Government's drug abuse program have been my travels to many of the countries represented at this Congress. These travels, plus the many international visitors to the National Institute on Drug Abuse in Washington, have convinced me that our responses to drug abuse problems can bring us together to share our knowledge and thus build new bridges between countries and cultures.

Psychiatry with its unique blend of scientific medicine, understanding of human behavior, and compassion for the human condition must play a central role in helping our nations cope with the vexing problems of drug abuse. Throughout the world, I have been privileged to work with psychiatrists who have assumed leadership roles in the drug abuse field. Our profession has much to be proud of, but far more remains to be done.

In my presentation today, I will briefly summarize the U.S. drug scene and highlight some of the common themes which have emerged from the preceding presentations. Based on these presentations and current experience from the United States, we can learn several lessons.

THE DRUG ABUSE SITUATION IN THE UNITED STATES AND OUR RESPONSE TO IT

A major national response to drug abuse, involving all segments of our population, has occurred in the United States during the last six or seven years. Since about 1970, drug abuse has been an important item on our national agenda. One important manifestation of this national experience is demonstrated by our new President. When Jimmy Carter became Governor of Georgia in 1971, one of the first problems in which he took a personal interest was drug abuse. While he was Governor, a system of drug abuse clinics was established throughout the State of Georgia, not only in the capital city of Atlanta, but also in the smaller communities. Mr. Carter created a national model for statewide drug abuse services. In 1971 and in subsequent years, he has spent time visiting drug abuse programs all over the country, talking personally to drug abuse workers and to drug abusers. We now have a U. S. President who is involved in our efforts.

Drug abuse is not only a political issue to Mr. Carter, it is a very personal issue and one about which he is personally knowledgeable. His special advisor on human needs, including drug abuse, is Dr. Peter Bourne who was the psychiatrist who started the Carter drug abuse program in Georgia in 1971. Peter Boume was one of the first persons to grasp the important international dimensions of the drug abuse problem outside the traditional law enforcement area. Peter is close to the President, and he is now placed directly within the White House. We can definitely count on a dedicated, high-level, and continuing commitment to drug abuse prevention from the U.S. Government.

As an expression of our current national response to drug abuse, today there are about 250,000 people receiving drug treatment in over 3,000 clinics and drug abuse programs in the United States. These treatment centers, which employ over 30,000 fulltime workers, are found not only on the coasts and big cities, but throughout the country. Physicians make up 600 of the total drug abuse workers. Paraprofessional counselors, numbering nearly 11,000, are the core staff members of these modern clinics. Nearly 40 percent of this large drug abuse treatment capacity is funded by the Federal Government. State, local, and private sources provide the remainder of the support for these programs.

Approximately 65 percent of the patients admitted to federally funded drug abuse treatment programs in the United States are treaded for heroin addiction. After heroin, the most often reported

drug problems at admission are marihuana, barbiturates, and amphetamines. Smaller percentages of U.S. patients report problems with cocaine, LSD, PCP, and volatile solvents.

Overall, about 30 percent of the U.S. treatment programs use methadone as part of their treatment for heroin addicts. Looking specifically at the persons treated for heroin abuse, we find slightly more than half receiving methadone as part of their treatment. I want to say an additional word about this because it is a controversial area.

In the United States, methadone is one part of a comprehensive response to heroin addiction; this treatment must also involve counseling and other supportive services. Methadone, which has no role in the treatment of drug problems other than opiate addiction, is desirable as a substitute drug because it can be taken orally and lasts for the whole day. Heroin, by contrast, has to be taken intravenously four or five times a day. The individual who is taking methadone can lead a relatively normal life with far fewer drug administrations, and these by the oral route in a treatment context, in contrast to his experience with heroin which is almost always taken intravenously by the U. S. addicts. I hope that those of you who have not yet seen a patient who is using methadone will visit a good methadone clinic. It is a striking experience to see how normal these patients appear. People who have never had this experience have a hard time believing that they are talking with someone who is taking a narcotic medication, when they first meet a methadone maintenance patient.

It should be emphasized that most opiate users prefer detoxification, with gradually decreasing doses of methadone, to longterm methadone maintenance. Outpatient methadone detoxification has proven to be particularly attractive to American heroin addict patients. Overall, about 33 percent of heroin addicts admitted to federally funded treatment receive detoxification, 27 percent receive maintenance, and the remainder, 40 percent, are treated in drug-free programs.

When considering the use of methadone, it should be emphasized that about two-thirds of all U.S. drug abuse treatment—for heroin and other drugs—is now drug-free; that is, no opiate is used as part of the treatment experience.

As we heard earlier this week, there are two promising new drugs for the treatment of heroin addiction. The first is LAAM, levo-alpha-acetylmethadol, an orally effective, synthetic opiate, which needs to be taken only three times a week. In the same way that methadone is better than heroin, so LAAM is better than

methadone: it lets the patient lead a more normal, less drug-centered life. Perhaps I should also add that we see no practical reason to use heroin as part of our U. S. treatment system, because heroin is not effective by the oral route and its short duration of action requires frequent administration and makes stabilization difficult to achieve.

The other new drug now being used successfully is naltrexone. It is a safe and powerful, orally effective, narcotic antagonist.

Although both LAAM and naltrexone remain in research status, we in the United States are optimistic that they will soon become part of our anti-heroin effort. But, once again, neither should detract from the important role of drug-free treatment.

Marihuana, like methadone, is a controversial issue. You will hear it said that the United States is moving to legalize marihuana. This statement is a distortion of reality. We in the United States are trying to get the marihuana user and the person who has small amounts of the drug for personal use out of prisons and out of the criminal justice system, and to get the suppliers of drugs into the prisons. The proposal that President Carter has made, and which I strongly support, is the introduction of a fine or non-criminal citation for marihuana possession offenses, instead of a prison sentence. That is known as decriminalization. Prison sentences remain and will remain for all marihuana traffickers in the United States. There will be no legal supply of marihuana, except for approved research studies.

OVERVIEW OF DRUG ABUSE: AN INTERNATIONAL PROBLEM

The United States is different from much of the rest of the world in that our heroin problem appears to have stabilized now after a decade of growth. Use of barbiturates and LSD has fallen slightly in recent years, but the use of marihuana and cocaine continues to rise in the United States. Other areas of the world are now seeing the same trends in heroin abuse that were evident in the United States some time ago: an increase in heroin use with heroin becoming the principal opiate of abuse, as well as the major source of drug-related health and social problems. In Europe and Southeast Asia, increases in heroin use appear to be particularly serious. Further, there is a global concentration of heroin use in metropolitan areas and, to a lesser extent, a spread of abuse into some rural areas.

Treatment approaches to heroin addiction also have spread throughout the world. Methadone is used widely around the world,

although—as in the United States—most countries do not rely on it as the sole treatment approach. Outpatient and residential therapeutic community programs are now found in all parts of the world. Although there are some communities in the world which still do not have substantial heroin problems, they are becoming fewer and fewer. There is increasing evidence all over the world of growing problems with heroin addiction and other drug problems.

Many wonder why this is happening. The answer is so simple it almost eludes us. Most drugs with psychoactive properties are what psychiatrists and psychologists call reinforcing substances, They are chemicals which, when taken into the body, produce feelings that the user enjoys. It is as simple as that. The effects of drug abuse on our countries and our communities are partly determined by the biological action of the chemicals we call "drugs." This biological effect does not depend upon one's age, sex, race, culture, or national origin. This means that no person and no country is immune from drug abuse. Drug abuse is not a unique characteristic of any particular segment of society, any particular geographic region, or any particular nation. It is a global human problem. Certainly demographic, geographic, political, and social factors do influence the levels of drug abuse throughout the world. However, it is important to recognize that none of these factors eliminates drug abuse problems and that epidemic spread of drug abuse is no longer infrequent, even in areas once thought to be safe from drug abuse. In fact, far more needs to be learned about how those complex social and economic factors do, and do not, influence drug use patterns.

In the past, the use of psychoactive drugs tended to be contained in isolated geographic and cultural islands with social controls on those who used them, how much they were used, when they were used, and what was done with people who used too much. Elaborately built-up cultural restraints on specific drug-taking behaviors can be identified in countries all over the world. Good examples of this are the traditional chewing of coca leaf in the Andes region of South America, the traditional use of cannabis in India and Mexico, and opium smoking in Iran or Laos. But, today, these cultural constraints which characterized most cultures of the world are dramatically breaking down.

The leading edge of this change has been the use of cannabis in much of the world. The global levels of cannabis consumption are truly remarkable. Heroin use, and other psychotropic drug use, has shown a similar growth in many parts of the world. One of the most fascinating questions is: What happened that suddenly brought

about a change in cannabis and other drug use in the last decade? Most of these drugs have been around for a millenium, but suddenly use has spread across the world in a dramatic fashion. How did this happen? Why now?

WORLD SOCIAL CHANGES RELATED TO DRUG ABUSE

Some of the reasons for this global epidemic can be fairly easily identified. Increased travel has brought us much more in contact with each other. International travel is no longer only for the privileged individual or the isolated sailor. Today, large numbers of our populations are in contact with each other. This contact brings tremendous benefits, but it also brings a contagion of behavior that helps explain how drug abuse can spread rapidly over global areas. Obviously, the increased travel has involved the traffickers too. They now have the ability to move quickly large amounts of drugs long distances.

Increased global communications have made a big impact in recent years. An event reported in a newspaper in one part of the world will be seen, experienced, and thought about by people all over the world. Drug use and drug trafficking have been big news during the last decade all over the world.

Some of the hallmarks of the modem world are increased individual responsibility, decreased traditional cultural constraints, and increased flexibility of behavior. These global cultural trends bring many benefits, but they also create serious problems. One example of this complex phenomenon comes from agriculture. Many parts of the world produce low levels of food partly because of the persistence of traditional, less effective, agricultural practices. Many governments try to change these practices so that the farmers will adopt new and more efficient techniques. But the same cultural barriers that have kept people from adopting new farming techniques have kept people from adopting new social behaviors such as drug taking. And the same relaxation of these barriers that produces a good effect in one area produces a negative effect in another. It is often the younger, better educated farmer who first adopts newer techniques, just as it is often the younger, better educated people who first adopt new drug-using behaviors. I do not suggest this as criticism of any lifestyle, but merely to point out that these conflicts between traditional practices and modem life affect all of us in complex ways.

Another important global social change relates to our attitudes toward tobacco and alcohol. One of the effects of our heightened awareness of drug abuse is the recognition by many of us that alcohol and tobacco are drugs. Most of us were oblivious to the effects of these substances in our own lives and in our cultures until the drug abuse epidemic of the last decade. Today you will find in the United States a widespread recognition of the fact that alcohol and tobacco are drugs and have all the characteristics—the reinforcing properties and the negative health consequences—that we associate with illegal drugs. The difference is that these common and generally accepted drugs have already gone through the extensive process of diffusion throughout most societies. We have become accustomed to paying a staggering social price for the privilege of individual choice in the use of alcohol and tobacco. In the United States, we pay about $35 billion a year for alcohol-related health problems. All of our illegal drugs together cost us about $10 billion a year in the United States in terms of health and social costs.

One consequence of this pervasive spread of tobacco, alcohol, and other commonly used drugs is that the practice of drug taking is already deeply ingrained throughout the world. With the wide availability and acceptance of these psychotropic drugs, it is but a short step to the use of other new drugs, especially by young and relatively affluent persons.

Drug abuse is not a fad. It will simply not go away, any more than alcohol and tobacco use will simply go away. Drug abuse is a characteristic of our lives and, judging from the social changes occurring throughout the world, it is going to remain a very serious problem. In addition to increased travel, faster communications, conflicting traditional and modern values, and the wide acceptance of alcohol and tobacco, important changes in the composition of our population have taken place in the last decade. These changes relate directly to drug-using patterns. A dramatic increase in the size of the youthful population took place in the United States in the decade of the 1960's. The so-called baby boom following the Second World War produced, 20 years later, a sudden upsurge in the size of the adolescent population most vulnerable to drug abuse. Given the other conditions outlined above, the change in the size and nature of our population fostered drug abuse. While other factors involved should not be minimized, the age-related changes in our population were also necessary for the drug abuse epidemic.

Similar demographic conditions now exist in many other countries. Reductions in infant mortality during the last decades

have increased the number of young people in the vulnerable age range in many countries, particularly in developing nations. Perhaps of even greater concern in many nations is the massive migration of youth to cities, producing a greater concentration of young people in urban areas, even in those nations where overall age patterns have not changed substantially. Such an increase of often underemployed youth in cities raises a nation's vulnerability to drug abuse. Many drugs are readily available in most, if not all, regions of the world. The widespread existence of heroin user groups; the decrease in traditional cultural restraints on adopting new—and often deviant—behaviors; increased affluence, travel, and communication; and the tremendous increase in the capacity of the global illegal heroin and other drug supply systems—all these factors bode ill for many nations.

LESSONS LEARNED IN THE UNITED STATES

In our attempts to meet the drug abuse challenge, there are several lessons we have learned in the United States. The first is that the complete elimination of drug abuse is not a realistic objective. The drug abuse problem has been with us a long time. In our modern society, it is unlikely that the drug problem is going to go away no matter how effective our approaches may be. The public is eager to be told that we will solve the problem—that it will go away. I suggest to you that this is not a realistic objective. On the other hand, the drug abuse problem can be limited; we can achieve realistic and important objectives, but elimination of the drug problem is not, candidly speaking, one of these. In the United States, recognition of this fact has encouraged us to place priorities on our programs and to focus on achievable objectives in the drug abuse prevention field.

The second lesson is the importance of balancing supply reduction with demand reduction strategies, and of balancing national and international efforts. At the same time that societies are attempting to limit the availability of abusable substances, it is also important to provide treatment, rehabilitation, and prevention services to help drug users. In the United States, about 60 percent of our national drug abuse expenditures are for demand reduction or health-related activities, and about 40 percent of our resources are now going to supply reduction or law enforcement efforts.

While treatment is provided, efforts to reduce access to illicit substances must continue to be supported. Some restraint, consis-

tent with each nation's values, has to be exercised in terms of what techniques are used to limit the access of the population to drugs. In other words, we do not want to use techniques of reducing access to drugs which produce more harm than the drugs themselves. Effective techniques that reduce illicit drug supply through law enforcement and pharmaceutical control are nevertheless necessary in all countries.

Just as efforts at reducing supply and demand should be balanced, it is essential that national and cooperative international programs be balanced as well. It is tempting to resort to a national protectionism, a feeling that one has to seal one's borders and keep out drugs from other countries. However, there is simply too much legitimate and economically necessary movement across national boundaries for this approach to work. But if we work together, we can produce realistic international strategies that will reduce the supplies of illicit drugs. We need a sense of balance and a sense of partnership. Both supply and demand reduction activities are essential. In addition, a sense of balance and partnership of national and international activities should be one of our main drug abuse prevention goals.

A *third* lesson concerns treatment. In the United States, only 1 percent of our national drug abuse treatment capacity is in hospital or institutional programs. We have learned the importance of outpatient programs in treating drug abusers and the very limited usefulness of hospital institutions for this purpose. This lesson is consistent with treatment outcome research for most illnesses, ranging from pneumonia to schizophrenia.

A *fourth* lesson, and this might be the most controversial of all, is that general service programs, including integrated health care approaches, do not, in general, respond to the unique needs of drug abusers. We have not had good experience putting drug abusers into general clinics, hoping that they would get their drug problems dealt with. Medical problems related to the drug use may be taken care of in a general health facility, but beyond this there seems to be a need for a critical focus of attention around the drug problem itself for programs to be effective. This can happen in a clinic or a mental health program, but most often it does not. There needs to be a specific focus on the drug-using behavior in order to get a therapeutic benefit. Of course, specific drug abuse programs do successfully operate as discrete parts of general health or mental health centers. This approach often achieves the benefits of both specific and general programs. But it has been our experience that

these benefits can be realized only when there is a specific focus on drug abuse in the general health program.

The *fifth* lesson we have learned is the necessity of a firm knowledge base in the drug abuse field. The assessment of drug abuse in a country is the first step in drug abuse prevention. Most countries have suffered by not having an accurate definition of their problems and by not knowing who is using which drugs, how much is being used, what the effects are, and what the trends are over time. There are now some very good techniques for drug abuse assessment.

A second example of the necessity of a knowledge base is the development of new therapeutic tools for drug abuse treatment. At the National Institute on Drug Abuse, we support both basic and applied research to clarify the nature of the biochemical interactions between opiate receptors in the brain and opiate drugs. Out of this work on the opiate receptors has come the discovery of endorphins, which are endogenous morphine-like substances in the normal mammalian brain. Endorphins appear to be peptides which mimic at least some of the actions of opiates. It is not clear at this time whether these substances are genuine transmitters in brain pathways, or whether they are degradation products of more powerful analgesic peptides. Biochemists in the United States and abroad are searching for enzymes that may be involved in the synthesis and deactivation of these peptides for clues to understand the biological roles they play in addiction, pain, and other physiological and pathological processes. The intensive research now under way is extremely important as it seeks to clarify how these substances are involved in the addictive process. Through these studies, new treatment modalities or more effective prevention strategies may be developed. We should not overlook the possibility that endorphins may be involved in more general processes that control normal behavior and influence mental health. Studies in the biochemistry of drug abuse are now in the forefront of scientific research and may increase our basic understanding of human behavior. The latest developments in this exciting area are summarized in one of the presentations of our Drug Dependence Section of the World Psychiatric Association.

The last example of the necessity of increasing our knowledge base is in the field of prevention. Both common sense and research findings on human behavior support the position that negative factors, such as boredom, feelings of failure, and lack of self-worth and community involvement, increase the probability of the occurrence of a variety of personally and socially destructive

behaviors. If drugs are available and if their use is valued by peers, these negative factors may lead to harmful drug or alcohol use. To prevent this, we support programs that reinforce positive behavior, that provide constructive alternatives to drug taking, and that intervene early in the process with minimal treatment to reduce the number of persons who will later require costly treatment and rehabilitation.

We must also be realistic in our prevention goals. Today about two-tenths of 1 percent of the U.S. population is addicted to heroin. Thus one could say, quite correctly, that 99.8 percent of the population of the United States has been prevented from becoming heroin addicts! Nevertheless, we consider 500,000 heroin addicts, costing the Nation over $6 billion a year, to be a serious social and public health problem. Stated this way, it becomes clearer why it is so difficult to develop effective prevention strategies, since the vulnerable population is such a small part of the total. With nearly 15 million current marihuana users in the United States, the prevention target is a bit larger if not more easily hit.

We at NIDA also support the development of the Resource Book on Demand Reduction by the Division of Narcotic Drugs of the United Nations. This practical guide to prevention, treatment, and assessment will assist all of us in carrying out better programs.

The major need in the drug abuse prevention area in the United States today is for additional evaluation studies directed at measuring the impact of programs to reduce harmful drug use. Available evidence indicates that the new prevention approaches, including effective education and parent-oriented and peer-oriented strategies, yield more positive results than the old approach of simply providing information about drugs or of using factually unsound scare tactics. We think effective approaches using peers and parents and programs which concentrate specifically on the most vulnerable youth are promising prevention measures worthy of rigorous evaluation.

The presentations we have heard today indicate that drug abuse is now endemic throughout the world, and that periodic epidemics superimposed on this large and enduring problem are to be expected. None of us individually, or even collectively, can solve all of the problems related to drug abuse; we can, however, honestly face them.

No area of the world, no social, religious, or political process will completely immunize our countries against drug abuse. With a search for new knowledge and a willingness to learn from each other, as we have done at this Conference, we have a unique

opportunity to contribute to the welfare of our fellow human beings. By working together and by collaborating with our colleagues in the United Nations and the World Health Organization, we can do a much better job in the future.

In conclusion, I want to thank especially my colleagues who have shared this panel with me today, and the others who did such an outstanding job in the earlier sessions of our Section, for their fine contributions.

Thank you.

CHAPTER 2

The Drug Abuse Scene in Nigeria

Tolani Asuni, M.D.

INTRODUCTION

It has often been stated that a number of communities in the world use drugs to enhance the spirit of such occasions as social gatherings, religious ceremonies, and the like. In some communities individuals may use certain drugs regularly for various nonmedical reasons. It has been observed in Nigeria that alcohol was used mainly on ceremonial occasions and also during traditional religious rituals. In the northern part of Nigeria, Kola nuts, which contain much caffein, are chewed regularly, much more so than in the southern part of the country, where they are mainly grown.* Tobacco is smoked in clay pipes by some older men and women. There is also a practice, mainly in some parts of the South, in which shredded tobacco leaves are kept in the middle of the tongue all the time and only taken out when the user wants to drink water, eat, or sleep. A similar practice is the keeping of a small ball of tobacco leaves or chewed Kola nuts in one cheek, again taken out only when the user wants to eat or sleep.

In the South, especially among the Yoruba people, Kola nuts are used as a symbol of peace and harmony on occasions of betrothal, settling a quarrel, important visitations, etc. They are also used by those who want to keep awake at night, like students and those who have to keep vigil.

The above brief account of traditional nonmedical drug use in Nigeria provides a basis for contrast with current use patterns.

*In the north, *Cola nitida* is the most commonly used of the various types of Kola nuts.

DRUGS OF ABUSE IDENTIFIED

In the last two to three decades, new drugs have been introduced for nonmedical purposes and used side by side with the more traditional ones mentioned above.

The use of alcohol has become more widespread and extended to nontraditional alcoholic beverages. There are now more than six breweries in Nigeria and more are expected. The demand so far outstrips the domestic supply that nearly 100 million Naira worth of beer was imported in one year. (A Naira is approximately $1.50 USA.) Distilled alcoholic beverages are also bottled in the country.

In the past most people drank local alcoholic beverages, which were sometimes distilled illegally, but the government has now legalised the distillation of local alcoholic beverages in approved situations. With affluence most people are now drinking bottled beer brewed locally or imported, as well as spirits.

With this enormous use of alcohol, and with little or no control of its sale, it is to be expected that a large number will become dependent on it. Asuni (10) reviewed the number of patients with psychiatric problems involving alcohol admitted to the Neuro-psychiatric Hospital, Aro, Abeokuta, Nigeria, between 1964 and 1973. The number was not indicative of the size of the problem in the country, for several reasons. Alcohol abuse and dependence are still hardly regarded as a psychiatric problem, and there is no recognised agency available for dealing with the problem of alcohol dependence except some traditional healers. Psychiatric service in the country is still very meagre and unevenly distributed. Even if the problem of alcohol dependence is regarded as a psychiatric problem, there are not enough treatment facilities available.

In Asuni's (10) study of 60 cases, he also included other drugs that were used in combination with alcohol: cannabis in 11 cases, pethidine in one case, and amphetamine in one case.

Amphetamine and its Derivatives

In the past students took Kola nuts to stay awake at night to study. Many still do, but some use amphetamine tablets, especially before and during examinations. The fact that users get dependent on amphetamines is not striking; rather it is the psychotic breakdown some of them have that makes the situation disturbing. Amphetamine psychosis has been well documented (Connell 14).

It has been observed by Oshodi (20) (personal communication) and confirmed by others that in the northern parts of Nigeria labourers take amphetamines. They are taken by the handful to enable them to do sustained hard work. It is also suspected that their employers provide these tablets in order to get the maximum work output from them. Some Moslems also take the tablets to Saudi Arabia on Pilgrimage both to use and to sell. The government of Nigeria has taken steps to stop the importation of amphetamines into the country.

In Ahmed and Akindele's (2) report, amphetamines figured prominently among the drugs of abuse seen in a University Teaching Hospital in Kaduna, Northern Nigeria.

Phenoharbitone

It has become common knowledge that phenobarbitone is an hypnotic, and it has been readily available at chemists' shops. From time to time one sees cases of dependence on phenobarbitone. It is suspected that in view of the ready availability of these drugs, many people are dependent on them but they have not been brought to the notice of psychiatrists, and their physicians may not even be aware that they have become dependent on the drugs.

Mandrax

Mandrax is a hypnotic which when taken with cola drinks gave a "high" experience. It was abused by older school children. It has since been withdrawn from the market and there is no evidence that it is being smuggled into the country.

LSD

Anumonye (7) mentioned 2 cases of the use of LSD in his study. LSD is not a common drug of dependence and it is certainly not readily available in the country.

Pethidine (Meperidine)

This is perhaps the most significant drug of dependence in Nigeria; significant because of the type of people who get involved.

They are usually highly trained people such as physicians, pharmacists, and nurses in a country which is short of such highly trained manpower. Akindele (4) reported twenty-two cases of teaching hospital personnel treated or followed up personally by him. Of these, twenty were males and two females. Ten were physicians and twelve were nurses. All the physicians used pethidine either alone or in combination with other drugs. The twelve nurses were on pethidine alone. These findings are in keeping with the observation of some other psychiatrists working in psychiatric hospitals.

An interesting observation by the author is that those dependent on pethidine who died, died as a result of what looked like tetanus. It is questionable whether it was real tetanus or a toxic effect of pethidine or of withdrawal. The reason for the doubt is that those involved are persons of relatively high status who lived in environments in which their needles were unlikely to be contaminated by tetanus bacillus. It would have been acceptable as tetanus if it occurred only in one case, but for it to occur in 3 cases raises doubt. This observation has not, to my knowledge, been confirmed by others. It is worth further investigation.

Unlike amphetamines and barbiturates which are not necessarily introduced to the user by a doctor's prescription, pethidine is usually initially prescribed by a physician, and then the user tries to get it without a prescription. To this extent, physicians are somewhat to blame for the initial introduction which later leads to dependence.

Some of those dependent on pethidine start with the tablets and later graduate to intramuscular injection of the drug. It is now under very strict control by the Federal Government.

Heroin

Heroin is practically unknown in Nigeria as a drug of dependence. In Akindele's (4) series, one doctor who was psychotic had used morphine, pethidine, heroin, and barbiturates. It is not known, however, if he was dependent on heroin or if he only used it on a few occasions. A male patient who had lived in Britain for many years and who used Cannabis told me that he had used heroin in Nigeria and that he got it in a famous market in Onitsha. The truth of this could not be ascertained, but he was not addicted to heroin when seen.

Morphine

Morphine is also practically unknown in Nigeria as a drug of dependence.

Cannabis

Cannabis is the most common drug of dependence used in Nigeria. Since Asuni's (8) first paper in Nigeria focused on the subject of Cannabis in Nigeria, there have been a few others—Lambo (16), Boroffka (12), Ahmed, M., and Akindele, M.O. (2), Adelaja (l), Akindele (3), etc. It is significant that all are psychiatrists. The reason for this is partly the fact that the psychiatrists are most likely to observe the harmful effects of the use of Cannabis.

As easily as Cannabis can grow in Nigeria, there is very strong evidence that it is not native to Nigeria. Asuni (8) wrote:

> *Cannabis sativa* is not indigenous to Nigeria, and evidence indicates that it was introduced to the country, and most likely to other parts of West Africa, during and after the Second World War by soldiers returning from the Middle East, the Far East and North Africa and also by sailors. There is less reliable indication that it was first introduced to the country during the First World War, but it did not gain a foothold, nor did it spread afterwards. It grows profusely in this tropical climate with little or no care. Farms of the plant, scattered over Southern Nigeria, have been reported by the police.
>
> The only purpose for which it is grown in Nigeria is for smoking, since it is not used for fibre. It is neither chewed nor brewed. It is not used in the herbal concoctions of traditional healers or in home remedies, as confirmed by Oliver (19). . . .It is significant that in his exhaustive collection of useful plants of West Africa, Dalziel (15) does not mention Cannabis.

The picture of the use of Cannabis has changed in Nigeria over the years. For instance, whereas it was earlier reported that it was only smoked, Adelaja (1) found among his soldier psychiatric patients that it is also ingested with alcohol—beer, palm wine, home distilled gin; brewed as tea, and even chewed.

There are also more cases reported all over the country; this may well be a factor of the increased number of psychiatrists and also increased number of people at risk, e.g., the phenomenal rise in the number of soldiers in the country as a result of the Nigerian Civil War in 1967 to 1970. In addition to this apparent increase in Cannabis use, there is some evidence that there is a real increase.

For instance, Asuni (8) reported 16 cases of Cannabis use, out of 380 cases discharged from Yaba Mental Hospital in 1962. Anumonye (7) reported 116 out of 1,061 inpatients in the same hospital in 1970, an increase from 4.2 percent to 10.9 percent.

There is also some controversy about the relationships between psychosis and Cannabis use. Akindele (3) doubted if there was any causal relationship between Cannabis use and psychosis. Adelaja (1) from his study in Military Psychiatric Hospital concluded: ". . .acute toxic psychosis often reported may be acute excitement states reported among Africans or an onset of other major psychotic illness." Asuni (8) suggested a "schizophrenic propensity" in those who break down with psychosis after using Cannabis. Boroffka (12) however distinguishes between those who smoke Cannabis as a symptom of an incipient psychosis, by this action escalating the psychotic process, and those who develop a psychosis *ab nouo* in a previously well integrated personality, and whose psychosis does not clear up in a few days as it would have done if it were merely toxic. Paton (21) also notes that distinctions need to be made between effects due simply to Cannabis, exacerbation of a personality disorder, precipitation of psychosis, and exacerbation of preexisting psychosis. A preliminary EEG study by Asuni, Schoenberg, and Oluwole (11) suggests that there may be a relationship between the psychotic behaviour of some Cannabis users and epileptogenic phenomena; that the use of Cannabis normalises mildly abnormal EEGs in some and deranges normal EEGs in others, and it is this derangement that is manifested in psychotic behaviour. This observation is comparable with the different effect of coffee on different people, While many need coffee to keep them functioning for long hours, a few become disturbed, agitated, and restless. The disorganisation is of course more severe with Cannabis use.

TREATMENT

Treatment policy of drug dependence depends on social, economic, and scientific factors. The patient almost never comes for treatment on his own initiative. He is referred from his place of work because of a decline in work performance, deteriorating habits, carelessness, indifference, sluggishness, dopiness, etc., and the suspicion that he is on drugs. Often a condition for his remaining employed is that he undergo treatment. Since he usually has others such as his wife, parents, and older members of his

family financially and socially dependent on him, they often encourage his having treatment, which in some cases they have failed to persuade him to take. Sometimes relatives take the initiative to bring the patient for treatment. As in psychiatric treatment in general, relatives are actively involved in the treatment programme.

Of course the drug-dependent patient usually denies being "hooked" on drugs until he is presented with incontrovertible evidence, e.g., many injection scars on the usual injection sites, or unusual behaviour during the period when he is under the influence of the drug.

The patient may appear to have good motivation, but it is usually spurious. This motivation is, however, exploited to have the patient admitted into the hospital; treatment is unlikely to be successful on an outpatient basis except in those very rare situations in which the patient can be kept under twenty-four hour surveillance by those around him who have been educated about the problem.

The objective of treatment is not just detoxification, but continued abstinence. While the patient may be voluntarily admitted, this may be converted into an involuntary admission if he goes out to use the drug while in the hospital or even after discharge. The rationale for involuntary admission is that drug behaviour constitutes a danger to the patient himself and, by extension, to his family, of which he is an integral part. The laws of Nigeria relating to mental illness are out of date, and in any case are silent on this matter of voluntary or involuntary admission and do not give any guidance. The psychiatrists in charge of psychiatric hospitals with facilities for involuntary admission, however, adopt this rationale.

For economic and scientific reasons the "cold turkey" method of sudden withdrawal is practised. This is another reason for admission into hospital. The patient is given the appropriate drugs to alleviate withdrawal symptoms. During admission to the Neuropsychiatric Hospital, Aro, Abeokuta, he is given individual psychotherapy by the staff, mostly psychiatric nurses and psychiatrists; he is involved in group psychotherapy with other patients, as well as in family therapy.

While he is hospitalized, efforts are made to identify and unravel the patient's emotional, social and economic problems. If he has any basic psychiatric problems such as anxiety state or depression, these are treated. He is usually kept in the hospital for not less than six weeks after complete abstinence and then discharged to the surveillance of his relatives with some anxiolytic drugs.

In a developing country like Nigeria, drug substitution, such as methadone maintenance, is not advocated. The reason is that where drugs for treatment of life-threatening situations are not always readily available everywhere, where antimalaria drugs cannot be distributed freely, it is not rational to keep some people on maintenance medication for drug problems at government expense. The anxiolytic drugs prescribed do not provide the same subjective experience, and therefore cannot be regarded as substitutes. They are meant to allay anxiety and also to minimise the need for the drugs of dependence.

FOLLOWUP

It is unfortunate that it has not been possible to do any systematic followup of cases treated with the regime referred to above. There are indications that those who have been weaned from their drugs often relapse; yet they seldom come back to us. One of the causes of this is that physicians and nurses dependent on pethidine, for instance, have good incomes and have grown away from their extended families. Because of their persistent behaviour regarding drugs they have alienated themselves from their family of orientation and extended family who can exert some influence on them.

Those cases who have been brought to hospital with psychosis related to Cannabis tend to comply better. It is as if they are frightened by their psychotic experience, and the dependence on Cannabis, if it can be termed dependence, is not as compelling and overwhelming as with pethidine.

The Federal Government of Nigeria is proposing to set up drug dependence units all over the country. Perhaps if these units are established in such a way that patients will not have to travel very far from their homes to use their services, and if the units are well staffed with mobile personnel, it will be possible to follow up cases which use the services.

THE ROLE OF TRADITIONAL HEALERS IN THE TREATMENT OF DRUG DEPENDENCE

It can be argued that since the problem of drug dependence is a new phenomenon, the traditional healers may not be equipped to deal with it effectively. Yet it is necessary to mention their possible

role in view of the increasing advocacy for the incorporation and integration of traditional healing practices in Africa into the health delivery system.

The common explanation of maladaptive behaviour given by traditional healers is curse, evil machination of others, violation of taboos, heredity, etc. I have not heard of any effective treatment based on this explanation. On the other hand I have heard of effective treatment of alcoholism by some medicinal powder being put on incisions made under the lower lip of the patient. It has not been possible to confirm this. Even if it is true, one wonders how this can be applied to the treatment of dependence on drugs taken by injection and not orally. This whole area needs to be explored.

PREVENTION

In spite of the legitimate preoccupation of the Government of Nigeria with malnutrition, infectious and contagious diseases, etc., consideration is being given to problems of drug dependence. In 1966 very severe penalties were prescribed for traffic in and use of Cannabis. These have since been relaxed considerably, as the penalties were considered too severe. Recently a drug unit has been set up in the Federal Ministry of Health. The importation and sale of such drugs as Mandrax, amphetamine, and pethidine have been either stopped or restricted. The Inspectorate Unit of the Pharmacy Division of the Ministry is being strengthened to provide better, more vigilant control of the sale of dangerous drugs by pharmacists. Education of the public against the use of drugs is also being contemplated. A Unit has been established in the Pharmacy Division of the Federal Ministry of Health charged with the duty of controlling drugs of addiction and drug abuse generally. No action has been proposed to reduce the risk of alcoholism which is likely to increase with the vast increase in the importation and brewing of beer in Nigeria.

CONCLUSION

In conclusion it can be noted from the above brief account that drug dependence is not of the same magnitude in Nigeria as it is in some other countries. There is, however, evidence that it will increase with increasing affluence, disintegration of the family and other cultural systems which have had a supportive and restraining

influence on the individual. This is therefore the time to take rigorous steps to arrest the growth of drug dependence before it gets out of hand.

Before appropriate and rational steps can be taken, more studies need to be done to identify some of the causative factors. Some studies have already indicated the role of peer pressure (Akindele 5), parental deprivation and parental influence (Odejide and Sanda 17), as contributory to abuse of drugs.

A study of drug taking among secondary school students by Olatawura and Odejide (18) indicated among other findings the reasons the students take drugs. These include: to keep awake for as long as they wish; feeling at ease only after smoking Cannabis; Cannabis providing courage to talk to superiors; to facilitate reasoning; to facilitate enjoyment of social gatherings; and to feel happier when unhappy or fed up. Some of these reasons, if confirmed by further studies, will point to the examination of the school system and the study habits of the students with a view to minimising the need to take drugs to keep awake at night to study.

There is therefore a need for more studies of drug abuse and drug dependence in Nigeria, since the findings in one country cannot be directly applied to another, especially where there are important social, cultural, economic, and other differences. The warning given by the American Academy of Pediatrics Committee on Drugs (6) that there are reasons for using caution in relating much of the seemingly relevant information from developing nations to Western populations also applies the other way around.

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CHAPTER 3

The International Challenge of Drug Abuse: The Mexican Experience

Guido Belsasso, M.D.

INTRODUCTION

The extreme complexity of drug addiction and the implacable organization of drug traffic are today, more than ever, a challenge that demands solidary action from all the nations of the Earth. Few other issues are so revealing of the close interrelationship between countries and of the extent to which anything one of them achieves or fails to achieve has a bearing on the others.

This paper undertakes the task of briefly weighing past actions, analyzing the present situation, and predicting future trends in the Mexican struggle against drug addiction and drug traffic, in terms both of internal measures and international collaboration actions.

INTERNATIONAL COOPERATION

Participation in international meetings

Long before the problem reached large proportions internally, Mexico chose the path of active participation in those international forums which have stated the need for energetic action against the traffic in drugs of abuse, Mexico first took part in the 1912 The Hague Convention which established cooperation on narcotic control as a matter of International Law. Our country thereafter participated in the 1925, 1931 and 1936 Conferences held in Geneva.

On February 16, 1946, the United Nations Economic and Social Council adopted the resolution creating the Commission on Narcotics. Mexico was one of the fifteen countries that composed the Commission.

Subsequently, in Paris and New York City, the 1948 and 1953 Protocols respectively were agreed upon. In 1961 New York City was host to the Sole Convention, and in 1971 the Convention on Psychotropic Substances was signed in Vienna. Mexico has adhered to all these instruments of international control (4).

COOPERATION WITH THE UNITED STATES

Parallel to its participation in international forums, Mexico has reached bi-national cooperation agreements with other countries. Owing to geographical proximity, joint actions with the United States—dating back more than four decades—are outstanding.

Juan Barona-Lobato (l), a prominent scholar on the subject, has divided the history of cooperation between Mexico and the United States into several phases. Phase one began in 1930 with an exchange of diplomatic notes through which both governments reached an administrative agreement on mutual police aid to prosecute those involved in drug traffic.

Phase two started around 1959. At the proposal of the United States, where the number of drug addicts showed an alarming upward trend, a series of informal and friendly talks were held which tended to reinforce operations against international drug traffic. In 1960, the U. S. Government for the first time provided at low cost air and land equipment to be used in the search and destruction of *papaver somniferum* and *cannabis* plantations. Subsequently, in May 1969, Mexico City was host to a new series of meetings which resulted in a report stressing the need for cooperation between both countries. Three months later, however, on September 21, 1969, American authorities ordered, on a unilateral basis and without previous consultation, severe measures of inspection of people, luggage, and vehicles crossing the border and arriving at U.S. ports of entry, thus generating complaints and inconveniences. These measures of inspection, known as "Operation Intercept," impaired relations between the two countries and hindered daily transactions between border towns on both sides, which initiated a so-called "Operation Dignity," emphasizing greater respect for the individual.

Diplomatic relations between Mexico and the United States could have come to an end but for the swift negotiation Mexican and American commissioners at the highest level carried out in Washington, thanks to which the inefficient "Operation Intercept," launched with complete disregard for Mexico's dignity, was replaced by "Operation Cooperation." This decision was made public through the October 11, 1969, joint communique marking the beginning of phase three.

Several meetings of the task forces presided by the Assistant Attorneys General of Mexico and the United States were held during the third phase of cooperation. Their duty was to submit a report to the Attorneys General who, in turn, assembled to discuss recommendations and dictate measures for their implementation. Achievements within the framework of "Operation Cooperation" have been highly rewarding.

Yet, in spite of efforts by both countries leading to a decline in international drug traffic in 1972 and 1973, in the following years—1974 and 1975—the United States registered a substantial increase in confiscations of heroin produced from clandestine cultivations of poppy in Mexico, and of cocaine finding its way from South America through Mexico. Both drugs were designed to meet the demands of more than a half million U.S. cocaine and heroin addicts.

Under these circumstances, former President Gerald Ford asked the Domestic Council Drug Abuse Task Force to undertake a study to determine the extent of the problem and to offer recommendations. As a result, a report entitled *White Paper on Drug Abuse was* issued. On the basis of data included in the above-mentioned report, President Ford called an urgent meeting on December 22, 1975, to discuss the drug traffic problem, with special emphasis on the Mexican and Latin American situations.

In 1976, from January 6 through 18, Congressmen Lester L. Wolff and Benjamin A. Gilman, with the purpose of gathering information on international drug traffic, made a tour of Mexico, Costa Rica, Panama and Colombia, exchanging views with their respective Presidents and searching for adequate cooperation formulas.

It was around that time that the fourth phase of cooperation between Mexico and the United States against drug traffic and drug addiction began to develop. The outstanding feature of this phase is the high priority both governments have placed on such actions. It has certainly been a period of fruitful achievements during which vigorous pronouncements, exchange of friendly letters between

Presidents, and programs for collaboration have been followed by effective and determined action (1).

FIGHT AGAINST PRODUCTION

The past few years have been witness to activities carried out by Mexico which are virtually unprecedented in the history of the battle against drug addiction and drug traffic.

Deterrent efforts against the supply of drugs have been paramount, especially in view of Mexico's geographical, socioeconomic, and political characteristics, and the fact that the world's greatest consumer market lies just north of its border. Figures describing this effort are highly eloquent. Between 1970 and 1976, Mexico destroyed more than 65,000 poppy plantations and more than 46,000 marihuana plantings, nearly two tons of opium, more than 1,000 kilograms of heroin, 35 kilograms of morphine, more than 1,000 kilograms of cocaine, 800 kilograms of hashish, 534 liters of cannabis liquid extract, 412 kilograms of poppy seed, more than six tons of cannabis seed, and more than 92 million tablets containing psychotropic substances. In addition, more than 18,000 persons were arrested, of whom some 2,000 were foreign citizens. More than 30 underground laboratories were dismantled, and many drug traffic gangs were broken up (1).

FIGHT AGAINST CONSUMPTION

Epidemiology

But Mexico is not only a drug-exporting country. A number of complexly interrelated factors have accounted for an alarming increase in domestic consumption.

Estimates show that the problem is essentially an urban one. In rural areas, although one can find certain towns where drugs still are employed in religious rituals or simply as an element in the subculture of the group, drug abuse as such is not considered a problem that affects public health.

The majority of urban drug abusers range in age from 12 to 21 years. The younger set uses inhalants and solvents, while the older group usually uses marihuana. It seems certain that the use of barbiturates and amphetamines is on the increase. Barbiturates and

tranquilizers are preferred by young adults. At present there is a problem of hard drugs such as opium and its derivatives among a group along the northern border of the country, where an increase has been observed in the number of Mexicans taking heroin (2, 3).

The highest percentage of drug experimentation and use appears to be among preadolescent and adolescent males and young adult females. In general, however, lower-class youths tend to use industrial-type solvents, which are cheap and easily obtainable, while middle- and upper-class teenagers and young adults favor marihuana, barbiturates, and amphetamines (table 1).

Certain figures may give a more accurate image of the magnitude of drug abuse in Mexico. Use of psychotropic drugs and opium derivatives affects great numbers of people. In 1974, 87 percent of the population 14 years and older then living in Mexico City had

TABLE 1

General Characteristics of Drug Abuse in Mexico

Geography: Urban (Heroin abuse in northern border.)
Age: Mainly between 12 and 21 years
Adolescents: inhalants
Adolescents and young adults: marihuana
Young adults: barbiturates and tranquilizers
Sex: Mainly male
Social class:
Lower: inhalants
Middle and upper: marihuana, barbiturates, and amphetamines

TABLE 2

Percentage of Drug Users, 14 Years and Older, in the Federal District

Drug	*Percent of Population*
Psychotropic drugs and opium derivatives	87.00
Amphetamines	2.34
Barbiturates	4.20
Marihuana	1.31
Inhalants	0.40
Hallucinogens	0.31
Heroin	0.10

taken one or more of these drugs, and 35 percent were doing so on a customary basis, that is, every day for a minimal period of one week during at least six months (6). Obviously, medical prescriptions are responsible for a high proportion of these cases. Use of amphetamines through prescriptions thus accounts for 90 percent of all users, who, in turn, represent a total of 2.34 percent of the Federal District population. For its part, barbiturate abuse affects 4.20 percent of the capital's dwellers 14 years of age and older (table 2).

Regarding marihuana, the estimates are that in the Federal District alone 66,000 nonregular users can be found (4). After the above-mentioned drugs, marihuana is the most favored drug among the age group 14 and older, of which 1.31 percent have already tried it. Furthermore, eight out of every thousand individuals between 14 and 24 years of age—0.84 percent—use it on a regular, customary basis (6).

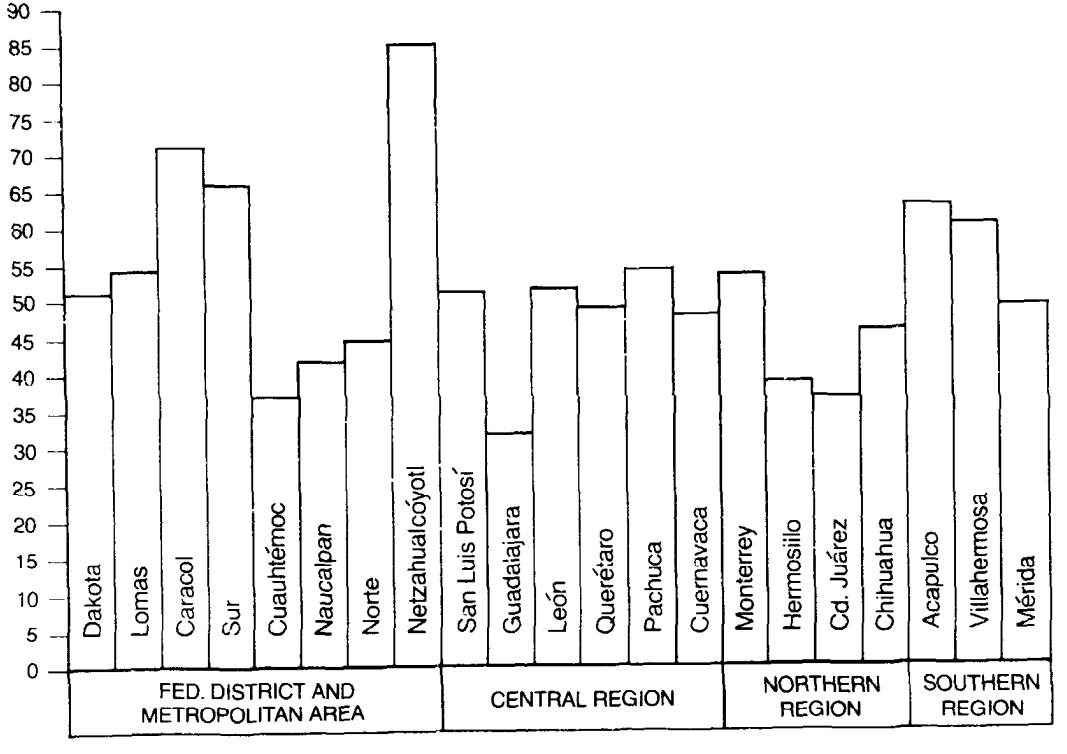
Inhalant abuse constitutes one of the worst problems of drug addiction in Mexico. It is estimated that 20,087 individuals representing 0.40 percent of the Federal District population 14 years and older, have used this kind of drug. Three of every thousand individuals between 14 and 24 years of age—0.31

percent—use it on a regular, customary basis (6). These figures, however, do not include two high-risk groups: the home-lacking population and the less-than-14 population, where inhalation is quite common. Indeed, the average starting age of inhalating patients at the Centers of Juvenile Integration—institutions which we will deal with shortly—was 14 years. Nevertheless, several community studies carried out in different areas of the Republic show that starting ages are much earlier, even 5 or 6 years (7). In fact, more than half of the patients treated at the Centers of Juvenile Integration—52 percent—come there because of substance inhalation problems (7). Figure 1 shows the annual incidence rate for each Center. It can be observed that the highest incidence rate is that of Ciudad Netzahualcóyotl, where 87 out of every 100 residents use inhaled substances. It is important to note that Ciudad Netzahualcóyoti is part of Mexico City's metropolitan area, and a majority of its population is composed of rural immigrants who are extremely marginal economically, socially, and culturally. Figure 2 shows the incidence curve representing the number of cases started in different years. An increase beginning in 1968 and continuing from 1970 through 1975 can be observed. One possible explanation for this may be the fact that these Centers of Juvenile Integration, only recently opened, are perhaps treating few cases which started before 1970. We must not dismiss the possibility, however, that a marked increase in the use of inhalants has actually taken place. The 1976 decline is explained by the fact that the diagram was done when only four months of that year had elapsed. This fact might suggest that in 1976 there was really an increase in use (7), although further epidemiological studies are required to give this phenomenon an accurate definition. It must be noted, however, that the growth rates of both inhalant and marihuana abuse, estimated from information obtained at the treatment centers, are far from encouraging: growth rates from 1970-1975 throughout the country are 40 percent for marihuana and 45 percent for inhalants (6).

Other relatively less used drugs are hallucinogens and heroin. Hallucinogens have been used by 0.31 percent of the capital's population 14 years and older, and heroin by 0.10 percent (table 2). It must be noted, however, that the latter figure refers to heroin use in the Federal District, whereas heroin abuse is alarmingly increasing in towns along the northern border of the country. Thus, 40 percent of the patients treated in 1973 at the Tijuana, Baja California, Center of Juvenile Integration used opium derivatives, and in 1974 there was a 5 percent increase. In Nogales, Sonora,

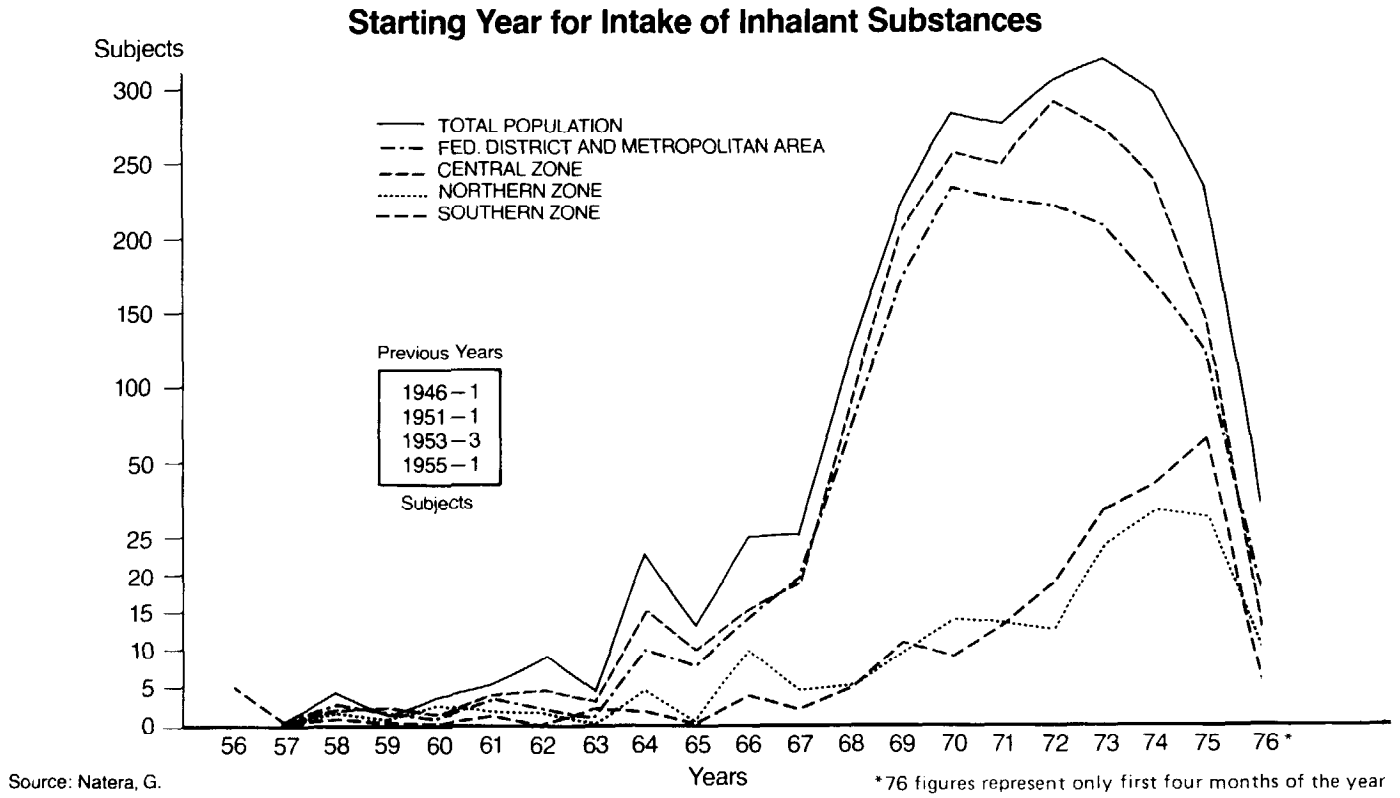
FIGURE 1

Substance Inhalation Incidence Rate for Each Treatment Center in the Mexican Republic 1976



Source: Natera, G.

FIGURE 2


Starting Year for Intake of Inhalant Substances
Subjects
300
250
200
150
100
50
25
20
15
10
5
0
TOTAL POPULATION
FED. DISTRICT AND METROPOLITAN AREA
CENTRAL ZONE
NORTHERN ZONE
SOUTHERN ZONE
Previous Years
1946–1
1951–1
1953–3
1955–1
Subjects
56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76*
Years
Source: Natera, G.
*76 figures represent only first four months of the year

incidence of heroin abuse was twice as great in 1973 as in 1972, and ten times greater than in 1971. Of the patients treated in 1975 and 1976 at the Nogales Center of Juvenile Integration, 75 percent were heroin addicts (6).

In view of this situation, it has been necessary to design an action strategy against drugs that is not limited to the repression of drug traffic but also contemplates, in an integral fashion, the prevention of drug addiction and the treatment and rehabilitation of affected individuals.

Creation of CEMEF

With the purpose of creating an organization to coordinate and promote different activities involved in the struggle against abused drugs, the Mexican Center for Drug Abuse Studies (CEMEF) was officially founded on August 4, 1972, by presidential instructions. In February 1975, it achieved legal status as a decentralized agency of the Federal Executive, with its own budget.

In accordance with its character as a coordinating and promoting organization, CEMEF has had a governing structure whose top authority is represented by the Board of Directors which, in turn, is presided over by the Secretary of Health and Welfare. The Secretaries of the Interior and Public Education, the Attorney General of the Republic, the Attorney General of the Federal District, and the Director General of the Center itself are also members of the Board.

CEMEF has carried out the following activities: biomedical and social research to determine the way in which the drug addict population is affected; evaluation of the incidence and prevalence of specific types of drug use and abuse; predicting the evolution of the problem; training of personnel in diagnosis, treatment, rehabilitation, and primary prevention; provision of research elements for those involved in the area, and technical advice for both public and private organizations on related aspects; publication of its research findings; and the conclusion of agreements with similar national and foreign institutions on matters within its province (5).

The government's solid commitment to the task of fighting drug addiction was internationally acknowledged when CEMEF was designated, in September 1976, as the World Health Organization's Regional Center for drug addiction research and higher instruction.

Centers of Juvenile Integration

The private sector and the community have played a major role in the struggle against consumption. Centers of Juvenile Integration created in March 1971 sprang from a pilot project initiated in 1970. The Centers have a tripartite structure which includes the federal government, the state governments, and the community. Currently there are 30 Centers throughout the Mexican Republic, which provide an infrastructure for treatment, rehabilitation and prevention work.

The Centers of Juvenile Integration are far-reaching institutions of high standing in the treatment and rehabilitation of drug abusers. Up to 1976, the total number of drug addicts treated at these Centers was 6,630 (7). Their staff includes psychiatrists, psychologists, social workers, psychiatric nurses, and volunteers. A wide range of treatment is provided at the Centers, including pharmacotherapy; individual, family and group therapy; occupational therapy; and recreational therapy. Some Centers run employment bureaus; one of them has a day center as well. In addition to secondary and tertiary prevention tasks, the Centers of Juvenile Integration perform community work leading to early case finding and implementation of primary prevention measures.

Other institutions for drug addiction treatment are currently in existence. Special emphasis must be placed upon the Community Mental Health Centers, whose primary purpose is to give both the family and the community the opportunity to learn to treat the patient. The Centers are not limited to illicit drug problems, but also deal with alcohol and other mental health problems. There are six Centers and two hospitals offering this kind of service in key locations throughout Mexico City. There is another in Veracruz, and the northern border will soon see the opening of still one more.

Mexico also benefits from a foster home program for children who inhale solvents. Under this program, ten adopted children are supplied with a home, food, schooling, and affection. The treatment pattern is behaviorally oriented, and the child is encouraged to abandon inhalation practices. The program has a year's duration, after which the child returns to its own home, if it had one, or is provided with one, with followup studies being done. This program is currently under experimentation at two Centers, one in Acapulco and the other in the Federal District.

On the other hand, a program against alcoholism involves the greater part of the rehabilitation budget. Under this program, an Alcoholic Rehabilitation Center provides a Federal District area

with psychiatric, detoxification, and control services benefitting approximately 300,000 residents. There are also aid centers for alcoholics and their relatives which are run by Alcoholics Anonymous. A program against alcoholism in the rural areas is currently under study.

Finally, one more effort in the struggle against drug addiction is embodied in a heroin addiction treatment program sponsored by the Ministry of Health and Welfare. Treatment is based on substitution of morphine for heroin, and it reaches approximately 40 people. This is an old program, now under evaluation. Methadone is not used in Mexico.

Mexico's experience in fighting drug-related problems has therefore covered all fronts of action, with the participation of wide sectors of society.

PRESENT POLICIES

With tile change of federal administration in December 1976, certain structural modifications have been made which seem logical in an ever-changing social and political environment. While it is still too early to attempt an evaluation, at least four well-defined policies can be singled out:

1. *The campaign against drug traffic continues.* The Attorney General of the Republic's Office and the Ministry of National Defense are multiplying their efforts to reduce drug production as well as domestic and international drug traffic.

2. *Small consumers are granted ammesty.* CEMEF has favored this measure in the past. Only recently, however, have solid steps been taken to treat individuals who obtain drugs for personal use as sick people rather than as criminals. This is encouraging, since it reveals a shift of emphasis from repression to prevention, treatment, and rehabilitation, even if repressive action is still taken against those who deserve it: drug traffic profiteers rather than consumers.

3. *Official support for Juvenile Integration Centers is maintained.* Another encouraging sign of the new policies is the fact that both state and federal governments—the latter through CEMEF—have maintained their support of the private sector participating in the struggle against drug addiction. This is indicative of a continued eagerness to have the national community join in this all-important task.

4. *A change in the political visibility of drug-combatting programs has been brought about.* This fact reveals an historical

trend which is not solely Mexican. When drug consumption became a serious public health problem, because it was a relatively recent problem towards which public opinion was not yet fully sensitized, it was necessary to create an organization with a high degree of political visibility, which would have its own budget and a wide margin of action. This explains CEMEF's birth as a decentralized agency. Once the initial—and most difficult—steps have been taken to face this complex problem and to create public awareness, programs against drug addiction have been able to find their place among general public health actions. This principle has been implemented in practice through the new regime's administrative reform, by virture of which decentralized agencies are integrated under a sector head represented by the corresponding ministry. Thus CEMEF has been integrated into the general mental health programs of the health sector. This need had already been considered in the formulation of the National Health Plan in 1974. The struggle against drug addiction is included in the Plan as a subprogram within the National Mental Health Program. Now this formulation has been carried into practice.

The time is past when it was politically necessary to emphasize CEMEF's actions; they have now been brought to their actual level as part of a more general project contemplating integral improvement of mental health. CEMEF therefore no longer handles its budget in an autonomous fashion, but follows instead the guidelines of the health sector head: The Ministry of Health and Welfare. There is nothing new in such a change. Other countries have experienced similar changes. In the United States, for example, the shift has been from a special agency reporting directly to the President to the wider-reaching Alcohol, Drug Abuse, and Mental Health Administration.

FUTURE TRENDS

Integral Strategy

Once the historical vision and an analysis of present policies have been put forth, it becomes necessary to expound the short term and long term trends that are likely to develop within the context of drug addiction in Mexico.

Firstly, the problem will almost certainly increase, at least in terms of absolute figures, as a function of population growth.

Secondly, a drug supply-combatting approach alone is unlikely to be successful. This has been found to be true in other countries as well as in Mexico. The time in which such an emphasis predominated is fortunately past. It is clear today that it is illegal demand for drugs that encourages supply and not the opposite, as was long believed. Supply and demand are dialectically interrelated factors, the reduction of the latter requiring a concomitant struggle against the former. The need for an integral strategy is therefore evident. While such a stretegy may be difficult to implement during an initial state, it is certainly the only one that will yield positive long-range results.

Education and Employment

Two elements of increasing relevance to youth can be distinguished in the complex of factors that determine drug addiction: the lack of educational opportunities and unemployment.

Estimates are that only 1,800,000 Mexicans between 14 and 25 years of age attend some type of school, while another 12 million have completed their studies, cannot pursue them, or have never attended a school. Furthermore, only 9.4 percent of those between 20 and 24 years of age have access to higher education (8).

Unemployment among young people is coming to represent a source of social conflict in many nations of the world. In Mexico, 17 percent of total unemployment occurs among the young. This is one of the major challenges the present administration has to face—the generation of more than 600,000 jobs or spiraling unemployment figures.

These two factors are closely linked with increased drug addiction amongst the young. Great effort must be made in the near future to improve educational and employment opportunities for the young, while simultaneously slowing down population growth and raising the general standards of living.

The answer to the complexity of drug addiction must be the implementation of an integral strategy that contemplates education and employment as first-line preventive measures, while pursuing treatment and rehabilitation programs, intensifying the struggle against drug traffic, and promoting international cooperation as an act of solidarity and respect among all the peoples of the world. Then, and only then, shall we be facing the challenge of drug abuse.

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CHAPTER 4

WHO's Programme in Drug Dependence With Special Emphasis on Developing Countries

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I. WHO'S RESPONSIBILITIES

The World Health Organization's programmes are dictated by resolutions of the World Health Assembly, its governing body, which meets once a year, usually in Geneva. All of its 150 Member States are invited to this meeting. WHO's responsibilities in the field of drug abuse and dependence, according to the numerous resolutions of the World Health Assembly and the international drug control treaties are:

(i) to collaborate with countries in planning, managing, and evaluating programmes concerned with the identification and magnitude of the problem, prevention of drug dependence, treatment and rehabilitation of those affected;

(ii) to collaborate with countries in the training of health, social welfare, education, and other professionals involved in the management of drug dependence;

(iii) to stimulate, coordinate, and promote research required for more effective programmes;

(iv) to recommend to the United Nations Commission on Narcotic Drugs whether a substance should be controlled nationally or internationaliy and the level of such control, based on the benefit and risk ratio;

(v) to give advice in the planning and implementation of drug dependence programmes sponsored by UN agencies and other intergovernmental and nongovernmental organizations.

The following is a description of the three different types of activities within the Division of Mental Health relating to WHO's obligations on the subject.

II. COUNTRY, REGIONAL, AND INTER-REGIONAL PROGRAMS

A major emphasis of current work is on the development of effective treatment programmes in developing countries, using operational research to optimize the use of resources. The objectives of these programmes are to develop, at national and local levels, flexible and dynamic management systems that will assist in the prevention and reduction of nonmedical use of drugs. The approach involves (1) the training of key personnel through fellowships; (2) epidemiological surveys in rural and urban target communities; and (3) the introduction and systematic evaluation of treatment programmes. In addition to the development of more realistic and effective treatment approaches, these activities are expected to contribute to knowledge about the aetiology and nature of drug dependence problems.

It is essential that planning and implementing of programmes at the national level be based on existing public health services, taking into consideration existing social services. By utilizing personnel with various types of training, treatment and rehabilitation programmes can be integrated into the basic health services. Priority is now being given to developing countries with serious drug problems where manpower and financial resources are limited. In such settings it appears unwise to develop specialized institutions for drug-dependent persons.

The treatment of drug dependence in such settings may require the use of medical assistants, primary health care workers, recovered addicts, and others to take up specific responsibilities with the support of physicians.

To select from and adapt the experience of other countries is a cardinal principle for the development of these programmes. There is also a need to develop more than one model so that alternative approaches may be developed to meet the needs for the specific drug abuse problems in each country.

A. Thailand

The first WHO/UN pilot treatment programme was implemented in Thailand in 1974. Initial effort emphasized the strengthening of existing services in Bangkok and the development of a hospital-based treatment service in Chiang Mai, near the opium-producing regions. During 1975, 1976, and 1977, the operational research component of the programme was emphasized. This is being achieved by assigning the in-country programme coordinating role to the Health Research Institute, Chulalongkorn University, Bangkok, and by strengthening the Institute's existing data management and laboratory facilities. This programme has thus been structured to (1) develop information on the extent and nature of drug addiction in Thailand; (2) identify through evaluation studies, effective low cost treatment and health delivery methods; and (3) develop data and experience to assist the government in planning and application of improved programmes throughout the country.

Community-based treatment services in Bangkok provide facilities for treatment evaluation studies and for intensive case-finding, monitoring, and intervention projects in high drug use target communities. In similar fashion, primary health care and drug dependence treatment services are being introduced in opium-using villages of the hill tribe region in conjunction with before-and-after case-finding surveys to determine the impact of the programmes on drug use. The initial village survey was carried out in October 1976.

Data collection and intervention programmes are underway in six villages, and dependent persons from the hill tribe area are being treated in the Chiang Mai Hospital.

Discussions have taken place with various existing treatment programmes in Bangkok to undertake programme evaluations, and planning has begun on establishing a treatment centre in slum areas. Preliminary work has been completed on the treatment evaluation of Wat Tham Krobak Temple treatment centre.

B. Burma

In May 1976, the Socialist Republic of the Union of Burma, the UN Division of Narcotic Drugs, and the UN Fund for Drug Abuse Control signed a five-year agreement to implement the UN/Burma Programme for Drug Abuse Control. This is a multi-sectorial programme involving agriculture, education, law enforcement, health, and social welfare components.

The major drug problem in Burma is opium dependence, much of this in the rural areas, particularly in provinces where the opium poppy is cultivated. With the strengthening of international drug enforcement activities, heroin laboratories have appeared in opium-producing countries, including Burma. This has resulted in the spread of heroin use in the major cities of Burma.

Early in 1977, the plan for implementation of the health sector was reviewed, and a work plan for the first two years was drawn up. During this period ambulatory and inpatient treatment services will be expanded and improved in Rangoon, Mandalay, and Taunggyi. The intent is to develop a flexible set of treatment facilities that will permit the testing and evaluation of different treatment approaches. An epidemiological data base will be developed through a compulsory registration system, and field surveys of "at risk" populations are planned to assist in determining the magnitude and nature of the drug dependence problem and in evaluating the impact of intervention programmes.

In addition, laboratory facilities will be expanded, and group and inservice training programmes for medical and paramedical staff will be developed.

C. Pakistan

An agreement has been reached with the Pakistan Narcotics Control Board for the implementation of a pilot treatment programme in urban and rural regions of Pakistan. The epidemiological component of this programme was initiated in 1976 with the visit of a WHO consultant who worked with country experts to carry out a one day prevalence count of visitors to all licensed opium shops in two cities. A second WHO consultant visited Pakistan in early 1977 to finalize the work plan for implementing treatment research programmes in four cities and in opium-using villages of the North West Frontier Province. Training activities have already begun, and establishment of the treatment centres will begin immediately after approval of the project some time this summer.

D. Iran

This project is carried out in collaboration with the Iranian Ministry of Health and Social Welfare; the United States Alcohol,

Drug Abuse, and Mental Health Administration; and the International Committee Against Mental Illness; and it receives financial support from the United Nations Fund for Drug Abuse Control (UNFDAC). It is a treatment evaluation study comparing the outcome of four groups of opium-dependent persons (50 in each group) receiving either (1) methadone, (2) mutabon—an antidepressant, (3) placebo, or (4) no placebo. In mid-1976 one hundred completed records (with 87 percent followup of admitted patients) were analyzed; it is hoped that final data collection on 200 patients will be completed by the end of 1977. A preliminary analysis of the data suggests (1) approximately 70 percent of patients did not relapse nine months after discharge, regardless of treatment category; (2) level of emotional depression during the followup period appears to be associated with relapse and with employment status, regardless of treatment category; and (3) patients who maintain contact with treatment staff tended not to relapse, while those who departed from treatment did tend to relapse. Data analysis and final interpretation will be carried out during 1978.

Other projects in Afghanistan, Egypt, and Vietnam, are at various stages of the planning process.

E. Studies of the Long Term Effects of Cannabis Use

The objectives of this multi-phased study which began in 1972 are to determine the physical, mental, and social effects of the long term use of cannabis and its preparations. These are retrospective and partially prospective studies comparing groups of long term cannabis users with matched controls. Investigations have been carried out in Chandigarh, Varanasi, Lucknow, and Lahore. These studies have assessed the incidence of bronchopulmonary and cardiovascular diseases, and chromosomal abnormalities, as well as dysfunctional behaviour and deficits in cognitive and other skills.

F. Seminar on Drug Dependence in Central America, Mexico and Panama

A seminar on drug dependence for countries in the region of Central America was held in November 1976. The objective was to improve knowledge of health professionals of this region about the prevention, epidemiology, causes, and treatment of drug abuse.

G. Working Group on Early Intervention Programmes in Drug Abuse

In December 1976, the WHO Regional Office for the Western Pacific convened a Working Group of participants from the region to work out strategies for tackling the problem of drug abuse. Emphasis was placed on the development of appropriate epidemiological instruments and practical programmes of action.

H. National Organizations

Further progress has been achieved in establishing WHO Collaborating Centres for Research and Training in Drug Dependence. The Centro Mexicano de Estudios en Farmacodependencia, Mexico, and the Addiction Research Foundation, Toronto, have been officially designated as WHO Collaborating Centres, and other institutes will be designated shortly.

III. EPIDEMIOLOGY AND TREATMENT EVALUATION RESEARCH

A WHO project concerning Research and Reporting on the Epidemiology of Drug Dependence became operational in February 1975 and is financed by the UNFDAC. The objective of the project is to strengthen the planning of effective prevention and control programmes through the international collection and exchange of data on the epidemiology of drug dependence.

The framework for implementing this project includes an annual meeting of collaborating investigators and consultants to review progress, priorities, and future plans. Data collecting activities are carried out by a network of collaborating institutions, the majority in developing countries with serious drug dependence problems. WHO staff and consultants coordinate and facilitate the work by designing instruments and methods and by assuming responsibility for cross-national analysis of data generated.

The initial activities have been organized around four study areas. The *first* involves the testing of an epidemiological case reporting form for collecting "minimum essential" data on drug users in contact with treatment and other institutions. The form is being tested on drug users in each of seven countries: Burma, Canada, Indonesia, Malaysia, Mexico, Pakistan, and Thailand. The results

will be reviewed by collaborating investigators in October 1977. The objective of the *second* study is to develop a general methodology for evaluation of drug dependence treatment. The instruments and methods will be tested in evaluation studies of treatment programmes in these same seven countries.

The *third* study involves the testing of self-administered drug use survey instruments on students in nine countries (India, Nigeria, and the United States of America, in addition to the majority of countries previously identified). It is hoped that agreement can be obtained by collaborating investigators on the essential data items and methods to be made available for international application. The use of these instruments will permit comparisons of data in this important area of epidemiological research.

The *fourth* study involves the pilot testing of previously developed WHO Guidelines for reporting available information on nonmedical drug use. Investigators responsible for this study at the Institute of Psychiatry in London have now selected experts to review a wide range of types and sources of epidemiological data. It is expected that a monograph will be produced to guide planners in other countries to recognize and use the types of epidemiological data that are either already existing or that can be generated.

In addition to the data and methodology being generated in these studies, the Research and Reporting project provides a collaborative mechanism for permitting investigators from developed and developing countries to work together, to learn from one another, and to share in the development of a common technology.

IV. INTERNATIONAL DRUG CONTROL TREATIES

Nations have responded to the need to take collective action against drugs which are liable to abuse. The first effort was that of the Shanghai Conference, in 1909. This was followed by The Hague Convention, in 1917. These efforts were aimed at the control of opium, morphine, heroin, and cocaine. After the Second World War, an additional need was recognized for the control of synthesized drugs which were being abused. The 1948 Protocol of Lake Success (New York), created a mechanism whereby the new products as designated by WHO automatically came under international control, and thus the role of WHO was established in evaluating drugs for international control.

The Single Convention on Narcotic Drugs of 1961 simplified and unified the earlier treaties and continued to assign to WHO the role

of evaluating drugs and making recommendations to the UN Commission on Narcotic Drugs, a 30-member body elected by the Economic and Social Council. This Convention continued to control drugs obtained principally from plant material, i.e., opium, cannabis, and coca leaves, as well as morphine-type synthetic drugs.

The increasing availability in recent years of a large number of synthetic psychotropic substances led to their widespread abuse in many parts of the world. Concern about this problem led to the Vienna Conference of 1971 which discussed international control of psychotropic substances. After ratification by 40 countries, the Convention on Psychotropic Substances came into force on 16 August 1976. This Convention requires WHO to recommend to the UN Commission on Narcotic Drugs whether and how a psychotropic substance is to be controlled nationally and internationally. The recommendations of WHO are determinative as far as medical and scientific evidence is concerned. The UN Commission on Narcotic Drugs has final authority in approving the scheduling of individual drugs, taking into account the WHO recommendations and economic, social, legal, and administrative factors.

Under the 1971 Convention on Psychotropic Substances, 32 substances were placed under four schedules. Schedule I contains generally hallucinogens, subjected to strict control measures, stricter than narcotics and substances in Schedule II (generally amphetamines and similar stimulants), Schedule III (generally shorter acting barbiturates and similar CNS depressants), and Schedule IV (generally longer-acting barbiturates and similar CNS depressants and minor tranquillizers), which are successively less strictly controlled. The basis for recommending control of psychotropic substances is their dependence liability, abuse potential, and actual abuse on the one hand, and their therapeutic usefulness on the other.

The testing and evaluation of drugs in general and psychotropic substances in particular is complex technical work and requires considerable expertise. Nevertheless, the Convention provides a mechanism for the international community to decide as early as possible whether a substance creates a drug abuse problem, so that remedial steps can be taken. As synthetic pharmaceutical products are increasingly available in all parts of the world, this drug control mechanism offers equal benefit to the developing and developed countries. Universal ratification of this Convention is essential for an effective combined effort on the part of the world community to use psychotropic drugs only when needed and to avoid their abuse. WHO plans to carry out this activity in close collaboration

with experts in the Member States located within WHO Collaborating Centres and other institutions.

In October 1976 a meeting of advisers was convened to advise WHO in the various fields related to the implementation of the 1971 Convention on Psychotropic Substances, and to review the functions and responsibilities of WHO. Their advice formed the basis of a WHO report (OMH/76.6) to the 27th Session of the UN Commission on Narcotic Drugs which discussed the implementation of the 1971 Convention.

In May 1977 the World Health Assembly discussed the functions and responsibilities of WHO with respect to the Convention on Psychotropic Substances and authorized the Director-General to carry out the functions assigned to WHO. The World Health Assembly also urged WHO Member States which were not yet party to the Convention to accede to it. The Director-General has since written to all Member States informing them of the decision of the Assembly.

An Expert Committee on Drug Dependence is scheduled to meet 26 September to 1 October 1977, to review the instruments for scheduling drugs under the Convention, and to consider necessary notifications.

A circular letter has been sent to all Member States requesting information on their experience relative to Articles 3 and 10 of the Convention. A meeting is planned for later in 1977 to review and suggest what WHO's position should be on the subject. This decision will be communicated to the UN Commission on Narcotic Drugs.

A review of the existing literature on "The Biological Activity of the Tetrahydrocannabinols," which will result in specific recommendations, has been carried out with scientists from the University of Utrecht.

Research on Dependence-liability of Drugs

Information is required on the dependence-liability of thebaine and other products derived from *papaver bracteatum,* a form of poppy believed not suitable for illicit heroin production. Studies to develop this information are essential before a decision can be taken to grow *papaver bracteatum* as a major source of codeine. A consultation was held to advise WHO on the methodology for implementing this project. Work has begun in seven centres to examine the dependence-liability of thebaine and alpigenine.

Preliminary data from these studies has been presented to a meeting in July 1977 in Boston. Planning is underway for a meeting of experts in October 1977 which will review projects and determine what further work is required.

V. CONCLUSION

The WHO programme on drug dependence will continue to be reshaped as the Organization faces new challenges and as we learn more about the special needs of developing countries.

CHAPTER 5

Drug Abuse in the Socialist Republic of Union of Burma

U Khant, M.B.B.S., D.P.M., and Ne Win, M.B.B.S., D.P.M., M.R.C. Psych.

In the presentation of this paper, an attempt is made to outline the nature and extent of drug abuse in the Socialist Republic of Union of Burma and the problems faced in its management.

HISTORICAL REVIEW

It is not known when opium was first used in Burma. The earliest recorded evidence we have of it is from Caesar Fredericke, a Venetian who travelled in the East for many years and who published an account of his travels in or about the year 1581. He describes at some length two sea voyages to Burma from the west coast of India carrying opium (1).

A memorandum of the Dutch East India Company also gives an account of the trade of the company in the year 1613, in which it is mentioned that 200 pounds of opium were sold annually in the Malaccas, and that the drug was profitably sold in Siam and Burma (1).

Under the Burmese kings, the use of opium was not encouraged. King Mindon objected to the smoking of opium, and later, King Thibaw, the last of the Burmese kings, prohibited it altogether. The prohibition, however, was not wholly effective, since the British-occupied areas of Burma were selling opium under license and because raw opium was available from Yunnan. Immediately after annexation of the whole of Burma by the British, a noble society in Rangoon submitted an appeal to the Secretary of the Government of India urging that importation of opium into Burma be prohibited totally or restricted as far as possible (4).

GEOGRAPHICAL AND SOCIAL CONSIDERATIONS

Poppy growing was introduced in the Frontier Areas from Assam. Some missionaries coming down from Assam to Ava in 1837 noted in their writings that poppy cultivation in Hukawng and Mogaung area was widespread.

The opium poppy is cultivated by various tribal groups in the highlands of the Shan State and Kachin State of Northern Burma. Previously, many tribal people in these areas depended upon the opium poppy as their sole or major source of cash income (5).

In accordance with the recommendation of the Hague Conference, the sale of prepared opium ceased at Government opium shops in Burma on 1 April 1921. This also led to the reduction of poppy plantation acreage, and in 1942 there were only three small areas where opium was grown. These were the Shan State territories east of the Salween, including the Wa States; the small area known as the triangle and the Hukawng Valley in the Kachin Hills; and the Naga Hills (1).

Opium smoking, common in the above-mentioned areas, was usually carried out by means of a bamboo piece. Its top is open, and it has a slanting spout near its bottom. Thus, it serves as a pipe (figure 1). It is filled with water to the level just above the base of the spout. Raw opium is cooked until it reaches the consistency of treacle. It is then mixed with finely shredded dried plantain leaf and made into small balls. These small balls are placed in the tip of the spout and burned by a lighted stick (4).

LEGISLATION

The Government of Burma had a complex body of opium laws and regulations dating back to the Opium Act of 1878. This was revised in 1909, and the Dangerous Drugs Act was passed in 1930. Separate regulations were passed for Shan States in 1923 and the Kachin Hill tracts in 1937.

After Burma gained its independence, the Government on 11 February 1948, prepared a plan to eradicate poppy cultivation and opium addiction within five years. To a certain extent, this was an overly ambitious opium policy. Subsequently, in 1953, the Union Government formed an Opium Enquiry Committee, whose task was to seek and recommend the ways and means to solve the poppy growing and opium addiction problems in the country.

With the advent of the Revolutionary Council in 1962, definite steps were taken to eradicate the scourge. They were:

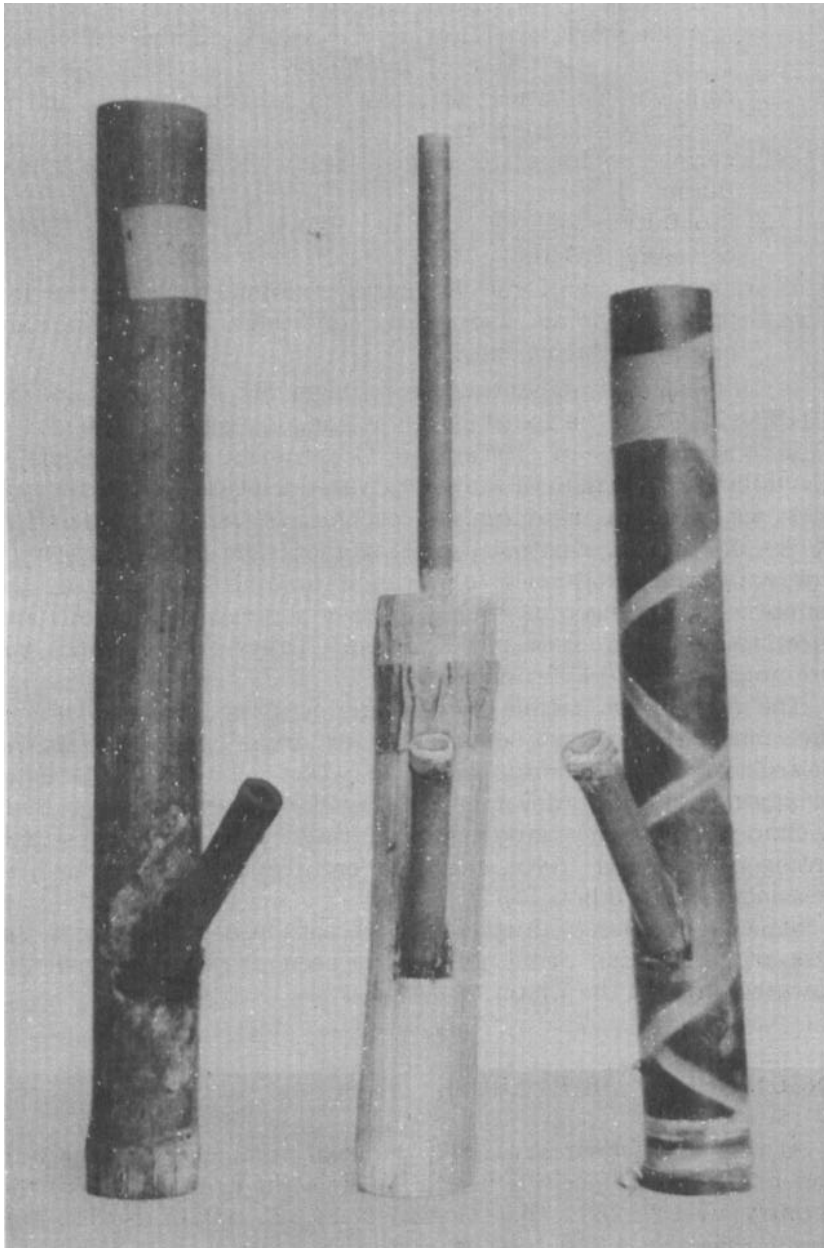

FIGURE 1

(1) Formation of an Opium Enquiry Commission in 1964 to compile statistics showing the exact number of opium addicts in the whole of the Union; to ascertain the main causes of addiction; to advise on substitute crops; and to revise the existing laws.
(2) Permission for a UN team to study the opium problem in Burma.
(3) Prohibition of the sale of opium in the Shan States beginning 1 October 1965.
(4) Formulation of the Kokang Development Project to improve economic and social conditions in the important opium-producing areas.

In spite of such measures, the problem did not abate, and by 1973, evidence of the use of heroin in Rangoon was established.

In the autumn of 1973, the Government of the Socialist Republic of the Union of Burma convened a meeting of administrators, agriculturists, agronomists, teachers, lawyers, drug manufacturers, doctors, psychiatrists, social workers, and representatives of law enforcement agencies to advise it in drafting a new law on narcotics and dangerous drugs. After a series of discussions and meetings, the Narcotics and Dangerous Drugs Law of 1974 was promulgated on 20 February 1974.

The reasons for passing the law are mentioned in its preamble: the abuse of narcotics and dangerous drugs could lead to the destruction of humanity; punitive action alone is inadequate; schemes should be developed to enable persons earning their livelihood by poppy growing to cultivate substitute crops; and arrangements need to be made to enforce compulsory medical treatment of all addicts (3).

Since registration of drug addicts precedes medical treatment, the task of registration of all addicts has been carried out in all the townships within the Union.

INCIDENCE OF DRUG ABUSE

At the end of February 1977, the total number of persons who had registered in specified health departments in the whole of the country was 20,269. These included 14,823 opium users, 1,106 heroin users and 4,340 using other drugs.

This figure does not represent the total number of persons who abuse drugs, and many feel that there is under-registration. The Government is using all means to get the correct figures. Some feel

that only about 20 percent to 25 percent of those using drugs have registered. Ignorance and fear of the law or of treatment are some of the causes.

The number of patients who registered and received active treatment at the Rangoon Psychiatric Hospital within the period from February 1974 to May 1977 were as follows:—

	Male	*Female*
Opium users	438	11
Heroin users	1,003	15
Cannabis users.	92	—
Other drugs	93	4
Total	1,626	30

An initial "rush" of applications took place in the first two months after the 1974 law was passed. A similar occurrence was reported by Lau in Hong Kong in 1967 (2). Thereafter, there was a fairly steady rate of registration and treatment of between 20 and 40 patients per month.

Opium addiction was most common among older persons (40-59 age group), while heroin abuse occured mostly in the young (20-39 age group). Statistics have shown that the age of onset of heroin abuse has fallen below 19 years.

Tables 1 through 5 give more detailed information concerning drug abuse patients: the number admitted into the Rangoon Psychiatric hospital, 1974-1977, occupation and education, mode of drug use, and distribution by age.

TABLE 1

Number of Patients Admitted into the Rangoon Psychiatric Hospital

	1974		1975		1976		1977 (Till end of May)	
	Male	Female	Male	Female	Male	Female	Male	Female
Opium	179	—	124	11	66	—	42	—
Heroin	119	2	225	—	382	11	276	2
Pethidine	31	—	23	—	7	—	9	—
Marihuana	54	—	15	—	14	—	3	—
Others	1	2	1	—	3	2	1	—
Multiple drug . . .	50	—	25	—	28	—	16	—
Total	434	4	413	11	500	13	347	2

TABLE 2

Distribution By Occupation

	1974	1975	1976
	%	%	%
Students	21.37	28.1	31.25
Workers	4.78	—	0.82
Farmers	9.6	7	4.08
Office workers	10.7	8.9	4.10
Business men	7.5	13.70	15.42
No Job	24.77	19.6	25.78
Others	21.28	22.7	18.55

TABLE 3

Distribution By Educational State of Students

	1974	1975	1976
	%	%	%
1. Primary education	—	—	—
2. Middle school	53.68	30.17	38.36
3. High school	38.94	59.48	48.12
4. College students	5.28	7.77	4.77
5. Graduates	2.10	2.58	8.75

TABLE 4

Mode of Drug Use

	Opium		Heroin	
	Smokes	Swallows	Smokes	Injects
	%	%	%	%
1973	70.6	29.4		—
1974	60.1	39.9	100	—
1975	52.5	47.5	84.4	15.6
1976	20	80	30.3	69.7

TABLE 5

Distribution By Age

Years	Opium %	Heroin %	Marihuana %	Others %
11-20	5.5	54.9	21	28.6
21-30	20	39.3	16.4	24.3
31-40	62	18.8	6.2	13
41-50	93.4	3.4	—	3.2
51+.	97.1	1.7	—	1.2

TREATMENT PROGRAMMES

In accordance with the law, all drug abusers after registration are given suitable medical treatment. To meet this need, treatment centres have been opened in various towns in the country. In these centres, multi-modality programmes are being introduced. These include:

1. Compulsory hospitalization
2. Ambulatory treatment
3. Detoxification
4. Acupuncture
5. Day hospital
6. Crisis intervention services
7. Treatment by religion or spiritual inspiration

At the Rangoon Psychiatric Hospital, the following modes of treatment are carried out:

I. Detoxification

(a) By use of Methadone in gradually decreasing doses
(b) By use of tranquillizers and other drugs
(c) "Cold Turkey" method
(d) Acupuncture

II. Rehabilitation

(a) Individual psychiatric counselling
(b) Group psychotherapy
(c) Family therapy
(d) Social counselling
(e) Locational rehabilitation

III. Ambulatory Drug Free Treatment

Withdrawal of drug of dependence is done through decreasing doses of Methadone and monitored through urine analysis.

IV. Day Hospital

This facility combines the advantages of residential treatment with those of ambulatory treatment. Patients live at the hospital during the day but are allowed to leave in the evening.

Inservice training of medical officers, nurses, and health educators is being organized by the Health Department. Priority is given to those working in the Shan and Kachin States and in other parts of the country where the incidence of drug abuse is high.

RESEARCH PROGRAMMES

Under WHO and Ministry of Health collaboration, research work is being carried out, particularly for the at-risk groups. Programmes in progress at present are:

1. *Epidemiological Case Reporting of Drug Users*
   This research programme is to improve epidemiological information on drug use by field testing of a case reporting form for collecting minimal essential data.
2. *Evaluation of Drug Dependence Treatment Method*
   The objective of this project is to improve knowledge of the effectiveness of low cost treatment methods in the management of drug dependence.
3. *Drug Use Surveys of Young People*
   This project is developing a model survey instrument for use in disease settings. Later, a full scale student survey is proposed.

CONCLUSION

The Government of the Socialist Republic of the Union of Burma adopted a resolution in its first session and fourth meeting of the Pyithu Hluttaw, held in October 1975, to combat drug abuse on a national campaign level. In view of the present administrative structure and functions of the Government, the resolution in practice amounts to an attempt to involve the entire population in combating this affliction. The civil, military, and legal branches of the Government are all involved in different ways.

Under guidance of the Burma Socialist Programme Party and with close cooperation of the People's Councils at different. levels, this campaign is making good headway, and we shall work on until we are rid of the scourge of drug abuse.

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CHAPTER 6

International Challenge of Drug Abuse: A Perspective From the United Nations

George M. Ling, Ph.D., and J. Gomez del Prado

International awareness and concern about the misuse and abuse of dangerous drugs have grown substantially in recent years. The increasing use of psychoactive substances indicates that we are living in a drug-oriented age. It is claimed that society has become more responsive to promotional advertisements for mood-modifying chemicals (alcohol, analgesics, sedatives, tranquillizers, etc.), but it also is worthwhile to recall that throughout recorded history, societies in all parts of the world have used a variety of substances in various forms to alter mood and behaviour. The use of drugs in earlier societies differed according to the region of the world, the period of history, the nature of the drug, and the frequency and consequences of use. Comparable variations in use and acceptability remain today. On the other hand, while the use of mind-altering substances in earlier times was limited largely to persons who had attained the locally accepted age of responsibility, such substances are now taken with increasing frequency and in greater amounts by younger persons as well as in a larger number of regions of the world.

Although the real extent of the problem emerges only partially, like the tip of an iceberg, indicators show an upward trend in the abuse of most substances. For instance, the total quantity of opium seized worldwide, after falling for two consecutive years, rose by 19 percent in 1976. Of this quantity, 69 percent was seized in the Far East and 27 percent in the Near and Middle East. A similar pattern has been noted with respect to morphine seizures, which, after decreasing for two consecutive years, rose by 129 percent.

In North America, the heroin problem appears to have stabilized after a decade of growth. The use of amphetamines and LSD has also decreased, while that of cannabis, cocaine, and phencylidine continues to increase.

In contrast, other areas of the world are now witnessing some of the patterns and characteristics of heroin use that were evident in North America some time ago. This is reflected in an increase in use, both orally by smoking and parenterally by injection, to the extent that heroin in some areas is becoming the principal opiate of abuse.

In Southeast Asia, there is an increasing interest in heroin use rather than in opium and morphine. This pattern of use is concentrated primarily in metropolitan areas, but it continues to spread to rural areas as well, and to younger age groups. As an example, in one city in the region an anti-drug campaign against narcotic addicts has resulted in the arrest of over 2,500 drug addicts of which 78 percent were between the ages of 16 and 25. In addition, the total amount of heroin seized in Asia and the Far East region increased from 417 kg in 1975 to 967 kg in 1976.

In Africa, heroin is at present little used as a drug of dependence, but there is an increasing use of amphetamines, sedative-hypnotic agents, hallucinogens, and synthetic opioid narcotics. In this connexion, the law enforcement authorities of Egypt have been increasingly effective in their seizure controls, and recently a smuggling group was arrested while trying to smuggle 6 million narcotic tablets into that country.

In areas around the Red Sea, the use of the khat leaves of the *catha edulis* plant as a stimulant, euphorant, and hallucinogen is on the increase. This plant has nitrogen-containing components (norpseudoephedrine, cathinone, etc.) with actions and effects comparable to those of the amphetamines. Khat is at present not under international control, but work is continuing in the UN Narcotics Laboratory of the Division of Narcotic Drugs and the World Health Organization to determine the degree of control which might be required for this substance.

In Lebanon, reports indicate that approximately 2,500 acres of opium poppies are now under cultivation in the Bekaa Valley, a tribal area which for years has long been the source of illicit hashish.

Moreover, in Europe, where in the past there has been a tendency to believe that the drug problem is only of particular concern to North America and the countries of the Far East, official sources as well as the lay press have emphasized the alarming spread of drug

abuse in this region and have called attention to increasing seizures in recent months of opiates, particularly heroin, at various Northern European transit points. The increases had been observed mainly in Denmark, Germany, Italy, the Netherlands, and Sweden, and quantities seized during 1976 have increased more than 120 percent over 1975. There are concerns also about the medical, social, and economic problems associated with the compulsive use of other types of drugs such as cocaine, cannabis and its preparations, methaqualone, the barbiturates, the amphetamines, and even trihexyphenidyl. In 1976, total worldwide seizures of central nervous stimulants increased 52 percent over 1975. Of these seizures, 72 percent were made in Europe and 27 percent in the American region.

A further problem is that drugs are being used either in sequence or simultaneously, and multiple drug abuse has become a common pattern in many countries, with unpredictable and even fatal consequences.

For many years, United Nations bodies, international organizations, and governments have given considerable attention to drug abuse, to the identification of dependence-producing substances, and to the control of their production and distribution, as well as to the reduction of demand.

International efforts to control drug abuse have also been focussed on the development of an international treaty system which will assist national control policies. In the international system, two categories of controlled drugs are recognized: narcotic drugs and psychotropic substances. At present, control is exercized over 86 narcotic drugs and 26 psychotropic substances. The narcotic drugs include opium and its derivatives, morphine, codeine and heroin, and other synthetic narcotics, as well as cannabis and cocaine. These drugs are controlled under the provisions of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol. The psychotropic substances comprise, broadly, the hallucinogens, the stimulants, and the depressants. These are controlled by the Convention on Psychotropic Substances of 1971. Both instruments have already entered into force.

The three main organs of international control are the UN Commission on Narcotic Drugs, the International Narcotics Control Board, and the World Health Organization.

The Commission on Narcotic Drugs is a functional organ of the Economic and Social Council of the United Nations and comprises representatives from 30 governments, elected with due regard to the adequate representation of:

1. countries which are important producers of opium or coca leaves;
2. countries which are important in the manufacture of narcotic drugs; and
3. countries in which drug addiction or the illicit traffic in narcotic drugs constitutes an important problem.

The Commission assists the Council in the application of international conventions and agreements dealing with drugs and carries out such functions as the Council has found necessary to assume and continue.

It advises the Council on all matters pertaining to the control of drugs and prepares such draft international conventions as may be necessary.

It further considers what changes may be required in the existing machinery for the international control of drugs and submits proposals to the Council.

The Commission has been operative for over thirty years. It sits annually in regular or special session and provides a continuous review of the global situation in regard to the international control of drugs of abuse and by its decisions and resolutions takes appropriate steps to remedy any weaknesses.

The World Health Organization has long been involved in activities designed to prevent and reduce the seriousness and extent of health care problems associated with the nonmedical use of narcotic drugs and psychotropic substances. In this context, the Organization's responsibilities relate, *inter alia,* to two important aspects of international control. These include, firstly, the assessment of those substances which may produce personal and public health hazards, and, secondly, the Organization's recommendations to the UN Commission on Narcotic Drugs of substances to be listed for control under appropriate schedules of the Single Convention on Narcotic Drugs (opiates, cannabis, coca, cocaine) and the Convention on Psychotropic Substances (e.g. hallucinogens, sedative-hypnotics and stimulants).

Another important international control organ is the International Narcotics Control Board, which comprises 13 specialists selected by the UN Economic and Social Council on the basis of their competence and impartiality. The Board's objectives are to ensure that the aims of the Conventions are not endangered by the failure of any government to monitor the licit production, manufacture, and trade in narcotic drugs and psychotropic substances required for medical and scientific purposes only, and to

ensure that there is no diversion of these compounds into illicit channels.

Financial assistance for many of these programmes is provided, where appropriate, by the United Nations Fund for Drug Abuse Control (UNFDAC). The establishment of UNFDAC was announced by the Secretary-General on 26 March 1971. In doing so, he was initiating action that had been called for by the General Assembly of the United Nations in its resolution 2719(XXV), the Economic and Social Council resolution 1559(XLIX) and the Commission on Narcotic Drugs. Seventy-two countries and one foundation are now actively supporting the Fund by voluntary contributions.

The objective of UNFDAC is to furnish assistance to governments and international organizations, including in particular the specialized agencies of the United Nations, in their efforts to:

- Limit the supply of drugs to legitimate requirements by putting an end to illegal or uncontrolled production, processing and manufacture;
- improve the administrative and technical capabilities of existing bodies concerned with the elimination of the illicit traffic in drugs;
- develop measures to prevent drug abuse through programmes of education and special international campaigns;
- provide facilities and develop methods for the treatment, rehabilitation and social integration of drug-dependent persons;

conduct chemical, pharmacological, medical, sociological and operational research on drug abuse and its control.

The Division of Narcotic Drugs, in consultation with the specialized agencies and international organizations, is instrumental in developing the overall plan for drug abuse control and in formulating those projects and programmes for which it is the executing agency.

The operational aspect of the Division's activities which has been enlarged by the support of the Fund continues to expand in several areas. These include, *inter alia,* analytical research and identification of controlled substances by the UN Narcotics Laboratory, assistance to developing countries to enable them to reduce both the supply of and the demand for illicit drugs, the reduction of illicit traffic, and the continuous provision of fellowships and training programmes to control drug abuse. As an example of the latter activity, the Central Training Unit of the Division of Narcotic Drugs

has trained since 1972 over 1,000 enforcement officers from approximately 88 developing countries. This training has stimulated further interest in control measures and has not only improved the effectiveness of national enforcement agencies but has fostered and increased international cooperation. The Division is also assisting the Government of Turkey to prevent the illegal conversion of opium gum into illicit morphine and its congeners by the use of the "straw process." In this context, the poppy capsules are not lanced, opium cannot be formed, and instead the dried capsules are delivered to a government for legal processing. Multidisciplinary country programmes with emphasis on the reduction of supply are also being conducted in countries in the Far East, the Near and Middle East and South America, where efforts are being made to determine the mutually most acceptable income and crop substitution programmes needed to overcome the farmer's reliance on the cultivation of crops which yield narcotic substances.

The United Nations organs dealing with the international control of drugs are convinced, however, that measures to reduce the illicit supply of drugs cannot be effective in the long run unless measures are taken concurrently to reduce the illicit demand for drugs. In this context, the UN Economic and Social Council adopted in 1975 a resolution entitled "Measures to Reduce Illicit Demand for Drugs," whereby it recommended that Governments, *inter alia,* should incorporate measures for the prevention and treatment of drug abuse in their integrated public health programmes.

The Commission therefore entrusted the Division of Narcotic Drugs to undertake a "study on measures to reduce illicit demand for drugs" with the collaboration of the World Health Organization, the United Nations Educational, Scientific and Cultural Organization, the International Labour Office, the International Narcotics Control Board, the United Nations Division of Social Affairs, and the International Council on Alcohol and Addictions. It is of interest that this provision for adequate measures to respond to the demand for illicit drugs was foreseen in both the Convention on Psychotropic Substances, 1971, and the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol.

A preliminary report on the first phase of the Study was prepared and considered by the Commission on Narcotic Drugs in February 1977. The report examined major issues concerning conceptual questions and policy alternatives which merit consideration for demand reduction activities. These include, *inter alia,* the assessment of drug abuse problems, the design and implementation of preventive, treatment, and rehabilitation measures, the evalua-

tion of the effectiveness of demand reduction programmes, and plans to meet future challenges and needs as they arise. The report also directed attention to the relationship between demand for illicit drugs and the irrational and unintelligent use of licit psychoactive substances. In this connexion, increased consideration should be given to the availability and self-administration of psychoactive substances as well as to the control of the manufacture, prescription, and dispensing of drugs considered to have an abuse liability. Members of the health profession are therefore urged to exercise continuing vigilance in preventing abuse of drugs by developing realistic measures of control and by exercising caution to prevent the overprescribing of psychoactive drugs with dependence-producing liability.

As a second phase of the Study, the Commission also adopted a decision requesting the Division, in collaboration with the specialised agencies concerned with illicit demand, to prepare a Resource Book on Demand Reduction. It is anticipated that its content would offer a practical guide for dealing with basic drug abuse problems of a community, and in particular would meet the needs of developing countries.

In a related area of demand reduction, governments are obliged to furnish data to the Secretary-General of the United Nations on different aspects of drug control, among which are the extent and patterns of drug abuse. On the basis of the information received from governments, the Division of Narcotic Drugs prepares a document on the abuse of drugs by regions of the world for consideration by the Commission. The sources of data collection utilized differ from one country to another and comparability of data is extremely difficult to achieve. To assist national authorities in assessing the characteristics of drug abuse in their countries and in structuring their annual reports, the Division, in collaboration with the World Health Organization, has structured a Manual on Drug Abuse Assessment. This Manual is now being tested in Malaysia, Pakistan, the Philippines, and Thailand.

The Division and the Commission have a special relationship with the International Criminal Police Organization (ICPO/Interpol) which involves reciprocal attendance at meetings and constant cooperation in all matters related to the international traffic in narcotic drugs and psychotropic substances. The Division also cooperates with the Arab Narcotics Bureau of the Social Defence Organization of the League of Arab States, the Council of Europe, the Colombo Plan Bureau, and the Customs Cooperation Council,

as well as with certain nongovernmental organizations and in particular the International Council on Alcohol and Addictions.

Integration and coordination of the work of these various organizations have fostered concerted international cooperation in efforts to control drug abuse and its associated problems, and developed industrialized societies must continue with their determination to assist the international effort both through declarations of intent and through allocation of appropriate resources. In this regard, it is worthwhile recalling United States President Carter's personal message to the 27th session of the Commission on Narcotic Drugs in February 1977: "As I begin my administration, I recognize that drug abuse, like so many problems that face us, is global in nature and can be solved only through concerted international cooperation. Drug addiction is the cause of untold human suffering, afflicting both the rich and the poor. Of particular concern to us, however, is the recent dramatic increase in addiction and its destructive effect on the limited human and economic resources of many of the less affluent nations of the world."

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CHAPTER 7

General View of Drug Abuse in Iran and a One-Year Report of Outpatient Treatment of Opiate Addiction in the City of Shiraz

M. R. Moharreri, M.D.

Drug addiction has been a nationwide problem in Iran since the 17th Century. Opium is the most widely abused drug, but with rapid industrialization and social change, Western patterns of drug abuse, including the use of heroin, alcohol, hallucinogens, and hypnotics are emerging.

In contrast to other countries, the addict population in Iran do not represent any specific socioeconomic or religious segment of the general population. For almost 14 years cultivation of opium poppies was banned in Iran. However, in 1969, the Government of Iran decided to permit limited and supervised cultivation.

In 1969 the Government initiated a nationwide opium maintenance program for individuals 60 years of age or older and for those suffering from chronic diseases for whom detoxification was not advisable.

In 1975 Government figures showed that 185,000 registered addicts were participating in the maintenance program, but this figure is believed to represent only one third of the actual number of nonauthorized addicts.

The nonregistered addicts are able simply to obtain their supplies from drug traffickers or registered addicts who sell a fraction of their supply. Although the measures taken by the Government against drug traffickers are quite severe, opium continues to enter Iran.

With the exception of a few centers located in Tehran, the treatment of addicts has been largely the responsibility of local physicians. The usual method of detoxification employed has been a gradual reduction in dosage of opium extract pills. Followup was not commonly done. Results of this treatment regimen were not satisfactory. Until 1974 in the large cities inpatient detoxification was the only treatment service offered to addicts. These detoxification centers were often located far from those drug abusers who live in small towns and villages.

From August 1973 to April 1975, the pilot project studied 533 addicts treated in an outpatient setting in Shiraz city. Outcome of this study showed better results, greater convenience for patients and staff, and much lower cost. In 1974, the National Iranian Society for Rehabilitation of the Disabled (NISRD) accepted the responsibility for treatment and rehabilitation of drug addicts. In the summer of 1975, Ramsar Medical Congress devoted its entire session to the problem of drug addiction. As a result of this congress, outpatient detoxification and rehabilitation programs received further impetus. The main resolutions of the Congress were as follows:

1. All individuals below the age of 50 who are on opium maintenance will be expelled from the program and immediately detoxified.
2. The dosage of opium maintenance for those who are in the age group from 50 to 60 will be reduced to 2.5. grams daily.
3. No new applicant below the age of 60 will be accepted into the opium maintenance program and only after meeting certain restricted criteria will a registration card be issued to new applicants over 60 years of age.
4. The minimum age limit for entering the maintenance program will be increased by one year annually.
5. Outpatient treatment was accepted as the most desirable and practical method to be established in all local NISRD offices throughout the country.

These resolutions were immediately accepted and put into operation by the Ministry of Health & Welfare. As a result, a drastic reduction in the number of registered addicts has occurred. A similarly increased demand for outpatient treatment and detoxification has been reported from various parts of the country.

In the tables that follow, I have tried to summarize the main findings of a study of 643 patients seen in our outpatient drug rehabilitation facility in Shiraz city from March 1975 to March 1976.

TABLE 1

Age and Educational Status Distribution of Drug Addicts Treated in Shiraz Rehabilitation Center (N=643)

Educational Status / Age Group	Illiterate		Elementary School		Secondary School		Higher Education		TOTAL	
	No.	%	No.	%	No.	%	No.	%	No.	%
Under 19 years	2	.31	4	.62	12	1.87	—	—	18	2.80
20 — 29 years	45	0.7	55	8.55	73	11.35	15	2.33	188	29.23
30 — 39 years	41	6.38	66	10.26	56	8.71	15	2.33	178	27.68
40 — 49 years	112	17.42	51	7.93	21	3.27	9	1.40	193	30.02
50 — 59 years	27	4.20	19	2.95	0.7	1.09	1	.16	54	8.40
60+ years	6	.93	3	.47	1	.16	2	.31	12	1.87
TOTAL	233	36.24	198	30.79	170	26.44	42	6.53	643	100

TABLE 2

Sex and Marital Status of Drug Addicts Treated in Shiraz Rehabilitation Center (N=643)

Sex	Single		Married		Separated		Widowed		TOTAL	
	No.	%	No.	%	No.	%	No.	%	No.	%
Female	8	1.24	37	5.57	4	.62	3	.47	52	8.09
Male	168	26.13	402	62.52	19	2.95	2	.31	591	91.91
TOTAL	176	27.37	439	68.27	23	3.57	5	.78	643	100

TABLE 3

Occupational Status of Drug Addicts Treated in Shiraz Rehabilitation Center (N=643)

	No.	%
Unskilled workers	129	20.06
Unemployed	83	12.91
Retired	14	2.18
Farm workers, Shepherds, etc.	40	6.22
Laborers, Janitors	12	1.87
Skilled workers, Artisans	87	13.53
Business	63	9.80
Governmental employees	79	12.29
Students	15	2.33
Housewives	33	5.13
Drivers	88	13.69
TOTAL	643	100

TABLE 4

Starting Age of Drug Addicts Treated in Shiraz Rehabilitation Center (N=643)

	No.	%
Under 19 years	120	18.66
20-29 years	267	41.52
30-39 years	164	25.51
40-49 years	81	12.60
50-59 years	8	1.24
60+ years	3	.47
TOTAL	643	100

TABLE 5

Type of Addictive Drug Used by the Addicts Treated in Shiraz Rehabilitation Center (N=643)

Type	No.	%
Tablet (Barbiturate compounds)	1	.16
Opium	335	52.10
Shireh (Cooked dross)	189	29.39
Heroin	53	8.24
Dross	4	.62
Opium and tablet	11	1.71
Shireh and tablet	11	1.71
Other mixtures	38	5.91
Valium tablet	1	.16
TOTAL	643	100

TABLE 6

Duration of Addiction in the Addicts Treated in Shiraz Rehabilitation Center (N=643)

	No.	%
Less than 2 years	82	12.75
2-5 years	262	40.75
6-10 years	157	24.42
11-15 years	66	10.26
15+ years	76	11.82
TOTAL	643	100

TABLE 7

Mode of Drug Use by Addicts Treated in Shiraz Rehabilitation Center (N=643)

	No.	%
Smoking	337	58.63
Swallowing	149	23.17
Smoking and swallowing	115	17.88
Swallowing and injection	1	.16
Swallowing and inhaling	1	.16
TOTAL	643	100

TABLE 8

Drug Intake (Per Day) in Addicts Treated in Shiraz Rehabilitation Center

Dose	0-2.5gm		2.6-5gm		5.1-10gm		10.1-15gm		15.1-20gm		20.1+gm		TOTAL	
Drug	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Opium	23	7.28	92	29.11	102	32.28	23	7.28	2	.63	—	—	242	76.58
Shireh (Cooked dross)	5	1.58	16	5.06	29	9.18	18	5.70	6	1.90	—	—	74	23.42
													316	100

TABLE 9

Dose of Opium and Shireh Intake Per Day in Addicts Treated in Shiraz Rehabilitation Center

Dose	0-1gm		1.1-2gm		2.1-3gm		3.1-4gm		4.1-5gm		>5.0gm		TOTAL	
Drug	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Opium	3	2.54	13	10.02	10	8.47	9	7.63	6	5.08	2	1.69	43	36.43
Shireh (Cooked dross)	5	4.24	20	16.95	16	13.56	10	8.47	11	9.32	13	11.02	75	63.56
													118	99.99

TABLE 10

Heroin Intake (Per Day) in Addicts Treated in Shiraz Rehabilitation Center

0.21 gm		.21-.50 gm		.51-1 gm		1.1-2 gm		2+ gm		TOTAL	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
2	3.77	14	26.42	24	45.28	9	16.98	4	7.55	53	100

TABLE 11

Distribution of Addicts According to Daily Cost of Addiction (in Rials*) During the First Six Months of 1975 (Before the Ramsar Congress)

	No.	%
Free	1	.3
1 — 50 Rls.	20	6.9
51 — 200 Rls.	126	43.8
201 — 500 Rls.	97	33.8
501 — 1000 Rls.	39	13.5
More than 1000 Rls.	5	1.7
TOTAL	288	100

*$1.00 = 69-71 Rials

TABLE 12

Distribution of Addicts According to Daily Cost of Addiction (in Rials*) During the Second Six Months of 1975 (After the Ramsar Congress)

	No.	%
Free	1	.29
1 — 50 Rls.	16	4.62
51 — 200 Rls.	99	28.61
201 — 500 Rls.	150	43.35
501 — 1000 Rls.	60	17.34
1000 + Rls.	20	5.78
TOTAL	346	99.99

*$1.00 = 69-71 Rials

TABLE 13

Way of Obtaining Drugs in Addicts Treated in Shiraz Rehabilitation Center in the First Six Months of 2535 (March 1976—September 1976)

	No.	%
Personal coupon	52	17.5
Other's coupon	84	28.3
Black market	98	33.0
Other's coupon and free market	50	16.8
Personal coupon and black market	1	0.3
Personal coupon and other's coupon	9	3.1
Personal coupon, other's coupon and black market	3	1.0
TOTAL	297	100

TABLE 14

Way of Obtaining Drugs in Addicts Treated in Shiraz Rehabilitation Center in the Second Six Months of 2535 (October 1976-March 1977)

	No.	%
Personal coupon	39	11.27
Other's coupon	104	30.06
Other's coupon and free market	31	8.96
Black market	164	47.40
Personal coupon and black market	7	.87
Personal coupon and other's coupon	4	1.16
Personal coupon, other's coupon and black market	1	.29
TOTAL	350	100

TABLE 15

Treatment Situation of Addicts Treated in Shiraz Rehabilitation Center (N=643)

	No.	%
Treated	357	55.52
Still in treatment	53	8.24
Treatment discontinued	204	31.73
Treatment not yet started	29	4.51
TOTAL	643	100

TABLE 16

Frequency and Dose of Methadone Intake (Per Day) in Addicts Treated in Shiraz Rehabilitation Center (N=643)

Dose	1-20 mg		21-40 mg		41-60 mg		61-80 mg		81+ mg		TOTAL	
Frequency of intake	No.	%	No.	%	No.	%	#	%	#	%	#	%
Once	10	2.15	22	4.72	3	.64	—	—	—	—	35	7.51
Twice	74	15.88	350	75.11	7	1.50	—	—	—	—	431	92.49

TABLE 17

Duration of Treatment in Addicts Treated in Shiraz Rehabilitation Center (N=643)

Duration	15 Days		16-30 Days		31-45 Days		46-60 Days		61+ Days		TOTAL	
Type of Treatment	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Opium Pill*	—	—	67	18.77	12	3.36	5	1.40	7	1.96	91	25.49
Methadone	3	.84	48	13.45	122	34.17	56	15.69	37	10.36	266	74.51
											357	100

*Opium Pill = contains opium extract (80 mg) and Largactil (chlorpromazine, 8mg)

TABLE 18

Results of Treatment in Addicts Treated in Shiraz Rehabilitation Center

	No.	%
Treated	115	19.69
Treatment discontinued	215	36.82
Relapse	114	19.52
Unknown	113	22.77
Methadone Maintenance	3	.51
Died	4	.68
TOTAL	564	99.99

TABLE 19

Causes of Addiction in Addicts Treated in Shiraz Rehabilitation Center (N=643) From March 1976-March 1977

Causes / Drug		Fun (enjoyment)	Sedation & tranquilization	Sexual satisfaction	Availability of drugs	Imitation	Friends' Influence	To improve job outcome	Belonging to addicts group	Physical pain	Curiosity	TOTAL
Opium	No.	156	52	5	19	10	21	40	21	107	4	435
	%	35.86	11.95	1.15	4.37	2.30	4.83	9.20	4.83	24.60	.92	100
Shireh	No.	113	40	1	4	2	24	19	19	47	3	272
	%	41.54	14.71	.37	1.47	.74	8.82	6.99	6.99	17.28	1.10	100
Heroin	No.	34	6	5	1	2	12	8	1	6	1	76
	%	44.74	7.89	6.58	1.32	2.63	15.79	10.53	1.32	7.89	1.32	100
Mixtures	No.	40	22	2	3	—	10	5	14	15	3	114
	%	35.09	19.30	1.75	2.63	—	8.77	4.39	12.28	13.16	2.63	100
Dross	No.	1	1	—	1	—	—	—	—	—	—	3
	%	33.33	33.33	—	33.33	—	—	—	—	—	—	99.99
TOTAL	No.	344	121	13	28	14	67	72	55	175	11	900
	%	38.22	13.44	1.44	3.11	1.56	7.44	8.0	6.11	19.44	1.22	99.99

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CHAPTER 8

Coca and Cocaine: A Perspective from Bolivia

Nils D. Noya, M.D.

INTRODUCTION

We have been aware for several years, of youth's consumption and abuse of cocaine in different parts of the world. However, we must say that this is a rebirth of an epidemic that had already begun during the last part of the nineteenth century and extended to the middle of the 1920's, especially in Europe (12). This epidemic, like any other infectious disease, involves a period of increasing intensity, a maintenance period and than a gradual descent. Nevertheless, as physicians and, specifically, as psychiatrists, we should be concerned about a number of disorders produced by cocaine, that sometimes an erroneously informed press tends to minimize (17). We are, then, dealing with a powerful drug that, although in a majority of cases does not produce physical dependency, produces very clear psychic alterations when used continuously. These occur apart from the paranoid type of psychosis, already described, that is caused by a chronic use of this drug.

HISTORY

Cocaine's history begins with its discovery by Karl Scherzer, in Cottingen, Germany, in 1859 (20). Initially, cocaine was utilized as a local anaesthetic; later, it was used in laryngology but mainly, according to Keller's work in 1884, in surgical and opthalmologic treatments (6). That same year, Dr. Sigmund Freud, the father of psychoanalysis, began to use the drug on himself and also as a

morphine substitute on one of his colleagues, who was a morphine addict (9). These methods of using cocaine had already been employed in the U.S.A. to treat morphine addicts (4), and in 1884, German psychiatrists adopted cocaine as a therapeutic means to reproduce their American colleagues' experiments (4).

When Freud described a cocaine-derived "good humor, together with a feeling of security, self-possession, increased strength, greater working capacity," he contributed to the possibly exaggerated spread, at that time, of the use of cocaine. However, we must join Jean Marie Gerbold when he says that, even when ill, Freud refused to use drugs, whatever their medical significance, and if, *in extremis* he resorted to drugs, it was in the final declination of his life, in order to end his hopeless agony as soon as possible.

Dr. Aschenbrandt was another European physician who also used cocaine as a tonic and as a stimulant. He was a German physician who administered cocaine orally to the soldiers, claiming that he had discovered it to have a refreshing and soothing effect (2). In 1887, Dr. Albrecht Erlenmeyer, referring to morphine addiction treatment, described the physical and psychical collapse of cocaine addicts, especially in those cases where morphine addiction had clearly developed into cocaine addiction. He suggested this type of treatment be given up as soon as possible (8). Later, in 1889, the Frenchman Magnan specifically described the tactile hallucinations — the feeling of small worms moving under his skin, or of being assaulted by millions of fleas. (Today we know this as the "Magnan syndrome.") There were patients who even pulled off their skin or cut themselves, trying to rid themselves of the imagined worms. By that time, the psychiatric alterations began to be described, especially paranoia or delusions of persecution or of reference (16).

It is interesting to point out that the real beginning of cocaine mania took place in the U.S.A. between the years 1902 and 1903. There are figures that indicate that in Cincinnati, Ohio, 10,000 people had already used cocaine by that time, and the states of Ohio and Kentucky passed special laws forbidding the sale of cocaine without a medical prescription (20).

It is interesting to speculate on the fact that in the critical prewar periods, the increase in the use of cocaine was especially significant. We can observe that before the First World War it had increased greatly in the European countries. The same phenomenon happened before the Second World War.

In 1924, the Paris police estimated the number of cocaine addicts at 80,000; mainly students and even school children (7). Some authors even mention cocaine as an important influence on the

development of some schools of art, i.e., cubism and dadaism. Color diffraction and the unfolding of objects represent the effects of disorders produced by this kind of drug (5). Jean Luis Brau in his book, *History of Drugs,* mentions some of the dadaists that utilized the drug.

In Germany, at the University Clinics, it was possible to observe clearly that the cocaine influence in the prewar and postwar periods created a really alarming situation. Of 1,000 patients admitted to the University psychiatric clinics between 1915 and 1924, the proportion of cocaine addicts increased from 0 in 1915, to 13 percent in 1924. The book, *Phantastica,* written by the Berlin pharmacologist, Lewin (14), also tells us about the great quantity of different preparations that can be made out of this drug, i.e., cocaine wine, cocaine champagne, cocaine cigarettes, etc. Later, a new type of wine appeared: it had a great impact in Europe at that time and was known as "Vin Mariani." It was made from a coca-leaf infusion (18).

In 1929, the first year that official data were available, the legal production of cocaine was estimated as 5,700 kg; 4,600 kg in 1934; 2,593 kg in 1955; 1,563 kg in 1963 and 1,038 kg in 1968. We must not forget that today, both legal and illegal cocaine production have considerably increased, specifically in the countries that grow the coca leaf. In these countries the proportion of increase in cocaine production cannot even be measured, because of the geographic and communication difficulties, lack of roads, and other factors. It is clear that even with the best intention of the local governments to control the cultivation of coca, the future appears extremely unpredictable.

COCA

For centuries the natives in the Ecuadorian, Peruvian, and Bolivian regions have been chewing coca. Coca, whose etymology means plant, was used during the pre-Inca and Inca periods as a divine drug that was exclusively meant for the royal Incas, supreme priests, and members of the Inca's royal family. Later, for reasons still unknown, the habit of chewing coca spread to all social levels, before the Spaniards reached America. In the books written by the Inca Garcilaso de la Vega (10) and by Jose Acosta (l), written in 1609 and 1590 respectively, the chewing of coca by the Incas ("coqueo") is specifically mentioned, as is its subsequent use by the

conquerors themselves. Years later, the Swiss naturalist J.J. Von Tschudy, in his book, *Croquis des Voyages,* (1842) describes a gloomy and highly harmful health situation among the natives who chewed coca (21).

However, the experience in Bolivia that is described in the works of Gutierrez Noriega and Ortiz Zapata is a different one (13). They dealt with several subjects, trying above all to eradicate cultivation of coca in their own country, Peru, as a way to prevent the chewing of coca, and of course, to prevent its being transformed into cocaine. These studies were highly valuable, as were those carried on by the UN Commission on Narcotic Drugs in 1964 and 1966, but they are not convincing from a medical point of view, when they refer to the chewing of coca leaf as producing. important damage or even any kind of disorder (19).

COCAINE

A different situation is seen with the chronic as distinct from the sporadic use of cocaine.

Lately, ***Newsweek*** magazine, in its volume LXXX-IX-22, dated May 30, 1977, describes the noxious effect of cocaine when used by human beings (17), but again, it does not mention the quality and quantity of this stimulant, that, at least in Bolivia, is used in a state of 97 percent purity. We realize that the statements made by the authorities in charge of drug abuse control, are a consequence of their experience of cocaine abuse with extremely low drug purity and where the regular dose is approximately 0.15 gr. Also, its value, in that same proportion, is about $20. In Bolivia the cocaine used is extremely pure, as already mentioned, and the usual dose is between 4 gr. and 6 gr. As its effect is quite transient, it produces a very strong psychological dependence that induces the addict to use approximately 20 to 25 gr of cocaine chlorhydrate per dose. This undoubtedly produces serious disorders in the psychic life of the drug-dependent individual. We must also consider the cost of cocaine in Bolivia, which is much lower than anywhere else in the world. Because of this, there is a great temptation to come to Bolivia to get cheap, high-quality cocaine. This is responsible for filling the prisons with foreigners, who, in spite of the strict Bolivian laws regarding drugs, come with the intention of doing illegal business.

SYMPTOMATOLOGY

We can group the symptoms based on the three ways cocaine is utilized in Bolivia today and in accord with our experience. This experience has led us to agree with the research carried on by Grinspoon and Bakalar in their latest book on cocaine (11).

When absorbed or inhaled, cocaine produces a feeling of relaxation and an emotional release of inhibition similar to that produced by the early effects of alcohol. There is a feeling of self-sufficiency, and, as some patients describe it, the sensation of being "the owner of the world." However, we must point out that, in the majority of patients treated, it was observed that the first nasal absorptions or injection of cocaine chlorhydrate produces almost no specific sensations. Symptoms appeared only after the third or fourth use. Patients said that then they experienced a general lulling sensation in the whole body and a feeling of "unfolding." We must not forget that when cocaine is used, it is generally among a group of people and that the other participants help the newcomer to inhale the cocaine. The cocaine is rolled inside a $100 bill. The insufflation must be violent so that it can reach the upper part of the nasal cavities, where the cocaine will be easily absorbed into the olfactory bulbs. In this way the consumers also avoid the possibility of cocaine being deposited on the nasal septum, thus preventing vasoconstriction in the nasal fossa, its necrosis and later perforation, as often happens to cocaine users.

The intravenous shot of cocaine chlorhydrate produces illusions or visual hallucinations, as well as auditory hallucinations of paranoid character, with threatening screams and attempts at self-damage, etc. Patients say that while the hallucinatory effect lasts, the typical coca flavor persists in the mouth of the consumer.

Contrary to current belief, we have discovered that coca produces a high degree of tolerance, apart from the possibility of a situation that could result in physical dependence. This is based on the following observation: among people who use cocaine by inhalation or intravenous injection, after a time the usual dose fails to produce the same state of intoxication as it did earlier. That is why the dose of cocaine chlorhydrate is gradually increased in order to produce the desired effect.

Regarding the experiences of our patients who consumed cocaine to feel a greater sexual excitement, we have found that, except in a few cases, there is no significant enhancement of sexual feeling. On the contrary, in some cases where there existed some apparent sexual excitement, mainly among men, the sexual act could not be

performed because of lack of erection. The use of cocaine as a topical anesthetic on the penis produces only anesthesia, with a feeling of increased size, but not necessarily an improvement or lengthening of the period of erection. Instead, it produces flaccidity.

Also, the use of cocaine, applied locally to the labia minora and clitoris produces a sensation of anaesthesia. In one case, because of its continuous use, it produced ischemia of the mucous membrane of the labia minora and of the vagina. (It also produced a subjective sensation that the partner's penis size was increased.) We must add that through our limited experience, we have seen no real cases of sexual excitement with the usual doses (5 gr to 10 gr/day, with a minimum degree of purity of 95 percent).

We have mainly described the inhalation and intravenous methods, and we must describe another very peculiar form of addiction that has led us to consider the possibility of the existence of tolerance, and also what could be called a situation of physical dependence.

The consumer of cocaine sulphate or cocaine base, mixed with ordinary golden tobacco, presents a completely different symptomatology from that observed through our experience. After the first inhalation of the "pitillo" (name given to the mixture of tobacco with cocaine base sulphate), the subject feels an immediate paranoid-like sensation, with delusions of persecution and potential harm. We have treated patients who, after the first inhalation, closed all doors and windows hermetically, "so that the police would not get them" (sic). Immediately afterwards, the patient experienced a compulsive need for continuous and exaggerated smoking: 60 to 80 "pitillos" in only one session, with the persistence of the paranoid sensation, as long as the "gathering" lasts. These gatherings usually take place among groups and only stop when both the cigarettes and the base sulphate are finished. As it is possible to obtain great quantities of cocaine base sulphate in our countries and because of the greater damage caused by its lack of purity and the possibilities of an intoxication by high doses of nicotine, we should focus our attention on this problem, from a public health point of view.

Another evident reaction observed in each smoking session of cigarettes made out of cocaine base sulphate, is an increase of intestinal peristalsis, as well as the presence of abundant diarrhea that appears as soon as the drug is inhaled.

The question is why, once the use of the cocaine base sulphate is suspended, one frequently observes "flashback-type" problems. This is how patients who have consumed this substance describe it.

They also mention the appearance of profuse perspiration, psychosomatic disorders, and even convulsions, that have a clear physiopathological explanation.

The appearance of deep depressions with suicidal ideas and intentions, is very frequent, and they are again associated with paranoid-type feelings.

It is also interesting from the point of view of our medical experience, that when consumers feel that they have had an overdose that could be dangerous, they can stop the state of excitement by drinking a solution of only sugared water and lemon juice. This simple measure controls the anxiety level, anguish, and excitement that is reached by some cocaine dependents.

Among the important and unusual data, lies the possibility of stopping the "bad LSD trips" with an inhalation of cocaine or the smoking of a "pitillo." Possibly in an entirely empirical way, this notion could lead us to discover some of the pharmacological properties of cocaine that are still unknown to us.

We also have been able to observe that the conjunctival injection, peripheral vasodilatation with reddening of the skin, and metabolic disorders appear only after a dose of more than 10 gr. of active substance using either base sulphate or cocaine chlorhydrate.

We do not pretend, through these statements, to announce new theories based on false hypothesis; rather, we want to introduce for consideration and discussion some of the problems that we observe through our experience. However, we must emphasize that the possibility of using extremely pure cocaine in high doses produces entirely different results from those observed in cases where doses of less than 0.5 gr/day have been sporadically used. This is, basically, the point at which we stand to sustain an approach to an hypothesis about the damage produced by cocaine in the human organism. We desire only that our experience be transmitted, without any intention of causing panic or alarm, to show, scientifically, how cocaine when consumed in high doses of high purity, produces unsuspected problems.

Our research infrastructure is stiil highly deficient but we are willing to accept suggestions and to receive help; and our medical and scientific staff is ready to offer to any institution or interested person, the possibility of a truly serious investigation, that can definitively clarify the cocaine question.

If we minimize or try to diminish the importance of cocaine as a powerful drug, we run the enormous risk that the future generations might have even more serious problems that those produced by other drugs. I firmly believe that it is better to exaggerate our

concern than to have an apathetic position or follow a weak policy that could lead us, in the long run, to face a serious psychosocial problem.

Those who have been able to see at first hand the physical and mental deterioration of the real cocaine addicts, will justify our concern and will understand the reason for the strict measures Bolivia has taken (15). As an example of this situation we observe that the deductive capacity in those individuals who can be considered abusers of cocaine sulphate, is notably diminished, as is their capacity for mathematical calculation, compared to the normal scholastic efforts of other young people. The most evident abuse that we have been capable of detecting is that found in smokers of cocaine sulphate cigerattes.

Perhaps because of a lack of better communication between countries of customary cocaine consumption in the form of chewing dry coca leaves ("coqueo"), we do not yet have clearer and more concrete information about the disorders that are produced. Therefore, we cannot concisely speak about the harm that the chronic chewing of coca leaf can eventually produce. This unknown factor should be one more challenge for the investigations that will be carried on in the future, in the countries involved. For this reason I wish to invite all professionals and researchers from Peru, Ecuador and Northern Argentina (where the habit of chewing cocaine is frequent among several social groups), to coordinate their actions toward investigation of specific pharmacologic and toxicologic action of the chewing of coca leaf. Our cooperation is important: in our country coca usage is an ancient custom, with deep social, cultural and anthropological roots, with no immediate possibility of eradication, not even under the conditions of other pharmaceuticals considered to be stupefacients. We have to establish, though, regarding use and abuse of cocaine, that only through our experience have we been able to classify it as a powerful drug, that easily leads to addiction, either exclusively psychological or, merely as an hypothesis, of physical dependency. These conclusions can evidently be discussed based on direct investigations of great duration, under specific conditions, so that we can all be sure of the kind of drug we are dealing with, and not adopt extremely rigid attitudes or, on the contrary, an attitude of decided permissiveness. The strict Bolivian control policy is inspired by the problems this drug produces within our society and because we have had direct experience with the damage cocaine causes among our youth. Its final consequences we must deal with as physicians, in our primary goal of saving lives, and as psychiatrists, within a basically social

setting, in order to enable youngsters to adapt to our life canons and to be useful to society. It is, therefore, of enormous importance for us, as psychiatrists, that we have complete understanding of drug induced behavior, specifically of these drugs derived from coca, so as to be able to establish more suitable control methods to minimize the future short or long term implications for consumers.

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CHAPTER 9

Drug Abuse in Indonesia

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INTRODUCTION

Drug abuse is a global problem. The phenomenon of opium smoking in Indonesia was known long before World War II; the Chinese segment of the population was especially known for this habit. They obtained their opium through a special rationing system under the colonial rule of the Dutch which ended abruptly with the Japanese invasion in 1942.

For a better understanding of the Indonesian background a few glimpses are given of its historical and cultural background.

Indonesia, Unity in Diversity

The land area of Indonesia—the world's largest island country—is scattered across a 3,500 mile span roughly comparable to an area somewhat bigger than Europe. Indonesia has more than 15,000 islands. About 300 ethnic groups exist, each with its own identity, and more than 250 languages are spoken; yet there is one universal language. The major world religions are represented. Economic activities range from stone age hunting in Irian Jaya (West New Guinea) through a variety of agricultural pursuits to the sizeable beginnings of a small but fast-growing modem industrial society, primarily centered around big cities like Jakarta (estimated population 5 million) and Surabaya (estimated population 3 million).

The Indonesian population (now estimated at 130+ million, of which roughly 60 percent live on the relatively small island of Java) is one measure of the urbanization pressure that confronts this country, if one compares with the recorded pre-World War II populations: Indonesia, 80 million; Jakarta, less than 2 million.

Throughout the 350 year colonial period as a Dutch colony, the Jakarta population grew slowly from 32,068 (1673) to 47,217 (1815), to 110,669 (1893). But according to the Indonesian Bureau of Statistics the population reached 1,636,098 in 1930 and in the subsequent 45 years it has more than tripled again. Today the total stands at more than 5 million.

At the beginning of the Christian era, most Indonesians still lived in communities which recognized no consistent political authority above the village level. Their religion was animistic, the worship of spirits and belief in a complicated multilevel world of the dead. No written history is available in a systematic form.

In the beginning of the third or fourth century A.D. a strong wave of Indian culture came to the Indonesian islands. Apparently it was not the result of a definite migration of Indians from the Indian continent to these southern islands. Rather, historians agree, local Indonesian rulers adopted Hinduism (or in some cases Buddhism) on their own initiative with the advice of wandering Indian Brahmans. From them the islanders learned the concept of divine kingship, a wide range of accompanying political techniques, and the uses of royal rituals.

At the start of the 12th century, Islam came to Indonesia. It entered the islands through the trading ports and got, footholds in the harbors of Java and Sumatra. Gradually it penetrated inland and was eventually accepted by the Hindu-Javanese ruling kings. Historians speculate that Islamism was utilized as a militant "religious force" capable of countering Christianity brought by the Europeans who at about the same time began to discover the islands of the Indonesian archipelago.

The Moslem sultans conquered Hindu kingdoms in Java, but were unable to gain a foothold in Bali, which remained until today an outpost of the pre-Moslem civilization. European influence was brought to Indonesia when the Portuguese came, who later established parts of their empire in the Far East. After the Portuguese came the Spanish, the British, and the Dutch, who in 1619 founded an establishment in the Jakarta area, called Batavia, through the well-known East India Company. Then the slow process of colonialization started and finally the Dutch East Indies, as the colony was known since, evolved.

The history of religion in Indonesia consists of successive layers of Hinduism, Buddhism, Islam, and Christianity over animistic beliefs that prevailed in the beginning. "Javanese religion" is considered a syncretism of these influences. Religion in its various forms is a fundamental integrating factor of the Indonesian

personality. The religious perspective is pervasive in almost every aspect of life: birth, puberty, adolescence, engagement, marriage, sickness, old age and death. Another basic integrating component in sociopolitical life in Indonesia is the Pancasila (Five Principles) which constitute the philosophy of the government in which belief in one God, nationalism, internationalism (brotherhood with other nations), representative government and social government are incorporated. Through this approach it is attempted that socio-political and socioeconomic freedom should be interwoven with a strong spiritual bond to build an authentic Indonesian community.

CONCEPT OF DRUG ABUSE AND RELATED TERMS

One of the basic difficulties confronting the medical and psychiatric profession is the difficulty of translating the already complicated term "drug abuse" in common language which is acceptable and agreeable to the public. If other terms are presented, the problem of translation is especially burdensome: addiction, nonmedical use of drugs, drug dependence. The challenge is to be informative to the interested public but at the same time not to be sensational or seductive. Also the extent to which nonmedical use of drugs is aimed at genuine self-medication is a problem which is increasingly difficult to delineate or define.

We are now in agreement with nearly all professionals everywhere that some sort of drug abuse does exist in every country. Once the phenomenon of abuse, especially of opiate drugs, enters a society, it is most likely to remain there for a considerable period of time.

Another observation is that when the country was faced with grave external and internal threats the problem of drug abuse was smaller or nonexistent. This was true during the Japanese occupation during World War II (1942-1945) and the following turbulent period of guerilla warfare against former colonializers (1945-1950).

Thus certain segments of society feel that drug abuse perhaps only emerges when people live in relative affluence, and when there is a relative loss of purpose of life.

COPING WITH EMERGENCY AND CHRONICITY

The first adolescent drug abuser came to the attention of the psychiatric profession in Jakarta in 1969. Since that early date an

increasing number of adolescent youth and young adults have come to our reception centers for treatment.

After an initial "shock reaction," the government responded by providing modest treatment and rehabilitation facilities in the major mental hospitals located in the urban centers. Government as well as private mental hospitals were requested to participate in this move. A small Drug Dependence Institute, Kebayoran, Jakarta, was established in 1972. General hospitals were also requested to admit drug abuse patients with acute intoxications for intensive care treatments. The Directorate of Mental Health, Ministry of Health, Jakarta, with its state mental hospital system, was assigned to monitor the drug abuse problem and admit patients to its facilities if they had problems of drug abuse. The Police Department in the Jakarta Metropolitan Area also established a facility which functions as an adolescent detention home for adolescents who are engaged in delinquent acts with or without concomitant abuse of drugs. The Social Affairs Ministry also has a facility whose main concern is the resocialization process of the drug abuser. These centers cooperate and cross refer their patients or clients as indicated.

Most drug abusers in Indonesia are multiple drug users. They usually start with marihuana smoking, although sometimes morphine or heroin may be the first drug used. Generally marihuana smokers become users of hard drugs if the smoking habit does not prove satisfactory. Morphine is smoked or injected (intramuscularly or intravenously). Packages of 4-6 mg (of dubious quality or purity) used to cost about US $3.50; the price has now doubled because of a scarcity arising from frequent police razzias or raids carried out in the urban centers of Indonesia. They may be one reason that many youngsters have now turned to alcohol, tranquilizers, barbiturates, or, more often, to a combination of all these.

One retrospective study of the first 100 drug abusers admitted to the Drug Dependence Institute, Kebayoran, Jakarta, Indonesia, showed the following demographic characteristics: The average drug dependent youth is between the ages of 16 and 26, and belongs to one of the major racial groups of the country: Javanese, Sundanese, Menangkabau (West Sumatra), Menado (North Sulawesi or Celebes), Batak (North Sumatra), or Chinese. His/her religious affiliation also reflects the major religions of Indonesia: Moslem, Christian, or Buddhist. He or she is usually unmarried and is either still registered as a high school student or is a dropout. He/she started his/her habit 6-24 months ago and prior to admission to the Institute was treated by a private mental hospital in Jakarta. Relations to the parents are

generally considered good; most of these young people were referred by their parents (3).

TREATMENT MODALITIES

Because of its short history, drug abuse treatment in Indonesia so far has only involved the usual modalities. Treatment and rehabilitation centers are only available in large urban centers. Obviously getting people off the drugs and keeping them off these compounds are different matters.

"Cold turkey" (the so-called treatment without treatment) is widely practiced. More popular, however, are detoxification methods using medication to relieve withdrawal symptoms. This method is especially popular with the helping professions of medicine and psychiatry. Acupuncture, hypnosis, religious and other meditative techniques, as well as other modalities are used, but rather inconsistently. They universally aim at "strengthening the inner forces" of the individual. Perhaps psychodynamically the matter can be approached from an "ego strengthening" point of view, and the psychological approaches are usually popular additional activities done in these treatment and rehabilitation centers. Maintenance programs have not been used but discussions have started to explore their feasibility. Therapeutic communities utilizing a religious framework have not been a major focus of interest. Outpatient counseling is increasingly popular. What is felt as a need are evaluative studies of these activities to determine if they adequately meet existing needs.

CENTRAL CASE REGISTER

From the point of view of the Ministry of Health, a drug abuser is basically an individual with a health and mental health problem. Since 1971 the Directorate of Mental Health has had a Mental Health Information System which utilizes a centralized recording system processed by computer techniques. It uses a psychiatric questionnaire (the GPPQ or General Purpose Psychiatric Questionnaire) as vehiculum to collect data on mental patients admitted to all mental hospitals in Indonesia. The data contain administrative information, demographic items, personal and family information, and summary data about the patient's previous illnesses. Thirty-four psychiatric and mental health facilities reported their activities in

this way to the central agency, the Directorate of Mental Health in Jakarta, in 1973. Of these, 13 hospitals reported having admitted drug abusers. Unfortunately no detailed information is available about the drug use, the amount used or routes of administration of these drugs. For this purpose a special record has to be devised. Numbers, figures, and other information in the section of this paper en titled, "Statistics Based on the Central Register," are based on this information system (5).

There is also a need to link this information system with data collected from other agencies active in the field of drug abuse, such as the Social Welfare Ministry and the Police Department.

Certain administrative constraints have yet to be overcome, and it is expected that through the restructuring of the Central Coordinating Body for Drug Abuse in Indonesia a better coordination of agencies working in this field can be effected. It is expected that eventually technical details such as a separate or unified identification numbering system, problems of confidentiality, and other matters can be approached more systematically.

AN "INDONESIAN" APPROACH

Since the problem of drug abuse is also determined by the local socio-cultural situation, it is felt that the problem as it presented itself in Indonesia should be approached in a more or less specifically "Indonesian" way.

Involvement of Ministries

By Presidential Decree, in 1971, a number of Ministries of the Indonesian Government were given the task of coordinating their efforts in supply reduction, treatment and rehabilitation as well as in the prevention of drug abuse. These Ministries are (1):

1. Ministry of Defense and Security
2. Ministry of Justice
3. Attorney General's Office
4. The Ministry of Finance (c.q. Directorate General of Customs and Excise)
5. Ministry of Health
6. Ministry of Information
7. Ministry of Foreign Affairs
8. Ministry of Social Affairs

9. Ministry of Education and Culture
10. Ministry of Home Affairs
11. Ministry of Religious Affairs

Another development was the adoption by the Parliament of a new Narcotic Law in 1976 which replaced the outdated law of 1927 (6). Based on this law, preparatory committees have been formed to formulate further implementations specifically for treatment and rehabilitation, and organizational provisions (dealing with matters on how coordination should be further improved). More emphasis will now be given to medical, mental health or psychiatric, social welfare, vocational, educational and other so-called "welfare" approaches (in contrast to "law enforcement" approaches). In this way it is the hope of all parties involved that a better balance can be achieved for demand and supply reduction efforts as part of an overall strategy towards drug abuse.

Guidelines for Drug Abuse Rehabilitation

One of the results of rather intensive discussions is a program outline for Guidelines for Drug Abuse Rehabilitation. This document will form the basic outline of drug abuse rehabilitation processes and phases which must be carried out by a comprehensive rehabilitation program. Every treatment and rehabilitation unit or agency will be asked to identify more specifically its modality(ies), so that a better-coordinated approach can be effected (see appendix).

STATISTICS

This is one of the most difficult areas in drug abuse. Some of our figures and numbers are estimates. Other statistics like those collected at reception centers (mental hospitals and the Drug Dependence Institute, Kebayoran, Jakarta) can be considered as very reliable and "hard data" although more detailed information may be desired (such as types of derivatives or types of drugs used, quantity, frequency of use, duration of use, route of administration, circumstances of use, degree of severity of dependence, etc.).

Estimates

It is officially estimated that drug abuse in Indonesia shows the following statistical trends (2):

1969 2 persons
1970 400 persons
1971 2,000-3,000 persons
1975 5,000-10,000 persons

In another survey it was shown that the majority of drug abusers were adolescents in high school (junior and senior) or even students in primary schools:

14.3% Students, Primary School (up to grade 7)
40.2% Students, Junior High School (up to grade 9-10)
38.75% Students, Senior High School (up to grade 12)

They use: ganja (marihuana), morphine and heroin, barbiturates and their combinations. It is generally known that although they are treated, a high relapse rate is likely, so that serious consideration should be given to possible new avenues of treatment and rehabilitation for these youngsters.

Statistics Based on the Central Register

(General Purpose Psychiatric Questionnaire as used by the Directorate of Mental Health, Ministry of Health, Jakarta, Indonesia)

*All Admissions in 1976**

The bulk of admissions were by the Drug Dependence Institute in Jakarta (64 out of a total of 122). The other mental health facilities which have admitted patients are all located within the Jakarta Municipal Area (Sanatoria Dharmajaya, Dharmasakti, Ongkomulyo, and the Navy Hospital). This again emphasizes that drug abuse in Indonesia is primarily a problem of large cities like Jakarta.

*Tables presenting full details of all drug dependence admissions to thirteen institutions in Indonesia from 1972-1976 have not been printed here. For this reason, some data from the tables, indicated by [ ], have been added to Dr. Setyonegoro's text by the editors. The institutions which contributed statistics are: Bandung State Mental Hospital; St. Carolus Hospital, Jakarta; Sanatorium Dharmasakti, Jakarta; Sanatorium Dharmawangsa, Jakarta; Jakarta State Mental Hospital; Lawang State Mental Hospital; Semarang State Mental Hospital; Department of Psychiatry, Indonesian Navy Hospital, Jakarta; Sanatorium Dharmajaya, Jakarta; Drug Dependence Institute, Fatmawati Hospital, Jakarta; Sanatorium Ongkomulyo, Jakarta; Palembang State Mental Hospital; Banjarmasin State Mental Hospital.

There is a clear predominance of male patients (88.5 percent) over female patients (10.7 percent).

The bulk of patients are within the age groups of 15-19 (36.1 percent), 20-24 (42.6 percent) and 25-29 (8.2 percent).

The source of referrals is predominatly the family (63.9 percent). Doctors and psychiatrists are much less important referral sources, referring respectively 9.8 percent and 13.1 percent.

The nominal religions reflect the demographic denominations in the population at large, although there are proportionately fewer Moslem patients (45.1 percent) compared to about 90 percent Moslems in the general population. Catholics, other Christians and Buddhists are relatively strongly represented in the patient population.

The family home is by far the primary developmental milieu (90.2 percent).

The language spoken presents no problem; most patients speak Indonesian, the dominant language (91.0 percent).

Again, "urbanity" is emphasized as place of upbringing in more than 82.8 percent of the cases.

Most patients are single; a minority are married (21.3 percent); others are separated, divorced or widowed.

Income level is very difficult to evaluate. Usually the salary received from the government or employer is not the main means of income. Figures in this area are therefore not very reliable.

The rapidity of onset of the present episode is generally not known (45.1 percent). Some report that it happened within 24 hours; others indicate that the episode built up during weeks. The same holds true for the duration of the present episode. We doubt whether these data are very relevant to the matter of drug abuse, which is one reason to adapt this questionnaire more adequately to secure information on drug abuse.

The prognosis of the majority of cases is considered as guarded (53.3 percent) or only fair (31.1 percent).

Finally, there is a wide variety of educational levels, with 7 to 12 years of schooling constituting the largest segment.

First Admissions in 1976

There were 80 first admissions in 1976 out of a total of 122 admissions. This may be an indication of the relative "virulency" of the drug abuse problem, although in absolute terms the condition is obviously a minor one (in comparison with neighboring countries like Thailand). Other data seem to conform with the general trends already indicated for "all admissions in 1976."

All Admissions in 1972-1976

[These data are generally comparable to those for 1976 alone as to sex and age distribution, marital status, nominal religion, and the like.] There seems to be a relatively greater number of admissions during 1973-1974 than is the case in the later years [198 in 1973 and 152 in 1974 compared with 130 in 1975 and 122 in 1976]. It is also the impression in clinical practice that nowadays fewer cases are seen of "clear cut" drug abuse compared to the situation in 1973-74. The exact reasons are not clearly known. Perhaps a supply reduction was one of the causes, in view of the many police raids that were conducted in 1976.

The age distribution remains basically the same [with 94-97 percent of admissions under age 30. In each year prior to 1976, when 36.9 percent were 20 years old or younger, more than half were in this youngest group]. In 1976 there was a further "stretch" into the older age groups [with 8 admissions over 40 years old—4 over 60—where there had been no more than 1 before].

The family continues to be the main source of referral (50-65 percent); also, the medical doctor and psychiatrist are stable agents of referral for drug abusers to mental health facilities for treatment (3.0-9.8 percent for doctors; 7.5-22.3 percent for psychiatrists).

An interesting phenomenon is the fact that in 1976, in contrast with earlier years, somewhat more people of lower educational level appear to be abusing drugs. [There were 23 admissions with less than 6 years of education, while the highest number in any earlier year was 11.]

Drug Dependence Institute, First Admissions 1972-1976

Generally data for first admissions over these years again underscore the earlier conclusions. [Of 636 patients, 97 were admitted twice, 42 were admitted 3 times, and 21 were admitted 4 times.] It is clear from these figures that a fairly high relapse rate should be anticipated. Provisions to meet this challenge are being contemplated but the impression is that mental health problems and situational circumstances are very intimately associated with the relapse rate and this may require more specific investigation.

CONCLUSION

In the course of our limited experiences in the field of drug abuse we have come to know that these problems are not just "drug problems." We also have the feeling that the approaches based on the "legal aspect" (that drug taking is a crime in itself), pharmacologic (that the study of the condition of acute and chronic intoxication or "addiction" can reveal all causes) and medico- or socio-psychiatric (that drug abuse is *a priori* a problem of mental disorder), although useful, do not contain the full answer to the drug abuse problem in Indonesia.

We now view more and more the "drug problem" as a problem of people, or perhaps more specifically a problem of young people. Based on this, a beginning has been made in involving as many disciplines as possible in a more comprehensive approach to the problem. In 1975 an International Seminar on the Non-Medical Use of Drugs was held in Jakarta (4) and another Workshop on Drug Abuse Prevention was held in Jakarta, 26 June-l July 1977, both in cooperation with The Colombo Plan Bureau, Colombo, Sri Lanka. In this way perhaps we may ask the question, as already asked by the WHO Study on Youth and Drugs: "How can a community best meet the adverse effects associated with a continuing or increasing rate of drug taking among both the young and old?"

APPENDIX

GENERAL GUIDELINES FOR DRUG ABUSE REHABILITATION

Referrals (Source)	I. Initial Intake	II. Detoxification and Treatment of Medical Complications	III. Stabilization	IV. Preparation for Reentry into Society	V. Resocialization (within community)
Through Heads, Provincial Health Service and Provincial Courts	(1) Provisional Diagnosis (2) Referrals to (i) Detoxification Centers (ii) General Hospitals, ICU (iii) Mental Hospitals (iv) Ambulatory Treatment Services (3) Provisional Therapeutic Strategy	(1) Overcome Chronic Intoxication (2) Treatment of Medical Complications (3) Treatment of Personality Decompensation	Stablization and Enhancement process (1) Physical (2) Emotional (3) Intellectual (4) Educational and Cultural (5) Socio-economic (6) Vocational (7) Other	(1) Overcome various Constraints (2) Enhance feelings of social responsibility	(1) Supervisory Guidance and Followup (i) Prevention of Relapse (ii) Adequate functioning without drugs (iii) Function in optimal physical and mental health
		Processing and Evaluation of Informational Data of Initial Intake (Personal Background Data (i) Psychiatric/Mental Health (ii) Intellectual/Educational (iii) Cultural (iv) Social (v) Vocational (vi) Legal Status (vii) Other		Reentry can be performed (i) Directly (ii) Through trial phase (iii) Through special guidance process	
	1 — 3 Days	1 — 3 Weeks	3 - 9 Months	3 - 12 Months	1000 Days (3 years)

←——— Rehabilitation Process ———→
(in Drug Abuse Rehabilitation Center)

APPENDIX

General Guidelines for Drug Abuse Rehabilitation

I. Initial intake

(a) Basic Policy

Referrals of drug abuse "victims" (drug abusers) are received through two channels:

(i) Chief, Provincial Health Service
(ii) Provincial Courts

and are based on articles 32 and 33 of the Law on Narcotics.

(b) Objectives

1. To establish a provisional diagnosis encompassing such data as:
   personal medical history
   patterns of drug use: experimental, casual or recreational, situational, intensified, compulsive dependent.
   level of dependence (on drugs)
   medical complications
   general physical condition
   mental health condition
2. To decide on the most adequate referral
3. To decide on the (provisional) therapeutic strategy, emergency therapy, etc.

(c) Course of Action

1. Special interview technique
2. Personal data and history of drug use
3. Clinical and physical diagnostic procedures:
   (a) vital signs/symptoms
   (b) skin
   (c) eyes
   (d) pupils
   (e) nose
   (f) chest
   (g) abdomen
   (h) central nervous system
   (i) motoric functions
   (j) pathologic reflexes
   (k) brief psychiatric examination
4. Laboratory examinations/tests
5. Thin layer chromatography
6. If necessary also: EEG, EKG, and other examinations

(d) Personnel

1. Doctors and nurses with special training in drug abuse treatment and rehabilitation
2. Laboratory technicians
3. Administrative personnel

(e) Other

Based on the provisional diagnosis, the drug abuser is now referred to the next phase of the rehabilitation process, the Detoxification and Treatment Facility for Medical Complications. Or he may be referred to one of the following facilities:

(a) the General Hospital, Intensive Care Unit
(b) the Mental Hospital for treatment of an underlying psychiatric condition
(c) an Ambulatory Treatment Facility which is authorized to carry out this type of treatment

II. Detoxification and Treatment of Medical Complications

(a) Basic Policy

1. A drug abuser, especially a narcotic drug dependent, is a patient suffering from a condition of chronic intoxication. For this reason the first phase of treatment should be to withdraw the intoxicating compound from his physical system.
2. A drug abuser rather frequently suffers from medical complications, and these should receive proper medical attention.
3. The withdrawal treatment is not without risk, especially if the patient abuses a number of drugs combined, such as narcotic drugs, alcohol, and barbiturates. Such conditions can be very severe and even have fatal consequences.
4. If withdrawal is done at once (abrupt withdrawal), a frequent mental condition can emerge, the so-called personality decompensation syndrome, in which the patient suffers from intense confusion and even from massive painful sensations. A medical clinical examination is therefore an absolute necessity during withdrawal treatment.

(b) Objectives

1. To withdraw (to "free") the abuser from a chronic intoxication (opiates, barbiturates, alcohol etc.)
2. To give proper attention to possible medical complications
3. To avoid "personality decompensation"

(c) Course of Action

1. Continuous 24-hour observation of patient's physical and mental condition
2. Monitor all modalities used in the withdrawal treatment (abrupt withdrawal, symptomatic treatment, substitution therapy, acupuncture, and other)
3. Treatment of emergency conditions
4. Avoid personality decompensation. Provide adequate treatment for this condition if it occurs
5. Treatment for medical complications

(d) Personnel

1. Medical doctors and nurses with special training
2. Medical specialists for consultation
3. Laboratory technicians and paramedical personnel

(e) Other

1. Based on medical principles certain conditions must be fulfilled in this area of medical care:
   (i) the facility should be a special section of an existing hospital or a special drug abuse hospital
   (ii) medical instruments and medicines necessary for the treatment of emergency conditions should be available
   (iii) medical instruments and medicines necessary to treat medical complications should be available

2. As soon as the general health condition of the patient has sufficiently improved (physically and mentally) further processing of the intake procedure can be carried out. Data should be compiled on areas of his mental and emotional background, vocational skills, intelligence and education, legal status, etc. The main objective of the processing of the intake procedure is to establish a comprehensive diagnosis. If time does not allow a complete workup, this can be further carried out during the next phase of the rehabilitation process, the phase of stabilization.

III. Stabilization

(a) Basic Policy

1. The drug abuser (narcotic dependent) is an individual who because of continuous use of the drug(s) has developed a physical and psychic dependence on the drug(s)
2. Some direct unfavorable effects of this condition are:
   (i) the general lowering of the condition of his health, physically and mentally
   (ii) failures in adjustment at a family level (in his home), socially and professionally
   (iii) economic and financial dependence
   (iv) tendencies to commit unlawful acts or crimes
   (v) if overdosage is the basic condition, even sudden death
3. Some of the known reasons to use drugs (narcotics) are:
   (i) feelings of alienation
   (ii) pain and feelings of discomfort
   (iii) frustration and feelings of inadequacy
   (iv) intense difficulties in work or academic performance
   (v) anxiety and depression
   (vi) feelings of being discriminated against
4. The drug abuser sometimes feels that he can perform or function better when he is taking drugs, but this is usually a very subjective statement
5. The stabilization phase aims at achieving a better general level of physical and mental wellbeing
6. Social stabilization covers goals which are directed to the enhancement of social responsibility feelings for the drug abuser under treatment and his family as well, so it can be considered a "social group process"
7. Cultural and educational stabilization mechanisms aim at the enhancement of the level of general knowledge, general skills, and aesthetic feelings
8. The stabilization of skills aims at developing flexibility and dexterity in carrying out household skills, adapting and adjusting to changing environments, and willingness to work
9. Stabilization of religious feelings aims at enhancing religious practices and religious harmony (understanding of other religions than his own)

(b) Objectives

To achieve stabilization in the areas of health, intellectual performance, emotion, education and culture, religious feelings, social adjustment, and general skills in order that the adolescent drug abuser after his

rehabilitation can function better and more meaningfully without the need to use drugs.

(c) *Course of action*

1. *Religious stabilization*
   (a) to be more conscious about the place of man within the framework of nature and universe
   (b) to understand human weaknesses
   (c) to understand the meaning of religion to man
   (d) to stimulate feelings of optimism baaed on religion
   (e) to engage in religious practices (pray, group reading of religious books, etc.)
2. *Stabilization of physical health*
   (a) diagnostic classification and evaluation of the individual's physical health condition
   (b) symptomatic therapy
   (c) physical therapy
   (d) relaxation exercises
   (e) physical exercises
3. *Stabilization of mental health level*
   (a) diagnostic classification or evaluation of mental health status
   (b) individual and group psychotherapy
   (c) psychotropic medication
   (d) medication to enhance cerebral metabolism or stimulative to central nervous system
   (e) family therapy
   (f) alternative approaches
4. *Social stabilization*
   (a) individual/social case work activities
   (b) social group work activities
   (c) family case work activities
   (d) community guidance at the abuser's residence or residential area
   (e) continuous information sessions for special groups of clients as well as for people associated with such clients.
5. *Stabilization in the areas of education and culture*
   To maintain and improve the level of general knowledge and skill adapted to his level prior to entering the rehabilitation process. Activities can be done in a number of ways:
   (a) individual or group instruction
   (b) evaluation studies of achieved results
   (c) special instruction classes for those who are relatively slow learners
   (d) special instruction classes for those who wish to learn special skills
   (e) special classes to enhance aesthetic feelings in the fields of poetry, writing, dancing, etc.
6. *Stabilization of vocational skills*
   (a) to establish the individual's capacity to acquire vocational skills
   (b) aptitude testing
   (c) to overcome barriers or constraints in placement of the individual

(d) to enhance or improve the individual's skills
(e) training of new skills

7. Other stabilization mechanisms as needed individually

(d) Personnel

1. Religious stabilization
(a) religious leaders who are interested in problems of adolescence
(b) religious leaders knowledgeable about the developmental problems of adolescent drug abusers and willing to associate with them

2. Physical stabilization
(a) medical doctors and nurses with special training
(b) acupuncturists
(c) sports leaders/specialists in physical education
(d) other supportive specialists
(e) information and education specialists

3. Mental health stabilization
(a) medical doctors and nurses, adequately trained
(b) ex drug abusers who successfully terminated the rehabilitation program with additional training in mental health
(c) other specialists with special knowledge in the area of "alternative approaches" or "meaningful alternatives"

4. Social stabilization
Social workers with special training in drug abuse rehabilitation

5. Stabilization in the areas of *education and culture*
(a) educators/teachers in special subjects
(b) other educational specialists

6. Stabilization of vocational skills
(a) special placement officers
(b) vocational guidance officers
(c) vocational training instructors

7. Other stabilization procedures
Specialist personnel as needed

(e) Other
This is a difficult phase with many complicating factors, and no "standard" approach seems to be possible. Emphasis is laid on efforts of integration and cooperation of all professionals and professional institutions active in this field.

IV. *Preparation for reentry info society*

(a) Basic Policy

1. Those drug abusers who successfully terminated the previous phases (detoxification, therapy of medical complications, and stabilization) can directly perform this "reentry into society" successfully if their parents and their community can accept them back in a positive way
2. A fairly large segment of drug abusers (although they have finished the previous phases successfully) appear to have difficulties in this phase of "reentry into society," Most difficulties are associated with their own personality, habits, family members, and the community where they live

These adolescents need a special preparatory program before their "reentry into society" can be performed reasonably successfully:

(a) through a trial phase
(b) through a special guidance program

3. If reentry is to be performed through a trial phase, a number of special activities are to be performed during the stabilization phase. These activities have limited goals and are specifically directed.
4. If reentry is to be performed through a special guidance program, certain vocational skills will be studied. A number of problems will be approached: economic or financial difficulties, problems in the areas of social adjustment, cultural adaptation, and other.

(b) Objectives

To enhance feelings of social responsibility towards society at large, his own community, and his family.

(c) Course of Action

1. Preparation for direct reentry into society involves a number of special arrangements:
   (i) to prepare this reentry in cooperation with his family, his direct community as well as with the adolescent himself with regard to challenges which will be faced in reality
   (ii) to plan further consultations with the appropriate agency or counselor with regard to problems which may arise not only in the area of concrete difficulties but also in the "spiritual sense" (e.g., social responsibilities towards his country's philosophy, Pancasila, etc.)
2. Preparation for reentry through special programs
   (i) Day centers
   (ii) Night hospitals
   (iii) Trial discharges

   which contain activities of a more limited nature compared to those during the stabilization phase
3. Preparation for reentry through a special guidance program which contains the following, among others:
   (i) problem solving of economic and financial difficulties
   (ii) difficulties of reacceptance by family or community
   (iii) overcome difficulties of personal nature: disgrace, lack of self confidence, etc.
   (iv) difficulties at school, job placement, and other socio-cultural difficulties

(d) Personnel

1. Reentry into society in a direct way will follow the general pattern as described for the Stabilization Phase
2. Preparation through special programs in day centers, night hospitals and trial discharges will need the same personnel as the stabilization phase
3. Preparation through special guidance programs will need personnel who have been trained as social workers with special abilities for guidance of adolescents

(e) Other, As Needed

V. *Resocialization (in Society)*

(a) Basic Policy

The ex drug abuser should be able to conduct a meaningful life (with due regard to the limitations set by the realistic situation), utilizing the

existing "societal infrastructures" and stable institutions such as school, "pesantre" (religious boarding schools), jobs offered by employers, and other agencies.

(b) Objectives

It is a reasonable expectation that those who have completed the previous phases successfully will be able to establish themselves in society in a more stable way, without the necessity of using drugs. If, however, a relapse should occur, they would be able to benefit from their past experiences so that they would be in better control of their behavior.

(c) Course of activities

Long term followup guidance by

1. family members (especially parents)
2. teachers
3. social workers
4. special placement officers
5. medical doctors and psychiatrists
6. nurses
7. other concerned individuals

(d) Other

Followup guidance should be done continuously over a period of "one thousand days" (about 3 years).

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II.

Biological Aspects of Drug Dependence

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CHAPTER 10

Bio-Socio Approach in Drug Abuse Treatment and Prevention

James M.N. Ch'ien, M.S.W., M.P.H.

THE GENERIC CONCEPT OF BIO-SOCIO APPROACH

In dealing with drug abuse, especially the problem of hard-core narcotic addiction, the different professions concerned have tended to adopt in the past a singular or simplistic approach, be it legalistic, medical, pharmacological, or sociological, none of which has achieved much success individually. Considerable time and energy have been wasted on the debate whether opiate dependents should be dealt with by law-enforcing or social-medical agencies (20), whether they should be treated by professionally trained rehabilitation personnel or nonprofessional exaddicts (12), and whether supply suppression or demand reduction is more important (25). After fifteen years of practice in the field and after studying the programmes of many countries which have a serious drug abuse problem, the writer wishes to propose a generic bio-socio approach which calls for the integration of all pertinent biomedical sciences and social sciences and the cooperation of all relevant professionals, paraprofessionals, and nonprofessionals in the treatment and prevention of drug abuse.

THE MYTH OF "OVERDOSE" AND MORTALITY OF MAINLINING

In order to illustrate the danger of a singular approach and the need to integrate the expertise of different disciplines concerned, the writer would like to cite the common misunderstanding even by professional people working with opiate dependents, of the term

"overdose," which is thought to be inevitably and closely associated with the mainlining or intravenous injection of heroin, Actually, deaths from such heroin abuse could be the result of acute reaction toward the unknown quantity and quality of diluents of street heroin (e.g., quinine, caffeine, sugar, etc.) or toward the bacteria, allergens, and other foreign matter introduced through the unsterilized needles, and not necessarily the result of an excessive dosage of heroin, far beyond the tolerance of the individual users.

A New York Medical Examiner reported not long ago that acute fatal reaction of true pharmacological overdose of heroin occurs approximately once in every 100,000 injections, yet "narcotic abuse" was listed as the leading cause of death among the age group of 15-35 of the city population in the late sixties (2). Obviously infectious complications, including hepatitis, tetanus, bacterial and mycotic endocarditis, etc., plus malnutrition, vitamin deficiency and plain dehydration contribute much more to the high mortalities among mainliners than direct overdose. The same report registered more than 150 deaths in 1970 as a result of homicide, suicide, and accidents among New York addicts — a fact apparently reflecting their high-risk life styles (5).

It is ironic that coroners in many places tend to label all deaths among heroin addicts as "overdose" when the exact cause cannot be determined and that the pusher who was known among street addicts as the supplier of a fatal bag is not shunned but rewarded with better business after such an incident. It is obvious that efforts by social workers or drug counsellors to warn their clients against the danger of "overdose" are often futile and occasionally counterproductive. More recent research indicates that sudden deaths through pulmonary and cerebral edema following heroin injection are more likely to be due to the combined effect of heroin and quinine or heroin and alcohol/barbiturates (4).

In Hong Kong, until very recently, heroin injection was a minor route of consumption by addicts, the majority of whom preferred to smoke their heroin with cigarettes ("firing the ack-ack gun") or to inhale the fume from the heated mixture of heroin and barbiturates ("chasing the dragon"). On account of rising prices in the black market in the past three or four years, the writer has noticed an increasing proportion of mainliners among the Society for Aid and Rehabilitation of Drug Addicts (SARDA) intake of voluntary male patients (rising from 25 percent in 1974 to 37.4 percent in the first six months of 1977), and simultaneously a certain number of reports of "overdose" deaths among its prospective clientele have recently emerged. Preventive education in Southeast Asian cities,

emphasizing the danger of death through heroin injection does not seem to stem the tide of "ack-ack gunners" and "dragon chasers" converting to mainlining under economic pressure. The writer suspects that many addicts in Hong Kong as well as neighboring cities are now injecting the brown coloured No. 3 heroin, which is a mixture prepared for smoking and which is proven to be much more lethal than the purely white No. 4 heroin prepared for exports (1). Only intensive interdisciplinary research could pinpoint the true causes of heroin-related deaths and thus guide our preventive efforts. Such a research project would require trained exaddicts to act as interviewers to elicit true information from active addicts as to the amount and method of consumption of heroin, type and quantity of other drugs including alcohol used and the life styles they lead. This is indeed an example of the advantage of the Rio-Socio approach in research over pure clinical or pharmacological studies.

BIO-SOCIO APPROACH IN HUMAN DEVELOPMENT AND ADDICTIVE LIFE STYLES

The National Institute on Drug Abuse compiled in 1975 a life style study of drug addicts in America which the writer finds to be quite universally applicable in other countries as well (16). They are summarized below:

1. *Paranoid life* could be rooted in the mistrust developed at neonatal and early childhood (e.g., rejection by mother). The person who has paranoid tendency is overly conscious of the impact of what he feels to be hostile reality. S/he needs drugs to still the anxiety and rage when considering his/her misfortune. S/he is suspicious, and therefore lonely. Through the use of drugs, the hostile environment becomes bearable.

2. *The pseudo life* feels like real life, but is counterfeit. It is lived out most dramatically by the "con-man." Rewards are received by exploitation of others, and his/her sense of shame is gradually dulled by the use of drugs. At length, the person can experience gratification only from the mistakes he has caused others to make. Because s/he continually lives on thin ice, s/he must continually be anxious. The taking of drugs gives him/her a sense of reality in a fake life.

3. There are three variants of the *passive life:* indifferent, dependent, and aggressive. *The passive-indifferent person* shows little initiative in anything and is full of weariness or apathy. A sense of defeat precedes every movement, even though one may not even have fought and lost. They tend to age prematurely and seem to leap from a childhood mentality to senility, bypassing an active adulthood.

4. *The passive dependent person,* faced with the complexity and cruelty of reality, tries to find a strong figure to lean on in order to make life easier. S/he lacks industry and feels inferior. S/he may

appear polite and cooperative, projecting an image of the "model patient" under treatment, but is seldom able to lead an independent or productive life. Chemical or emotional crutches are needed to sustain life,

5. *The passive aggressive person* despairs about his/her lack of identity. Confused with roles, s/he suffers from impotence and passivity, which turns his/her mood into irritation, with anger at those around him. S/he will sometimes attack physically, if not narcoticized or tranquilized.

6. *The obsessional life* is oriented around rituals and codes (e.g., secret society practices) and the practitioner is compulsively obedient to both. Therefore s/he is unable to develop an intimate relationship with nonpractitioners and isolated from the "square world." The obsessed individual seeks in drugs the way of extinguishing the need for tender emotions.

7. *The depressed person* finds the present empty and boring and is pessimistic about the future. Nothing generates any interest and his/her life is full of stagnation. Drugs provide an exciting break in this otherwise grey, colorless life.

8. *The retreatist* is filled with anxiety about the world; he/she particularly fears that his/her ego is falling apart. S/he uses drugs to provide a sense of illusory integration and to suppress despair.

To the above eight life styles, the writer wishes to add a ninth one which is based on his observation of elderly opium smokers in Chinatowns on the East and West Coasts of the United States, as well as Chinese communities in Southeast Asia, as follows:

9. *The waiting to die group.* Having wasted one's adult life on opiate drugs yet managed to survive till a relatively old age, the elderly person is afraid both to look back and to look ahead. Whatever family wealth or prestige he once enjoyed has been squandered. Lonely and fearing of death, he feels too far gone to try to salvage something out of life. An opiate provides a little comfort while he is waiting to die.

According to Erikson, there are certain psychological and emotional conflicts which have to be resolved at each stage of human development (15) which the writer believes could be the crucial determinants of one's life style. Conversely, in order to change a person's life style, the unresolved conflicts and the consequent retardation of his/her personality development must be treated and bridged to enable him/her to catch up with his/her bio-socio growth. Erikson's "Eight Ages of Men," based on psychoanalytic theory, contributes much to our understanding of personality formation (15), yet he failed to clarify or elaborate the influence of education and socio-cultural conditioning. Piaget's child psychology (13) and his theory of "Moral Judgement Development" (17) could be used to fill the gap and complement Erikson's Epigenetic-gram to form both a biosexual and a sociocultural axis.

The Confucian School of Chinese philosophy teaches that education of our younger generation actually begins from the embryo stage and forms a continuous process from cradle to grave. Prenatal education depends on the mother's inner peace and tranquility as well as the environment she lives in and provides for her unborn child, which in modern language could be called "maternal characteristics" (26). After the child is born, both parents should be responsible to serve as role models and to create a home environment conducive to learning. Confucius said, "A man should refine his learning skills at the age of 15, stand firmly on his feet by 30, keep an open mind at 40, be aware of his life mission at 50, confident of truth at 60, and fulfill his destiny by 70" (10). He also taught his disciples that if a man is confident of his destiny and learned of TAO (the way and the truth) why should he be afraid to die! Therefore, the writer has constructed a composite model combining the thoughts of Erikson, Piaget and Confucius to form a guideline for counselling and guidance of opiate abusers in Hong Kong, many of whom seem to be middle-aged adolescents who have not yet resolved their identity crisis. (See figure 1).

Naturally, a detoxified or a rehabilitated drug user also has diversified biological and material needs which have to be met under aftercare. With Bio-Socio approach, social work is not merely a problem-solving process, but also a goal oriented developmental process. Therefore the client system of SARDA is constantly motivated and stimulated to develop self-help and mutual aid activities which will be explained in the next section.

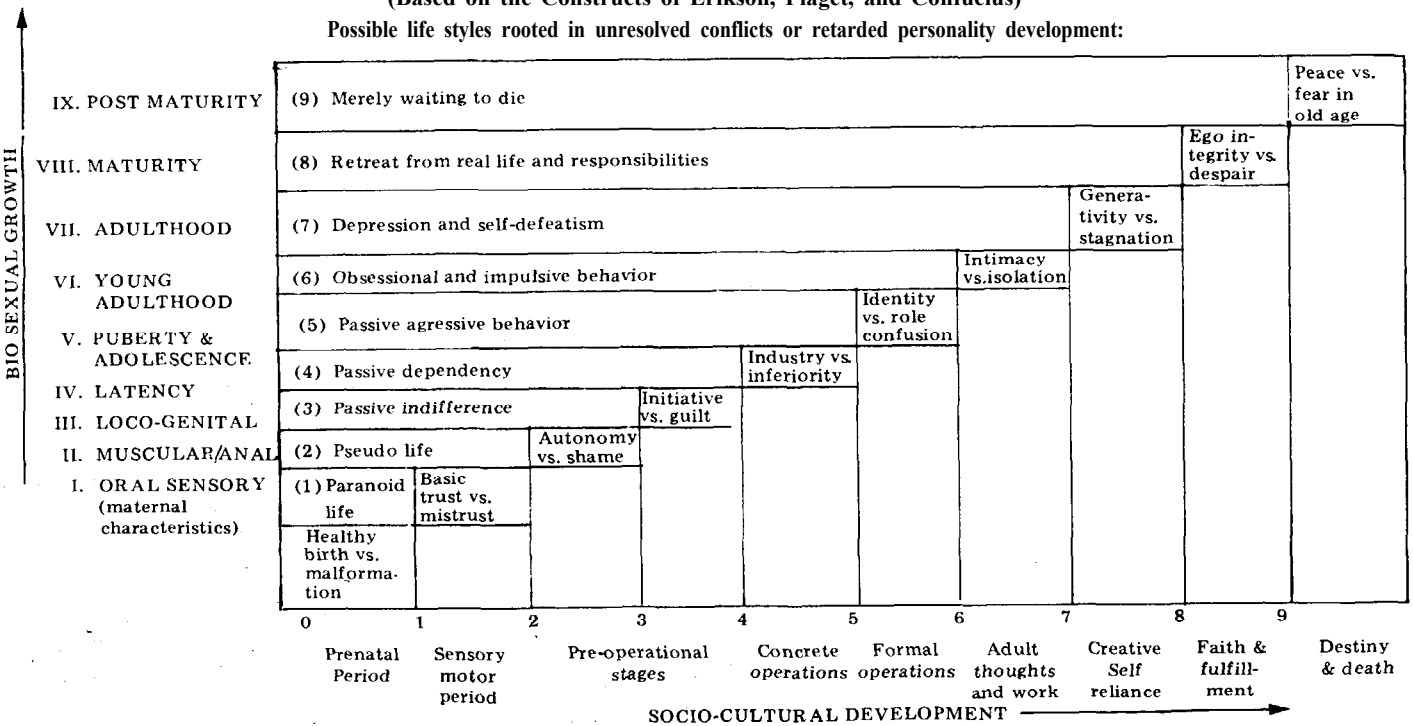
BIO-SOCIO ENVIRONMENT AND COMMUNITY SUPPORT

Urban ghettoes and physically depressed areas are often described as breeding grounds for crime, delinquency, and addiction. Scientific studies however indicate that the causal factors of such dysfunctioning or deviant behavior are mostly psychological and social in nature (6, 7). Therefore environmental manipulation as part of our rehabilitation service must aim to meet both the physical needs for decent housing and the psychosocial needs of our clients, who often require community support to cope with stress and anxiety (9). In order to promote adjustment to his/her environment of working and home life and to change his/her undesirable life style to a more constructive one, a treated opiate dependent requires as support information or action leading him/her to believe that:

1. S/he is cared for and loved
2. S/he is esteemed and valued

FIGURE 1

The Composite Model of Human Growth and Bio-Socio Conflicts as Determinants of Life Styles
(Based on the Constructs of Erikson, Piaget, and Confucius)



3. S/he belongs to a network of communication and mutual obligation.

Simple as it may appear, the writer's experience in working with drug dependents in Hong Kong and alcoholics in Denver, Colorado, convinced him that such support cannot be organized by professional service alone. The client systems in total (individuals, families, peer groups, and the functional community) must be involved for self-help and mutual support. Therefore, using Alcoholics Anonymous as a reference model, the writer encouraged and motivated a small group of fully rehabilitated exaddicts who had successfully completed the three year followup service to form an Alumni Association in 1968 to provide continued support to each other as well as to new dischargees of SARDA's treatment centers (23). The name was chosen by its founding members to symbolize their bond with the rehabilitation agency whose programme was considered an educational experience to them and which coincidentally has the same initials as Alcoholics Anonymous. The A.A. of Hong Kong was registered as an independent nonprofit society and began to recruit additional members as more men and women continued to graduate from SARDA's programmes. In the beginning, the Association depended very much on the writer or his representative for direction, and in the absence of such an "advisor," their board meetings would sometimes bog down in confusion over parliamentary procedures or rivalry for power and prestige. Gradually, the indigenous leadership was stabilized and a workable structure emerged. All members are required to pass a one-year probationary period of drug and crime free life in the community before qualifying for full voting status. Membership of those who relapsed to drug abuse is suspended until drug free status is again proven by urine tests. As membership expanded, the Association branched into six district chapters which are located in different neighborhoods of Hong Kong and Kowloon. Annual elections are held both at the chapter level and the central Board of Directors' level; to avoid excessive power concentration, their constitution stipulates that no chapter chairman shall serve more than two years and no board chairman shall serve more than three consecutive years. As self-assumed roles, they took on the casefinding job of encouraging active drug users to seek treatment and relapsed members to apply for readmission into SARDA's programme. The Association also organized "vocational cooperatives" which included a "sanitation and cleansing team" to serve the residents of housing projects, a "tailor shop" to make, mend, and alter dresses for A.A. members/

families as well as SARDA staff, and a "carpenter shop" to make furniture and interior decorations. All of these activities provide short or mid-term employment for former patients until better jobs can be found in the open market (1). In the past three years, the Association has built parks for senior citizens, beautified neighborhoods with plants and flowers, and established hostels or halfway houses in different districts to offer transitory accommodation to new "graduates" who do not have a suitable home to return to. So far they have managed to open three hostels and kept all of them clean and drug free. There are now approximdtely one thousand members who each pay a membership fee of $10 per annum and enjoy all the recreational and educational facilities provided in their respective districts. The need of affiliation and mutual emotional support is thus met, and by binding together, the members are finding the pressure of social prejudice or injustice no longer so difficult to bear and the temptation of drugs and crime no longer so overwhelming to resist. Since 1970, the A.A. has, by invitation, participated in each year's anti-narcotic campaigns organized by the Government-sponsored Action Committee Against Narcotics, and on their own initiative, has sent out entertainment teams to various neighborhoods, institutions, and schools to present variety shows and musical programmes with a theme focused on preventive education. This coming summer, the A.A. will celebrate its tenth anniversary, and it is gratifying to see that the Association has managed to change not only the values of its own members from selfishness to altruism but also of the community from that of reciprocal rejection and suspicion to that of mutual acceptance and cooperation (8).

PURPOSIVE BEHAVIOR & RECIPROCAL ALTRUISM

Biologically speaking, all animal behaviors are purposive, although goal intended action does not always achieve its purpose (28). When street addicts flock to a pusher whose previous supplies are known to have caused "overdose" death, they are taking a calculated risk based on the purpose of achieving the high benefits of a "kick" at a reasonable cost. Many are, of course, disappointed by the fact that a particular pusher's supplies of heroin are not purer or more potent, but they continue their search for the potent stuff like ants scouting for food and bees hunting for nectar. Some American users even cross the oceans to look for the pure No. 4 heroin in the East. Without understanding this "vocational drive" and the values of heroin addicts, therapists and social workers often

waste their time as well as their clients' time by lecturing them about foolish actions or taking unnecessary risks. On the other hand, when a client says that he is unable to change his behavior or life style it is very often a refusal to change. Self-help and self-programming groups can be effective to induce change if the therapist helps to clarify group values and establish the group norms in the beginning. Sid Simon, the founder of Identity Therapy, advocates that each group member be asked to publicly affirm his values and to act upon them (22). William Glasser underscores the necessity for consistency and repeatedness in behavior until it is indeed owned by the patient (23). If there is little progress or change, either the involvement is insufficient or one has bitten off more than one can chew in designing the working plan. The Bio-Socio approach is congruent with the "Teleological Explanation" of life (3). Where there is life, there is always the possibility of change and of catching up. The patient never fails; only the plan fails, but the plan can be revised, and the involvement of both the patient and therapist can be intensified. So, there is no giving up; only more work to do.

The Bio-Socio approach is therefore also a philosophy to sustain both the patients and the therapist. No chemical substitutes of opiates alone, no antagonists and no neuro-endocrinal stimulation (including acupuncture) can in themselves change behavior (21,24, 27). Only the motivated and determined individual can change his/her behavior, but a wholesome reference group with which he/she is identified can certainly help to motivate and strengthen the determination of the individual to change. The writer's belief in such potentials is further strengthened by his recent experience with a group of ex-heroin users maintained on naltrexone in New Bedford, Mass. With the encouragement of the chairman of this symposium who is directing research on antagonist therapy at the McLean Hospital, Belmont, Massachusetts, the writer was able to motivate those former patients who came from and returned to New Bedford to form a mutual aid association there. In a short span of six months the writer was gratified to see improved communication and interpersonal transactions along with better human relationships among the group members. An experienced drug counsellor is continuing to work with this group, whose goal has now extended from wholesome recreation and fellowship to reciprocal support.

Sociobiology is traditionally defined as the study and application of biological sciences for the development of natural resources in the service of the human race, to the improvement of environment

quality, and to the clarification of fundamental truth underlying human behavior (19). However, modern sociobiologists tend to focus their attention on the genetic basis and bio-programming of behavior. Altruism thus becomes genetic self-interest: maternal love being genetic investment; friendship and sacrifice being rooted in reciprocal obligation to propagate the same or similar set of genes (18). However Bio-Socio approach is broader and more generic than modern sociobiology and does not deny that there is an ultimate purpose in creation nor downgrade the values of education and socialization in human societies. Whatever the explanation, the writer has seen altruism at play in groups of exaddicts. The A.A. members in Hong Kong donate instead of selling blood to the Red Cross, and they voluntarily offer time, money, and energy in community development projects. Although they gain community acceptance and social recognition in return, the writer does not believe that they act with any ulterior motive in giving blood as well as themselves to the service of the community.

In this respect, the writer would like to quote Dr. Robert DuPont, who said at the recent National Conference on Drug Abuse, in San Francisco (14):

> NIDA's highest priority during the next year will be on the development of self-help programs for drug abusers which are independent of both government funding and treatment professionals and paraprofessionals. The goal is not to eliminate the Institute, but to complement our treatment programs the way Alcoholics Anonymous complements alcoholism treatment programs. We need Weight Watchers, SmokEnders, and AA for drug users.

The writer submits that every community which has a drug problem should accept this challenge and support voluntary programs to promote self-help and voluntary service of former users, whose life styles can thus be changed through reciprocal altruism demonstrated by the community as well as the AA members.

EVALUATION OF MICRO AND MACRO INTERVENTION

For micro-intervention, we have already seen that an individual should not be compartmentalized in treatment. A drug dependent's physical, psychological, and social problems must be dealt with in total; otherwise the effort of medical treatment, no matter how intensive, may very well be wasted. The many facets of an addictive life style are interlocked but equally important; the use of drugs is but one surface which attracts professional attention. Delong

cautioned against the dichotomy of assessment in the following words (11):

> After treatment, an addict might hold a job, support a family, refrain from criminal activity, and still go on occasional benders of drug use. Or, he might continue to commit crimes but fewer than before. His physical health might be improved even if nothing else was changed. It is also possible for a programme to have a reverse effect. It might, for example, eliminate opiate addiction at the price of alcoholism — a dubious gain . . In short there is a range of possible benefits and adverse effects that can be produced . . . . An objective examination of treatment programmes should ideally use varying measures rather than only two categories — "success" (total abstinence only) or "failure" (anything else).

In line with this thinking, the following major criteria of program evaluation were formulated recently by the UN Fund for Drug Abuse Control at a Geneva workshop participated in by the writer (25):

- reduction in drug abuse, such as drug-free periods following each withdrawal treatment, the decrease of the amount of drug taken or the change in the form of consumption, e.g., from injection to smoking.
- the improvement or lack of improvement in family relationships and in reference peer-groups.
- increasing or decreasing capacity to engage in occupational or vocational activities.
- involvement or lack of involvement with criminal or anti-social sub-cultures.

As to macro-intervention, national and international policy makers will do well to view the community or country as an organic whole and not compartmentalize the drug problem as a single segment's dysfunction or a single government department's responsibility. The same workshop submitted a set of recommendations to the United Nations in 1976 which are summarized below for convenient reference (25):

a. Drug abuse should be dealt with in the social context as a whole and the control of drugs should be considered only as one element of action, albeit a necessary one. It was considered important not to limit society's vigilance to those drugs placed under international control, but to extend it to all drugs whether "controlled," sold over the counter, or otherwise available. International controls were indispensable in the fields of regulating production, manufacture and distribution of drugs, and international treaties established minimum requirements which should be flexibly adapted to national situations.

b. Up to the present, principal attention has been given to the reduction of supply and the suppression of illicit traffic. To restore the balance, more effort should be directed to programmes for the reduction of demand, to assist both the individual country which

initiates the programme and other countries as well, by curtailing the market for production and distribution. The international community should support country studies, selecting both developed and developing countries, and provide assistance on an inter-agency basis with a view toward producing model information systems and demonstrating the integration of all pertinent data.

c. In order to be able to estimate future incidence of drug abuse, more research has to be done to identify the nature and scope of the problem. Simple standardized methods should be developed, capable of application in both developed and developing countries for monitoring drug abuse, at least its patterns and trends. It is possible to do this within a reasonable time frame. Methodology for data collection and analysis should provide means to measure not only the extent of drug abuse but also the impact of intervention programmes. Early action to identify new patterns of drug abuse is important, especially in developing countries, to assist in designing effective and integrated programmes.

d. In the national context there should be concentration on the social environment, not just the individual, on the reactions and resources of the whole society, not on any particular service. All community and government services, public and private, should collaborate. Law enforcement by itself is not enough. Parallel efforts for example in education, treatment and rehabilitation are also necessary. Police action is necessary however to apply pressure upon drug supplies and traffic to reduce the levels to those which society would find tolerable and directly upon drug dependents to seek treatment.

e. The rehabilitation of drug users should take place within the community, not by long-term isolation or institutionalization of individuals. Drug users should not be considered mere objects of experiments but should be participants in a group process for their own rehabilitation. Treatment should be directed not only at drug use but also at changing life styles. Success should be measured by realistic criteria of quantitative and qualitative improvement and reintegration into family, gainful employment and a wholesome social environment.

The above-recommended principles truly reflect the generic concept of the Bio-Socio approach in dealing with drug abuse. The planet Earth can be viewed as a spaceship for the human race to travel in time; and in order to protect our external and internal environments from drug pollution, reciprocal altruism must be promoted regionally, nationally, and internationally.

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CHAPTER 11

Behavioral Pharmacology of Narcotic Antagonists

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Narcotic antagonists are currently the major pharmacological alternative to methadone for the long-term treatment of narcotic addiction. The clinical utility of antagonist treatment is undergoing continuing evaluation (11, 43, 57, 58, 59, 67). Within the last five years, there have been several comprehensive reviews of research on narcotic antagonist drugs (3, 34, 35, 41). This review will focus upon some recent behavioral studies of narcotic antagonist drugs in man and in animals.

It is now apparent that antagonist drugs may have a number of complex behavioral effects, in addition to antagonism of the pharmacological effects of opiate drugs (86). Recent explorations of the aversive properties of some antagonists (7, 8, 21, 26, 27, 75) have been complemented by studies of the positive reinforcing qualities of antagonist drugs. The finding that opiate dependent monkeys will work to *produce* an infusion of a narcotic antagonist under certain conditions (16, 86) suggests the complexity of the process of drug-related reinforcement (52). Narcotic agonists and antagonists each may maintain behavior that leads to their administration.

Of the several compounds which have narcotic antagonist properties (34, 42), only two appear to be relatively "pure" antagonists with minimal agonistic activity. Consequently, *naloxone* and more recently *naltrexone* have become the antagonists of choice for most behavioral studies. The antagonists *cyclazocine* and *nalorphine* have been found to be partial agonists. For example, nalorphine may produce dysphoria and psychotomimetic effects in

man, as well as autonomic effects similar to those produced by morphine (34). Although some antagonists have analgesic potency, adverse side effects have limited their clinical use for analgesia (34). However, it is important to recognize that even the "purest" antagonists may have some agonistic properties at sufficiently high doses (1, 2).

Naloxone and naltrexone differ in potency and duration of action. Naloxone is estimated to have a duration of action of approximately four hours, which makes it especially useful for behavioral studies. Naltrexone is estimated to be between two and eight times more potent than naloxone, depending upon the test system employed (1, 2, 76). In man, the antagonist actions of naltrexone appear to persist beyond 24 hours (43), even though analysis of urinary excretion patterns indicate that naltrexone is cleared within 16 to 24 hours (32). Recent evidence suggests that beta-naltrexol, the major urinary metabolite of naltrexone, may contribute to its long duration of action in man (32). However, chronic high doses of naltrexone (100 mg/day) do not result in the accumulation of either naltrexone or beta-naltrexol (77). Although beta-naltrexol is the predominant urinary metabolite in man, nearly equal proportions of naltrexone and beta-naltrexol are excreted in the urine of monkey (32). The implication of these findings for the apparent difference in duration of naltrexone blockade in man and monkey remains to be clarified (cf. 29, 53).

ANTAGONISM OF OPIATE EFFECTS

The primary effects of narcotic antagonists are to reverse or to block the pharmacological effects of opiates. Pre-treatment with a narcotic antagonist will prevent the physiological and behavioral effects of acute opiate administration. Chronic administration of narcotic antagonists also blocks the development of tolerance and physical dependence upon opiates (6, 42, 69). Administration of narcotic antagonists to an opiate dependent person or animal will precipitate an opiate withdrawal syndrome (4, 69, 78, 79). The severity of antagonist precipitated opiate withdrawal appears to be antagonist-dose related (cf. 4, 53). The capacity of these compounds to reverse respiratory depression induced by opiates has long been an effective tool for emergency ward treatment of overdose.

There has been considerable progress towards understanding the mechanism of action of narcotic antagonists within the past five

years. Several laboratories have found stereospecific opiate receptor sites in brain which appear to be binding sites for endogenous neural ligands termed endorphins (22, 66, 70, 71, 72). It has been hypothesized that endorphins may act to inhibit or modulate neural responses to painful stimuli (cf. 31). Opiate antagonists may compete with exogenous morphine-like drugs for stereospecific opiate receptor sites. However, Jaffe and Martin (34) suggest that the notion of competitive antagonism at a single receptor site cannot account for many of the interactions between opioids and opioid antagonists. For example, although most antagonists do not induce tolerance or physical dependence, antagonists of the nalorphine type may produce a withdrawal syndrome which is qualitatively different from the morphine withdrawal syndrome. Moreover, partial agonists of the nalorphine type may substitute for morphine at relatively low levels of physical dependence and precipitate withdrawal at high levels of morphine dependence. These and other observations have led to the hypothesis that specific receptors or receptor configurations may exist for antagonists and for opiates (42).

SOME EFFECTS OF ANTAGONISTS ON FOOD AND SHOCK MAINTAINED BEHAVIOR

Over the past decade, behavioral pharmacologists have studied a variety of narcotic antagonists. There is little question that narcotic antagonists will effectively block or reverse the behavioral effects of opiates in nondependent animals, in a dose-related manner. Behavioral effects have been variously defined as rate of response for food and efficiency of avoidance responding under a variety of single and multiple schedules of reinforcement (9, 17, 25, 28, 29, 49, 50). The effects of narcotics and antagonists on multiple fixed interval-fixed ratio schedules of food presentation have been reviewed recently (48).

It is generally found that high doses of morphine decrease the rate of operant responding for another reinforcer such as food. However, very small doses of morphine may increase a pigeon's rate of response for food. Increases of about 50 percent have been observed in the fixed interval component of a multiple fixed ratio-fixed interval schedule. Certain antagonists have also been shown to increase rates of responding in the fixed interval component of the multiple schedule at low doses and decrease rates at high doses (17, 48). Narcotic antagonists can block the rate

decreasing effects of opiates at dose levels which do not produce direct behavioral effects, For example, pretreatment with naloxone (0.1 mg/kg) blocked both the rate increasing and the rate decreasing effects of morphine on schedule-controlled performance for food reinforcement. However, naloxone doses as high as 30 mg/kg did not antagonize the rate decreasing effects of cyclazocine (48).

Naltrexone and diprenorphine (0.1 mg/kg) appear to have comparable potency for blockade of the effects of an acute dose of morphine (30 mg/kg) on food-maintained responding in pigeon (9). Those antagonists appear to be as much as three times more potent than naloxone (2, 9). Naltrexone can block the effects of morphine administered as long as six hours after acute antagonist administration in pigeon (9).

Species-related differences in response to narcotic antagonists have been reported (17). For example, nalorphine decreased rates of food-maintained responding in squirrel monkeys and increased response rates in pigeons under comparable schedule conditions and across a comparable dose range, whereas high doses of naloxone decreased response rates in both monkeys and pigeons and produced gross tremors and vomiting (17). Naloxone did not antagonize the rate decreasing effects of nalorphine at doses which completely antagonized the effects of morphine. The interactions between antagonists and consequent effects on behavior do not appear to be reliably predicted from the behavioral effect of an antagonist plus a narcotic drug.

EFFECTS OF ANTAGONISTS OF OPIATE SELF-ADMINISTRATION

Clinical Studies

Since narcotic antagonists can block the effects of opiates, proponents of narcotic antagonist maintenance for the treatment of heroin addiction argue that pharmacological blockade will eventually eliminate opiate self-administration (cf. 83). However, recent studies of the efficacy of naltrexone maintenance in modulating heroin self-administration on a clinical research ward have shown that some addicts may continue to sample heroin during antagonist blockade (55, 59). The frequency of heroin self-administration during antagonist blockade was influenced by a number of factors, including whether or not the heroin addict was told that he was

given naltrexone. When subjects were not told who was receiving naltrexone and who was receiving naltrexone placebo, seven of the nine subjects maintained on naltrexone blockade (75 mg/day PO) sampled heroin an average of 13 times (range: 2 – 46) over a ten-day period of heroin availability. Assessments of temperature, blood pressure, pulse, respiration and pupil diameter revealed no physiological effect of heroin during naltrexone blockade. Although all subjects took less heroin during naltrexone blockade than under unblocked conditions (X occasions = 55.07; range: 32 – 78), the frequency of heroin sampling after naltrexone appeared to be related to the duration of addiction history. Addicts with a long history of heroin addiction persisted longest in heroin self-administration under conditions of naltrexone blockade (59). Parallel findings have been observed in animal models where consumption of etonitazene during naloxone blockade persisted longest in rats with the longest history of addiction (56).

When heroin addicts were given access to heroin during naltrexone blockade (50 mg/day PO) under double blind conditions, each of 22 subjects studied sampled heroin occasionally. Eleven subjects took heroin on an average of 15.9 occasions, whereas the other 11 subjects took heroin on an average of 4.3 occasions over a ten day period. Unlike addicts in the first series of studies, six of the 11 subjects who sampled heroin most frequently showed respiratory depression and pupillary constriction after the first few heroin doses. Comparable physiological changes did not occur after later heroin use. Meyer and Mirin (55) suggest that these autonomic effects were not due to inadequate antagonist blockade, but rather were classically conditioned responses which extinguished after repeated blocked heroin injections. Insofar as subjects were aware of these autonomic changes, these may have contributed to the persistence of heroin self-administration as secondary reinforcing discriminative stimuli (55).

Heroin addicts stabilized on either cyclazocine or naltrexone also reported some sensation of rush, high, and taste when permitted to self-inject an acute dose of hydromorphone or saline under double blind conditions (65). Pupillary constriction was observed in some instances. The pleasurable response to saline or to hydromorphone under naltrexone blockade was less intense and prolonged than under cyclazocine blockade. After repeated systematic extinction trials, the self-injection procedure became neutral and then aversive. The observation that saline could induce subjective and pupillary change equivalent to hydromorphone, during antagonist blockade,

suggests the importance of conditioning effects associated with the ritual of self-injection (65).

Animal Models of Opiate Self-Administration

Stimuli associated with drug infusions can come to control behavior leading to presentation of the stimulus, even in the absence of drug infusion. Most recently it has been shown that operant behavior can be maintained for periods as long as one hour by intermittent presentation of a stimulus previously associated with infusion of cocaine or morphine. A single drug reinforcement is then delivered at the end of the hour upon completion of the response requirement (18). Discriminative stimulus control of drug reinforced behavior is an experimental analog of the complex external situational stimuli alleged to contribute to the maintenance of and relapse to drug abuse in man (83).

Stimulus control of opiate withdrawal signs has been observed in several species under a variety of experimental conditions (14, 84). Stimuli which are repeatedly associated with antagonist precipitated opiate withdrawal can acquire the ability to produce withdrawal signs and behavior changes (13). For example, a light associated with nalorphine injections continued to suppress food maintained responding and to decrease heart rate for two to four months after morphine dependence was terminated (15). Conversely, stimuli previously associated with opiate infusions can maintain responding leading to presentation of those same stimuli plus saline, when opiate dependent monkeys are in withdrawal (68). Consequently opiate acquisition and the physiological and behavioral concomitants of opiate withdrawal can be modulated by external stimuli associated with drug infusions or antagonist precipitated drug withdrawal (cf. 12, 13, 86).

Acute administration of the antagonists naloxone, nalorphine or naltrexone usually increases the rate of response for opiates in opiate dependent animals (19, 20, 53, 81, 86, 87). However, high doses of antagonists may also suppress morphine maintained responding (20). As a function of repeated experience with low doses of antagonists, morphine dependent monkeys may learn to initiate morphine self-administration more rapidly following antagonist infusion (20, 53). Despite the early increases in opiate maintained responding usually seen after antagonist administration, the total daily morphine intake level may not change significantly from the preantagonist baseline. During a 25 hour period following

high acute doses of naltrexone (0.035-0.065 mg/kg), opiate dependent monkeys maintained a stable level of morphine self-administration (53). Varying periods of morphine deprivation have also been followed by no significant increases in the total amount of morphine self-administered over a 24 hour period (87). Monkeys appear to be exquisitely sensitive to any deviation from their accustomed level of morphine intake and are able to adjust morphine self-administration behavior with considerable precision to maintain baseline morphine levels (53). The nature of the discriminative stimuli which permit an opiate dependent monkey to adjust morphine self-administration to maintain a stable daily level of morphine dosage is unknown.

Chronic antagonist blockade with high doses of naloxone (200 mg) has been shown to inhibit relapse to morphine self-administration in postaddict rats (61). The effects of lower doses of naloxone on relapse were variable, and some animals took enough morphine to overcome blockade and reestablish dependence (61).

AVERSIVE EFFECTS OF ANTAGONISTS

Clinical studies indicate that administration of narcotic antagonists such as nalorphine and cyclazocine may produce dysphoria, anxiety, and a spectrum of feelings of unreality, including hallucinosis in some individuals (23, 34). Comparable effects have not been reported following acute administration of naloxone. Dysphoric and psychotomimetic side effects do not appear to be a prominent feature of naltrexone administration.

Some morphine antagonists have negative reinforcing properties in opiate naive monkeys (26). Monkeys worked to avoid or escape nalorphine (10-500 mcg/kg/inj) and cyclazocine (2.5-10 mcg/kg/inj); however, naloxone (5-100 mcg/kg/inj), pentazocine and propiram (50 mcg/kg/inj) did not maintain escape or avoidance behavior at rates higher than saline (26). These data suggest that the aversive properties of certain antagonists are not solely a function of opiate dependence.

Primates will work to avoid or to terminate infusions of narcotic antagonists under a variety of conditions (7, 8, 21, 26, 27, 75). Nalorphine. naloxone, pentazocine, and propiram have been shown to maintain escape and avoidance behavior in morphine-dependent monkeys. Primates will also work to terminate a discriminative stimulus which was previously associated with the administration of a narcotic antagonist (7, 8, 16, 21, 27, 75). However, a number of

compounds other than narcotic antagonists have also been shown to maintain behavior leading to termination or postponement of injections (cf. 27, 30).

ANTAGONIST SELF-ADMINISTRATION

Primate Studies

The behavioral effects of narcotic antagonists are usually concordant with expected predictions of what the effects of these agents should be. What is more intriguing and perplexing are the recent findings that, under certain conditions, opiate dependent monkeys will work to *produce* an infusion of a narcotic antagonist (16, 86).

In 1972, Goldberg, Hoffmeister, and Schlichting (16) reviewed their behavioral studies of the effects of morphine antagonist administration to morphine dependent monkeys. When either saline or nalorphine was substituted for morphine during a seven and one-half hour session, it was found that responding which was followed by nalorphine injections decreased less rapidly than responding followed by saline injections. In fact, nalorphine maintained responding occurred at a higher rate than either saline maintained responding or morphine maintained responding (16). These data indicate that response produced nalorphine injections (100 mcg/kg/inj) can maintain responding when monkeys are physiologically dependent on morphine.

In 1975, Woods, Downs, and Carney (86) reported that morphine dependent monkeys, trained to avoid infusion of naloxone, will, under certain schedule conditions, work to produce injections of the narcotic antagonist naloxone (.002 mg/kg) on a second-order schedule. Every 30 responses produced a secondary reinforcement stimulus (a 1.5 second flash of light), and every 300 responses produced an injection of naloxone followed by a one minute time out and the same light signal. When the naloxone infusion pump was disconnected, and the secondary reinforcing visual stimuli and the basic schedule remained unchanged, monkeys ceased to respond. When the naloxone pump was reconnected there was a resumption of naloxone maintained responding and the response requirement was reduced from 300 to 150 responses for naloxone reinforcement. Under these conditions, morphine dependent monkeys could earn about 10 naloxone injections over the course of an hour (86).

These data illustrate that the experimental history of the subject and the behavioral schedule under which a stimulus event is presented, rather than the type of event, may determine the effect that an event will have upon behavior. The importance of the schedule of drug injections in determining how drugs affect behavior has been a general finding in behavioral pharmacology (36, 37, 39, 62, 63). The crucial point is that drug reinforcement, or the maintenance of behavior by drug self-administration, is conjointly determined by the pharmacological effects of the drug and the schedule of drug presentation.

Implications for an Analysis of Drug Reinforcement

Response-produced antagonist infusion by opiate dependent monkeys is a recent entry into the now considerable literature which describes behavior maintained by the presentation of "aversive" events. Response-produced antagonist self-administration is a direct parallel of another behavioral phenomenon usually termed *response-produced shock.* It has been found that the *same* electric shock events that can maintain escape and avoidance behavior, may under certain conditions, be self-administered by the same monkey. Identification of this phenomenon evolved from the observation of Kelleher and co-workers in 1963 that responding increased during a pre-shock stimulus and decreased if the terminal shock was removed (40). Response-produced shock has now been observed in many laboratories, across several species and has been shown to be a reliable and persistent phenomenon (5, 10, 38, 44, 45, 46, 62, 64, 73, 74). Under certain conditions, monkeys will continue to self-administer electric shock for months and even for years (62).

Electric shock has been the favorite "aversive" event of generations of psychologists. The effectiveness of electric shock for maintaining escape and avoidance behavior and the punishing effects of electric shock on ongoing response behavior for reinforcers such as food are general findings too familiar to require documentation. However, the discovery that electric shock may be a *positive* reinforcer challenges common-sense assumptions about what constitutes a "positive" and "aversive" event and what classes of events will be reinforcing.

The view that events do not have inherently reinforcing or punishing properties, but rather should be defined in terms of behavioral effects, has been most fully developed by Morse and Kelleher (62, 63). There is now considerable evidence that the *same*

stimulus may have either reinforcing or punishing effects, depending upon the conditions (or schedule) under which it is presented. A schematic summary of this formulation appears below. If the presentation or removal of a stimulus event increases the behavior leading to that consequence, it can be defined as a reinforcer. If the presentation or removal of a stimulus event decreases the behavior leading to that consequence, it can be defined as a punisher (62, 63).

AN EVENT	BEHAVIORAL EFFECT	
	Increase Behavior	Decrease Behavior
Present Stimulus	Reinforcement	Punishment
Remove Stimulus	Reinforcement	Punishment

This conceptual framework can accommodate a number of otherwise incongruous illustrations of behavior maintained by "aversive" consequences, for example: (1) chronic opiate or alcohol abuse may lead to profound anxiety, depression, and agitation during intoxication rather than to the expected "euphoria" (24, 51, 55, 60); (2) monkeys will work to self-administer the same electric shock they previously worked to avoid (62); (3) opiate dependent monkeys will self-administer a narcotic antagonist that they previously worked to avoid (16, 86).

The extent to which "aversive" consequences comprise an important aspect of the complex process of drug reinforcement in man is unknown. Clinical data indicate that both alcohol and abused drugs may have aversive subjective consequences for the naive or occasional user (33, 52, 80, 85) and for the addict (54, 55, 60). These findings challenge the assumption that persistent drug abuse can be accounted for solely by its "rewarding" or "euphorogenic" consequences. The process by which an initial drug experience, which may involve nausea, vomiting, and dysphoria becomes translated into recurrent drug abuse or drug addiction is unclear. The details of this transition are perhaps impossible to study in man.

However, if drug abuse is examined in terms of its actual effects on behavior, rather than in terms of time-honored a priori assumptions, it may be possible to identify more accurately the

determinants of its reinforcing properties. A better understanding of the process of drug reinforcement would be valuable for the development of optimally effective techniques for modifying drug abuse in man. Behavior which is maintained by events such as antagonist self-administration by opiate addict monkeys may offer one model for exploration of the complex determinants of drug reinforcement. Over 25 years ago, Wikler (82) observed that partial withdrawal may enhance the gratifying effects of morphine injections in human addicts. The nature of the interactions between narcotic agonists and antagonists, and the effects of these interactions on behavior remain to be determined in future research.

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CHAPTER 12

Plasma Testosterone Levels During Chronic Heroin Use and Protracted Abstinence: A Study of Hong Kong Addicts[1]

Jack H. Mendelson, M.D., and Nancy K. Mello, Ph.D.

According to clinical reports, heroin addicts experience both diminished sexual drive and impairment of sexual function when actively using narcotics (14). Diminished sexual drive has been characterized as lack of desire for initiation of, and unreceptivity to, sexual interaction. Impaired sexual function has been reported as difficulty in initiating or sustaining penile erection and significant prolongation of ejaculatory time. There is also evidence that plasma testosterone levels in man may be correlated with sperm count and sperm motility (7). The mechanisms by which narcotics use produces suppression of sexual desire and function are unknown.

It has recently been shown that heroin (1, 11), high-dosage methadone (1, 11), and alcohol (10) suppress plasma testosterone levels in addicted subjects. The duration of the suppressive effects of narcotics on testosterone is not known and the mechanism of inhibition is unclear (11). It is not known if chronic use of heroin for varying periods of time causes long-lasting or short-term suppression of testosterone levels. This study was undertaken to determine if chronic narcotic use produces permanent impairment of androgen levels. No data have been reported previously on testosterone levels following abrupt *cessation* of heroin use and during protracted abstinence.

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Attempts to relate plasma testosterone levels to heroin use or to abstinence present several methodologic problems, First, it is difficult to study heroin addicts for months or years following initiation of abstinence because of the high frequency of recidivism. Secondly, many narcotic addicts have polydrug abuse problems and it is difficult to ascertain whether alterations in endocrine levels are specifically associated with heroin or with use of other drugs alone or in combination with heroin. For example, it has been shown that many American heroin addicts, both in drug-free status and on methadone maintenance, develop significant alcohol abuse problems (4). Alcohol abuse has been shown to be associated with a suppression of plasma testosterone levels (10).

In order to examine the long-term effects of heroin on plasma testosterone levels in an addict population where polydrug abuse was uncommon and alcohol abuse was relatively rare, a study of Hong Kong heroin addicts was undertaken. Hong Kong has probably the largest number of heroin addicts per capita in the world. There are estimated to be over 100,000 addicts in a population of about 4.2 million (9). In Hong Kong, addicts have access to a high-quality and relatively pure heroin that they can obtain at low cost on the illicit drug market.

There are two types of heroin for sale on the illicit drug market in Hong Kong. "Number 3 heroin" is sold primarily for smoking. An average packet contains 300 mg of heroin and is 30% to 50% pure. "Number 3 heroin" is sometimes mixed with a trace of barbiturates to produce a slower burning mixture. In 1973, the average cost of a packet of "Number 3 heroin" was 5 Hong Kong dollars, which is equivalent to 0.4 £ or one U.S. dollar. "Number 4 heroin" is sold primarily for intravenous use. An average packet contains 40 mg of heroin, which is 60% to 95% pure. A packet of "Number 4 heroin" costs approximately 2 Hong Kong dollars, which is equivalent to .17 new pence or 40 U.S. cents.

Until recently, the preferred mode of heroin use in Hong Kong was by smoking the drug in cigarettes or by inhaling vapors of volatilized heroin, a technique known locally as "chasing the dragon," which consists of placing heroin in a tinfoil cup, igniting the heroin and deeply inhaling the smoke and vapors. During the past two years an increasing number of addicts administered heroin intravenously, and it is currently estimated that in 15% to 20% of all addicts, intravenous heroin is the preferred mode of use (9).

This study was undertaken in an effort to determine if alterations in plasma testosterone levels persist during early and late phases of heroin abstinence.

SUBJECTS AND METHODS

The subjects were 31 male heroin addicts, between the ages of 15 and 43 ($\bar{X}$ = 30). All were Chinese residents of Hong kong who reported a history of heroin addiction ranging from 2 to 20 years' duration. Plasma testosterone samples were obtained from all subjects between the hours of 10:30 and 12:30 each morning. Plasma testosterone levels were determined by a commercially available double-antibody radioimmunoassay modified from a procedure used for protein hormones as described by Niswender and associates (12).

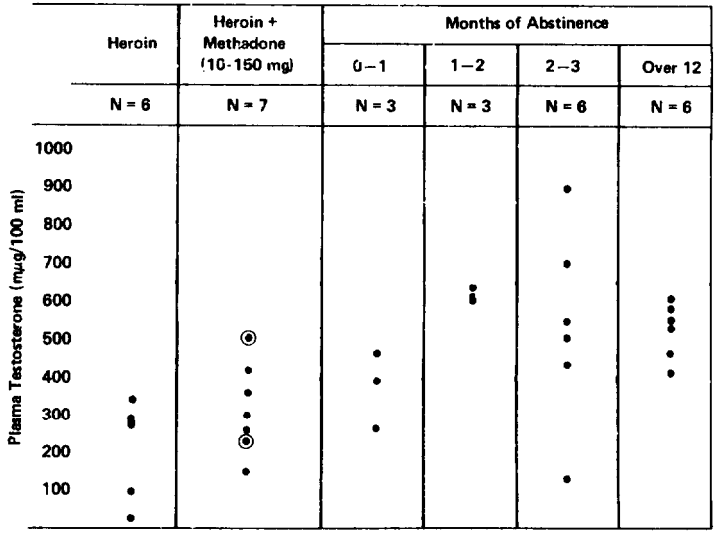
In order to reconfirm the suppressive effects of chronic heroin use on testosterone levels, and to examine the effects of varying periods of abstinence, 4 groups were studied. The chronic heroin group (6 subjects) had plasma testosterone levels determined on the morning of their admission to a residential treatment center. The recent abstinence group (12 subjects) was studied during the course of their residential treatment program (1 to 3 months). The long-term abstinence group consisted of "alumni" members of the treatment program who had totally abstained from heroin use for over 12 months. A fourth group of 7 subjects was studied during the course of their methadone maintenance program at a clinical facility on Kowloon.

All subjects had initiated heroin use by smoking and most subsequently began to "chase the dragon," Twelve subjects reported total abstinence from heroin within the past 3 months after 2 to 20 years of chronic heroin use. Seven of these recently abstinent subjects had routinely used the drug intravenously.

Three of the 7 subjects on methadone maintenance had either used or were currently using intravenous heroin. Six subjects had been abstinent for over one year, and 2 reported a history of intravenous heroin. Thus, in all 4 groups, in one-third or more of the subjects intravenous heroin was the preferred mode of administration.

Arrangements for the study were made possible through the assistance and cooperation of the Society for the Aid and Rehabilitation of Drug Addicts, a nonprofit organization with headquarters in Hong Kong. The study was carried out in three facilities operated by the Society: The Acute Admissions Center, Administrative Headquarters and Alumni Group Center on Hong Kong Island; the residential treatment center on the island of Shek Kwu Chau in the South China Sea; and the methadone maintenance clinic on the peninsula of Kowloon.

FIGURE 1



Plasma testosterone levels of heroin addicts during active heroin use, during combined heroin use and methadone administration, and following initiation of abstinence for periods of less than 1 month to over 12 months. Circled points in Col. 2 represent subjects who stated that they were not concurrently using heroin. All other subjects in this group report recurrent heroin use while on methadone maintenance therapy.

RESULTS

Plasma testosterone levels for each group of subjects are shown in figure 1. The 6 subjects sampled within 4 to 5 hr of acute use of heroin had testosterone values that were below the normal average for adult males observed in our laboratory (400 to 1,000 mμg/100 ml). There was, however, no correlation between the reported duration of heroin use or the reported dose employed and degree of suppression of plasma testosterone levels.

Comparable suppression of testosterone levels was found in 5 of 7 subjects maintained on methadone. These data are shown in column 2 of figure 1. Methadone dosage ranged between 10 and 150 mg per day. All but 2 of these subjects reported concurrent use of heroin.

One subject who reported using no heroin but received 60 mg of methadone per day had normal testosterone levels (506 mμg/l00 ml). However, another subject who used only 10 mg of methadone

per day had quite low serum testosterone values (132 mμg/100 ml). Because urine screening was carried out only occasionally for patients on methadone maintenance, it is difficult to ascertain if their reported use of abstinence from heroin was accurate.

Three subjects who abstained from heroin for less than 1 month (13 to 18 days) had either borderline or low serum testosterone levels (figure 1, column 3). The subject who had abstained for only 13 days had serum testosterone values that were consistent with the very low values observed for active heroin users. Three subjects who had abstained from heroin for approximately one month had normal testosterone levels (figure 1, column 4) and 5 of the 6 subjects who abstained from heroin use for 2 to 3 months also had normal plasma testosterone values (figure 1, column 5). The single exception, a 15-year-old male, had very low plasma testosterone values (118 mμg/100 ml). This subject was the youngest studied and he reported initiation of heroin use when he was 12 years of age. He began smoking heroin and after 4 months started "chasing the dragon." He was the only subject who initiated heroin use prior to the onset of puberty, and his very low plasma testosterone levels may reflect a persistent and severe impairment of sexual development.

Six subjects who abstained from heroin use for a period of 1 to 4 years had plasma testosterone levels that were within the normal range for adult males. These data are shown at the far right of figure 1, column 6.

DISCUSSION

Data obtained in this study are in agreement with previous findings that both heroin and methadone suppress plasma testosterone levels in male narcotic addicts (1, 11). Since polydrug abuse problems were not encountered in the patients studied in Hong Kong, it is likely that heroin per se has a direct suppressive effect on plasma testosterone. The mechanism of action of heroin suppression of plasma testosterone is not known. It is possible that heroin may inhibit secretion of gonadotrophins from the pituitary in humans since this phenomenon has been demonstrated in experimental animals (5). Martin and his associates (8) found that follicle-stimulating hormone and luteinizing hormone were decreased in a group of male patients studied during a cycle of methadone maintenance and withdrawal. These patients also reported a diminished sexual activity during the induction phase of

methadone maintenance but tolerance to this effect developed as methadone administration was continued (8).

Cicero and associates (2) found marked reduction in seminal vesicle and prostate gland weights of rat following implantation of morphine pellets. Associated with these changes was a significant decrease in seminal vesicle secretory activity. In more recent studies Cicero and associates (3) found no changes in seminal vesicle and prostate weight and function in hypophysectomized rats given morphine but maintained on human chorionic gonadotrophins (3). These findings converge to suggest that heroin may inhibit secretion of pituitary gonadotrophins and thereby decrease the level of plasma testosterone. It is also of interest that spontaneous penile erection and ejaculation has been observed in rat during abrupt morphine withdrawal following induction of physical dependence (13).

The role of plasma testosterone levels for regulation of sexual behavior and function in males is complex. In Hong Kong, common folklore reports that males often initiate heroin use with the expectancy that the drug will enhance their sexual desire and function. Clinical reports obtained from heroin addicts in the United States suggest that impairment of sexual function and desire is the usual concomitant of heroin use (14). However, the relationships between plasma testosterone levels and sexual potency are ambiguous, since low testosterone levels have not been found in impotent but otherwise healthy males (6).

The finding of normal testosterone values in subjects who had not used heroin for at least one month indicates that heroin suppression of plasma testosterone levels is of relatively short duration and that even protracted heroin use (e.g., up to 20 years) does not appear to inhibit the recovery of plasma testosterone following abstinence. The persistence of significant suppression of plasma testosterone in a single young adult male who initiated heroin use prior to or at the onset of puberty, suggests that chronic heroin administration at a critical age may cause long-lasting sexual impairment.

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CHAPTER 13

Biological Aspects of Cannabis Use

Costas Stefanis, M.D.

Cannabis research has flourished in recent years and publications dealing with the biological, psychological and sociocultural aspects of cannabis use have flooded the literature. Inspired by the public's concern over the worldwide cannabis epidemic that challenged traditional values and disregarded barriers of culture, sex, age, and class (52, 67), these studies yielded valuable information that largely contributed to revising official and lay attitudes towards the problem. Whereas in the past reports on cannabis use reflected only horror and rejection, the majority of recent papers refute old myths and project a more benevolent picture of this enigmatic plant. The tide has reversed to the point that laws are being passed to decriminalize its use and reports questioning its innocence are currently the least popular.

From 1970 we have been engaged in a multidisciplinary and long-term study of cannabis use. The first and major part of this study was performed in our Department in collaboration with Drs. M. Fink, R. Dornbush, and J. Volavka of the United States. Findings from this part of the study appeared in several papers (7, 8, 21, 23, 24, 55, 86, 87, 88, 89, 90, 91) and in a recently published monograph (84). The second part of the study, which is still in progress and for which the same previously studied experimental group (54) was used, is mainly directed towards the elucidation of biological mechanisms of cannabis action in man and involves a variety of approaches suitable for answering questions left open from our previous work. Part of the results from the histochemical investigation have already been reported elsewhere (85).

It is the purpose of this paper (a) to present a critical review of our previous and current work on cannabis with a particular reference to findings pertaining to the biological aspects of its use;

(b) to emphasize the fact that despite recent advances in cannabis research only a few of the vital questions regarding mechanisms of its action and implication of its chronic use have been answered; and (c) to urge further. investigation in order to avoid premature and unwarranted conclusions with serious social repercussions.

MATERIALS AND METHODS

Findings to be reported in this paper were obtained from a population of forty-seven chronic hashish users and forty control subjects. The users were selected on the basis of a number of strict criteria (among them maximum age of 58 years, no use of other addictive substances except for occasional or moderate use of alcohol, and a minimum duration of hashish smoking of ten years), and they came largely from refugee families from Asia Minor residing in a working class, low income, section of Athens. Controls were nonusers but cigarette smokers, matched to our users for age, refugee origin, upbringing, educational and socioeconomic characteristics.

The hashish data reported by the subjects are presented in table 1.

TABLE 1

Reported Hashish Data

	Starting Age	Years of Use	Times Per Day on Day of Smoking		Quantity in Gms on Day of Smoking		Abstinence Periods	
			Past Use	Current Use	Past Use	Current Use	Times	Total Duration in Months
Mean	17.61	23.10	4.5	2.32	7.48	3.13	1.21	10.06
S.D.	4.12	9.70	3.76	1.01	5.98	1.81	1.01	10.84

A variety of clinical, neurophysiological, psychological, psychophysiological, histochemical and biochemical methods were used. Whenever necessary, reference regarding methodology is given in the appropriate section of the text. The reader may also consult two of our previous publications (84, 85) for methods and procedures pertaining to this presentation.

FIRST PART OF THE STUDY

The first part of the study proceeded in three phases:

1. Identification of chronic cannabis population and its comparison by a variety of biological, behavioural, and social characteristics to the control sample;
2. Experimental assessment of the effects of various strengths of cannabis preparations; and
3. Assessment of possible withdrawal effects.

Comparison of Chronic Cannabis Users With a Control Sample

In an extensive medical examination associated with a diagnostic laboratory investigation, chronic cannabis users were found not to differ from nonusers with respect to incidence of any clinically defined physical disability. A higher incidence of enlarged liver was encountered in the group of users, but this correlated more closely to alcohol use rather than to cannabis consumption. No clinically evident toxic effects commonly identified with chronic alcoholism or opiate addiction were detected (8, 84). Moreover, resting electroencephalograms (EEGs), recorded from 46 of the 47 users and from 40 nonusers failed to reveal abnormalities that would distinguish users from nonusers. Normal, borderline, and abnormal EEG records were almost evenly distributed in the two groups (23, 84, 89). These results signifying absence of brain disfunction manifested in EEG are in agreement with some (14, 17, 73) but not all (11) previous reports. Measurements of the third ventricle size by echoencephalography (Echo-EG) in 14 users and 21 nonusers have shown an average width of 6.6 mm for the users' group and 6.3 mm for the nonusers' group, a difference not statistically significant. These results do not support Campbell et al.'s (10) pneumoencephalographic findings of ventricular dilatation.

Chronic cannabis users and nonusers could not be distinguished on the basis of their global IQs in both the WAIS and the RAVEN tests (84). However, as shown in table 2, significant differences in performance between the two groups were noted in a number of subtests in the WAIS test. The impaired performance in the Comprehension and Similarities subtests indicate possible defect in the verbal sphere, i.e., in verbal comprehension, expression memory, associative thinking, and verbal abstraction. The low score in the Digit Symbol Substitution subtests indicates possible defect in

TABLE 2

Statistically Significant Differences Between Hashish Users and Controls in W.A.I.S. Subtests

Subtests	Cannabis Users (N = 47) (Mean ± S.D.)		Controls N = 40 (Mean ± S.D.)		t	p
Information	7.49	2.58	8.46	2.51	1.76	0.10
Comprehension	8.53	2.67	10.05	2.38	2.79	0.01
Similarities	6.34	2.84	8.15	2.59	3.09	0.005
Digit symbol	6.49	2.01	7.39	2.11	2.01	0.05
Picture arrangement	6.57	3.05	7.77	3.10	1.79	0.10
Object assembly	6.38	2.72	7.38	2.46	1.79	0.10

visual-motor coordination and memorizing capacity. It is reported that cannabis consistently affects performance on this subtest during the postsmoking period. Performance in the Picture Arrangement test that measures primarily logical sequential thought was found to be inferior in the users' group. This difference however did not reach the level of statistical significance due to the high dispersion index of the results (S.D.=3.10). It is at present not clear whether the impairment manifested in the above subtests is a sign of permanent deterioration related to hashish long term use, or whether it is a transient. phenomenon due to persistence of an acute drug effect at the time of testing.

The issue of long term effects of cannabis use on mental health is still debated. In recent years an attempt has been made to systematize research in this area by well designed controlled studies on representative samples of population (73, 74). Although these studies yielded essentially negative results regarding an association between cannabis smoking and psychopathology, there are still reports in the literature (12, 50) indicating that such an association may exist which may not be revealed by small group assessment methods but only by clinical follow-up of individual cases. Different conclusions may be drawn by using traditional psychiatric clinical approach and structured psychiatric assessments and this is clearly reflected in the conclusions reached by the same author in two different studies (3, 48).

In our investigation the psychiatric assessment of the two groups included a psychiatric history and a mental status examination based on a structured format. Information from the psychiatric history revealed that 9 (19%) of the users had previous psychiatric

TABLE 3

Incidence of Psychiatric Disorder

Type of Disorder	Hashish Users (N = 47)		Controls (N = 40)		x^2	P
	No.	%	No.	%		
Personality disorder → Antisocial	5	10.63	0	—	4.51	<.05
Personality disorder → Other	7	14.89	3	7.5	1.16	N.S.
Neurosis	3	6.38	3	7.5	0.04	N.S.
Depressive illness	0	—	1	2.5	—	N.S.
Unspecified schizophrenic disorder	3	6.38	0	—	—	N.S.
Total	18	38.28	7	17.50	4.56	<.05

treatment, compared with 2 (5%) of the controls. The results concerning incidence of psychopathology are shown in table 3. No subject displayed signs or symptoms of an organic psychosis. Three users were diagnosed as psychotics of schizophrenic type. Two of these had had prior psychiatric and outpatient treatment. A positive family history was also recorded for two of the three. The diagnosis of personality disorder was defined in 25% of the users and in 7% of the controls. The antisocial type of personality disorder was the main diagnostic subcategory that distinguished users from controls.

In comparing incidence of mental abnormalities with those aspects (7) discriminating users from controls it was found that more mentally abnormal users were sentenced for offences not related to cannabis (83%) than were mentally normal users (48%). This finding is consistent with prevalence in our group of antisocial type personality disorders.

It is clear from our results that no specific psychotic disability is related to cannabis use. The three users with psychotic symptomatology were indistinguishable from typical schizophrenia cases, and there were no clinical features suggesting their mental state was related to drug-induced brain damage (174). The higher incidence of personality disorders in our population of users has also been noted in another recent controlled study (30) but needs to be further investigated. It is most likely that it is more closely associated with sociocultural and legal aspects of cannabis smoking in a country in which cannabis use is proscribed, severely punished,

and largely alien to its cultural tradition (88). It is thus reasonable to assume that psychopathic personalities are more prone to dissociate themselves from the prevailing sociocultural value system by smoking illicit cannabis, rather than that the pharmacological action of cannabis is instrumental in modifying personality structure. However, conclusive evidence for or against this assumption can only be derived from well designed prospective studies.

Relevant to psychopathology is the question of the so-called "amotivational" syndrome (60), which was claimed to be associated with prolonged cannabis use (50). Several recent studies on subchronic users, mainly derived from the student population of North America (61), as well as on chronic users in Jamaica (73) and Costa Rica (74) refuted this claim. In fact motivational rather than amotivational properties were ascribed by some (15, 73) to cannabis, in such areas as work efficiency and socially productive activity. In our study no clear-cut evidence was obtained to support an association of prolonged hashish use and an "amotivational" syndrome. Indirect evidence may only derive from employment and work records of the two groups, which show that significantly more users were unemployed when seen and significantly more nonusers were skilled workers (7, 84). Such differences may not be related to hashish smoking but either to the higher incidence of psychopathy in the group of users or to psychosocial factors linked to cultural and legal aspects of cannabis use in Greece (88). Several of our subjects reported that hashish improved their work performance. Objective measurements are needed to confirm such subjective and expectedly biased information deriving from subjects prone to rationalizing and in great need of social acceptance. However, if this is true, one should not hastily ascribe to cannabis motivational properties before the alternative interpretation of a state of dependence is adequately explored. In line with Wikler's thinking (101), once a drug-induced state-dependence is established, inclination to work may first require satisfaction of drug-dependency needs. Also to be considered in evaluating drug effects on motivation is a possible differential effect depending on the type of work and the level of performance complexity associated with it. As noted by Soueif (79), the lower the nondrug level of proficiency on tests of cognitive and psychomotor performance, the smaller the size of functional deficit associated with drug usage.

In summarising results obtained by comparing users and nonusers with respect to their physical, mental, and social functioning we may conclude that users are essentially indistinguishable from nonusers for the investigated parameters. Our results in particular

failed to provide support for claims that an organic brain syndrome may develop following prolonged cannabis use. Similar conclusions derive from the Jamaican (7, 13) and Costa Rican (13, 74) studies. It should, however, be emphasized that these two studies as well as ours (a) were all retrospective and were based on reported and not on controlled information; (b) were based on small samples, the representativeness of which was not documented; (c) were subject to sampling bias, since only subjects who could be reached and were willing to participate were included in the study while others possibly not equally resistant to cannabis' ill-effects might have been missed; (d) were limited by their investigative instrumentation which may not be capable of revealing more than overt and gross physical and mental pathology at a group level.

Acute Experiments

The acute experiments were designed to measure degree of tolerance by long term users to various cannabis preparations and to determine if in long term cannabis users the immediate subjective, psychophysiological, and psychological test responses are altered compared to the immediate responses observed in casual or short term cannabis users. Twenty users from our original group volunteered for the experiments in which various strengths of cannabis (U.S. marihuana with THC-Δ-9 content of 78 mg, low potency hashish with THC-Δ-9 content of 90 mg, high potency hashish with THC-Δ-9 content of 180 mg and pure THC-Δ-9 of 100 mg) and placebo were inhaled and assessed in terms of their psychological, behavioural, EEG and psychophysiological effects (21, 23, 24, 55, 84, 89).

Regarding the question of tolerance, it was shown in these experiments that our subjects tolerated in a single smoking session and without any adverse reactions or discomfort cannabis preparations of a very high THC-Δ-9 potency (up to 180 mg). Considering the fact (20, 52) that the subjective feeling of "high" as well as a variety of autonomic and adverse effects are produced in occasional users by preparations equivalent in strength to 20 mg or less of THC-Δ-9, the amount inhaled by our subjects should be evaluated as an indication of tolerance (84).

Subjective responses to acute cannabis inhalation in our subjects were no different from those reported by less experienced users (20). Although set and setting were noted to contribute to their

subjective responses, all participants in the acute experiments easily differentiated active preparations from placebo.

Psychological tests were adversely affected by THC and in a way similar to that observed in naive subjects or short term users (21, 84, 100). The adverse effects on mental functioning were short-lived and died away 70 minutes after the cannabis inhalation.

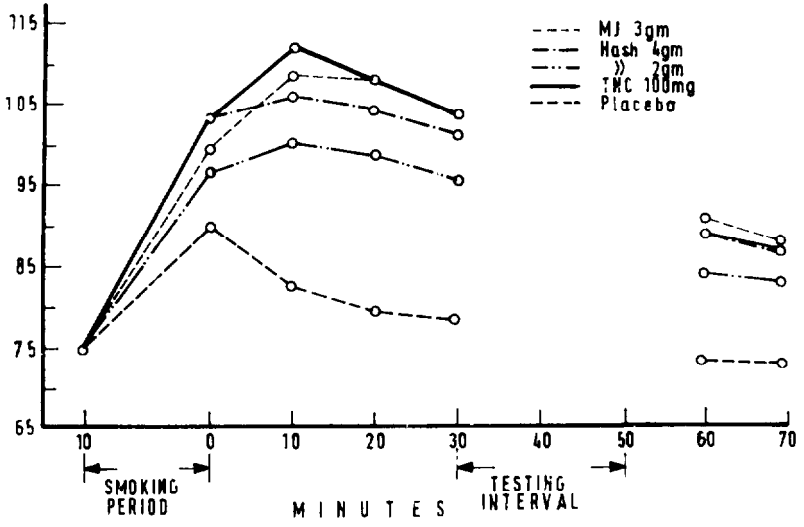
The EEG recorded at fixed time intervals before and after smoking and analysed quantitatively by hierarchical multiple regression analysis was affected by all active but not by placebo preparations. An increase in alpha activity, a decrease in alpha mean frequency, and a decrease in fast beta activity was observed (21, 23, 84). The degree and the duration of cannabis effects on the EEG parallelled the THCΔ-9 potency and were inversely related to the cannabidiol (CBD) content of the smoked preparations. These results are not essentially different from those obtained from naive or occasional users (20,84) and they may indicate a sedative central action of cannabis in both long term and short term users.

Visual evoked responses (VER) were only slightly changed by cannabis inhalation. The change was confined to an increase in the amplitude of the late VER component. Similar findings were obtained in less experienced users by Tinklenberg, et al. (95) and Tassinari et al. (94) and tend to support evidence from animal experiments indicating cerebral association areas and their related subcortical structures as the principal sites of THC-Δ-9 action (9, 18). Since the increased late negative VER component has been related to excitatory postsynaptic potentials, a stimulant action of THC-Δ-9 on cortical association areas may be postulated.

Of all the psychophysiological parameters, pulse rate of our chronic users was found to be most closely and consistently affected by acute cannabis inhalation (55, 84). As shown in figure 1, pulse rate significantly increased following administration of all four active preparations at all time periods tested. Although a dose-response relationship seems to exist, it is to be noted that hashish inhalation produced pulse rate changes less pronounced than expected on the basis of the preparation's potency in THC-Δ-9 content. Similar dissociation between potency and response was found in the EEG and may be attributed to an antagonistic interference of CBD to the THC-Δ-9 effect as already suggested by Karniol et al. (44). In addition to pulse rate, other psychophysiological parameters were affected. Finger Plethysmography showed a decrease of blood flow 20-30 minutes after smoking, pupil size measurements showed slight pupil dilation lasting up to 70 minutes

FIGURE 1

EFFECTS OF CANNABIS ON HEART RATE [N=20]
(FROM LIAKOS ET AL: 1976)



after smoking, and "basal" skin conductance measurements showed a significant decrease after smoking (55, 84).

In summarising our results from the acute experiments we may conclude that acute cannabis inhalation by chronic users, despite their tolerance to high doses of the active material, evokes responses which are not essentially different from those evoked by low doses in casual smokers. The kind of responses indicate that in man both a sympathetic arousal (manifested by changes in pulse rate, pupil size and FPV) and a sedative effect (manifested by the reported feelings of relaxation and changes in EEG and conductance) are associated with the cannabis pharmacological action.

Withdrawal Studies

Although old reports in the literature indicated that tolerance and physical dependence may develop in man following prolonged cannabis use (102), most researchers until recently held the view, explicitly voiced by the National Commission on Marihuana and

Drug Abuse (67), that cannabis does not lead to physical dependence. The issue resurged and is still in the center of current cannabis research following publications documenting cannabis dependence in animals (45) and either supporting (4, 42, 43) or refuting (2, 24, 63, 72) such a dependence in man. In our study, 16 chronic hashish smokers from the original pool of experimental subjects were used. They all volunteered to be hospitalized for six consecutive days during which half of them smoked U.S. marihuana *ad lib* twice a day during the first three days and were subsequently switched to placebo for the following three days (order I) while the other half followed the reverse order (order II), i.e., they smoked placebo during the first three-day period and active substance during the second three-day period. During the experiment subjects were assessed on a double blind basis and at fixed post-smoking periods by a variety of clinical, psychological, psychophysiological and behavioural measures (84, 9 1).

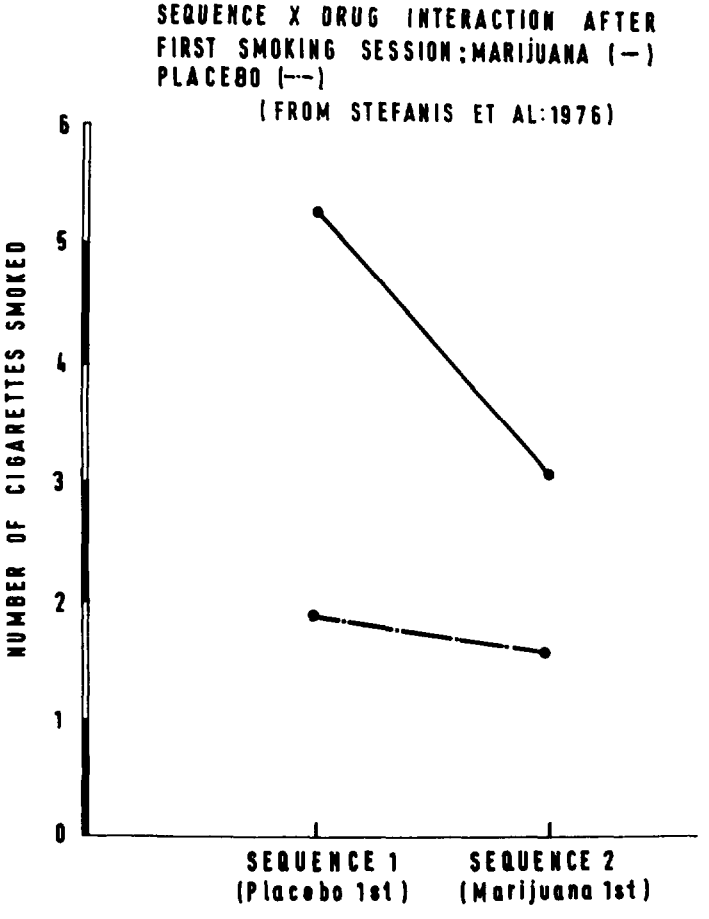
Psychological testing provided no evidence for tolerance or withdrawal (84). What could only be inferred from these studies was that practice effect in the tests, although not abolished by the consumption of marihuana, is lower than that observed under placebo conditions.

Medical laboratory and behavioural assessments all failed to provide definite evidence in support of an abstinence syndrome (84). Subjects were scored higher in their adjustment in the ward while smoking marihuana irrespective of the order of smoking. Those who started with the sequence placebo-marihuana were more irritable and less cooperative while on placebo than those who started with the reverse order. It is to be noted that despite the lack of objectively assessed differences between marihuana and placebo periods, the "blind" personnel in the ward could easily tell which of the subjects was on or off marihuana.

In most of the psychophysiological measurements including quantitative EEG analysis, only small and insignificant differences were found between drug and placebo periods (84, 91). Differences were only found in temperature, blood pressure, and finger plethysmography. Since these differences were observed two hours after smoking and they were not seen immediately after smoking, they may suggest a mild abstinence syndrome.

A rather interesting finding derived from measuring the ad libitum amounts of marihuana consumed by the subjects. As shown in figure 2, they smoked more marihuana cigarettes in order I (placebo-marihuana) than in order II (marihuana-placebo), and in

FIGURE 2



each case they smoked more on the first smoking each day than on the second. They also smoked increasingly smaller amounts of marihuana in the three-day sequence of the drug period (84, 91) whether this preceded or followed the placebo period. This might indicate development of a "reverse tolerance" with regard to the subjective effects of cannabis. The opposite was noted by Mendelson et al. (63) in their study in which experimental subjects were less experienced, however, and less heavy users. Moreover their experimental design was different from ours.

The observation that our subjects smoked more marihuana cigarettes the first day of testing when the marihuana smoking period followed the placebo period calls for some further comment.

It has been reported (53) that the half life of THCΔ-9 is 28 hours in the blood of chronic users and 57 hours in the blood of nonusers and that the metabolism of THCΔ-9 is increased with repeated administration. The increased consumption of marihuana following the placebo period could thus be interpreted as representing the need of the organism to replenish the tissue with the active material that was depleted during the 3-day abstinence period. The alternative, but not basically different, explanation would be that as with other addictive substances, materials ordinarily blocked by THCΔ-9 accumulate in its absence and by producing withdrawal dysphoria motivate the user to rapidly replenish the tissue losses and reconstitute the cellular homeostasis (84).

In closing this review of our withdrawal study we may conclude that under the described experimental conditions no clear-cut evidence of an abstinence syndrome has been obtained. However, in view of the described suggestive findings the possibility of such a syndrome cannot be excluded, particularly in areas not explored or inadequately explored in our study. Withdrawal symptoms recently obtained by Jones et al. (43) under conditions of long and continuous cannabis ingestion suggest, as already proposed by Wikler (101), that more rigorous criteria are needed in future research, to define withdrawal states.

SECOND PART OF THE STUDY

Histochemical and Electron-Microscopic Investigation of Blood Cells and Sperm

This study was instigated by our findings in the past few years indicating an interaction of psychoactive drugs with metabolic processes in the cell nucleus affecting its synthetic capacity. [1]Such a study is further justified by recent reports in the literature (37, 40, 65, 83) indicating that cannabis, and THCΔ-9 in particular, interferes with cellular metabolism in animals and affects ribonucleic acid (RNA) and protein synthesis. Such effects are both interesting and alarming since they may not only provide useful information regarding the drug's mode of action but they may also be potentially harmful to physical and/or mental health. A rigorous

[1]For review see "Short and long term effects of neuroleptics in relation to their cellular mechanism of action," C.N. Stefanis and M.S. Issidorides, in *Perspectives in Psychopharmacology,* ed., F. Vartanian. Pergamon Press, 1977. In press.

scrutiny of THC interaction with human cell systems under in vivo conditions is therefore badly needed.

In our investigation easily accessible tissues were studied, i.e., blood cells and sperm. The subjects who were used in these experiments (34 cannabis users and 18 nonusers) were recruited from the same groups that were previously used for the first part of our study.

Nuclear Morphology

Using the routine May-Grünwald-Giemsa staining method, smears were made from peripheral capillary blood for the study of nuclear morphology of neutrophils. It was found that 21 out of 34 chronic hashish users (i.e., 61 percent) displayed in their neutrophils drumstick-like appendages similar to those normally found only in females and in about 1-7 percent of their granulocyte population (5). In males they are rarely encountered (in only about 1 out of 500 males and in less than 1 percent of their neutrophil population). It is to be noted that in about one fifth of the users with "drumsticks" in their neutrophils sessile nodules were also observed. These findings clearly indicate that chromatin is altered under the effect of prolonged cannabis use.

Histochemistry of the Nucleus

Subsequent to the above morphological findings indicating an interaction of cannabis with chromatin, an histochemical investigation was carried out mainly directed to chromosomal proteins. Basic proteins mainly consist of histones (arginine and lysine-rich) which are known to maintain chromatin structure and repress gene expression (81). Non-histone acidic proteins, on the other hand, are involved in selective template activity, acting mainly as activators but in certain conditions as repressors of chromatin transcription (99).

Histochemistry of Basic and Acidic Nuclear Proteins

By using the PTAH anionic metachromatic stain (see 85), the basic proteins of leucocytes of 34 users and 18 control subjects

were studied. It was found that all cells of all control subjects displayed the expected metachromatic reaction indicative of a high concentration of basic groups. Conversely in all cells of all users the reagent failed to bind to the nuclei, indicating that binding sites are not available. This may not necessarily signify absence of basic proteins but their binding to DNA phosphates.

By using the carbocyanin cationic reagent (28) which stains selectively nuclear acidic phosphoproteins it was found that while the leucocyte nuclei in the control group did not show the dark blue staining indicative of phosphoproteins the leucocyte nuclei in the user group reacted intensely to the stain. This finding, in addition to providing evidence of high concentration of acidic proteins in the cell nuclei of the users, may partly explain the nonbinding of the anionic PTAH reagent to some of the histones since their reactive (positive) groups could be neutralized by the phosphoproteins (103).

Electron Microscopy

In view of the histochemical findings an electron microscopic (EM) study was carried out by using the EM adaptation (58) of the Black and Ansley ammoniacal silver reaction technique for histones (6). With this technique the integrity of the deoxyribonucleoprotein (DNP) complex is preserved and a parallel light microscope (LM) study of the thick Epon section of the leucocyte pellet is feasible. In the latter case arginine-rich histones appear in the LM brownish black and the lysine-rich histones yellow. Blood cells and spermatozoa were studied.

Blood Cell Studies

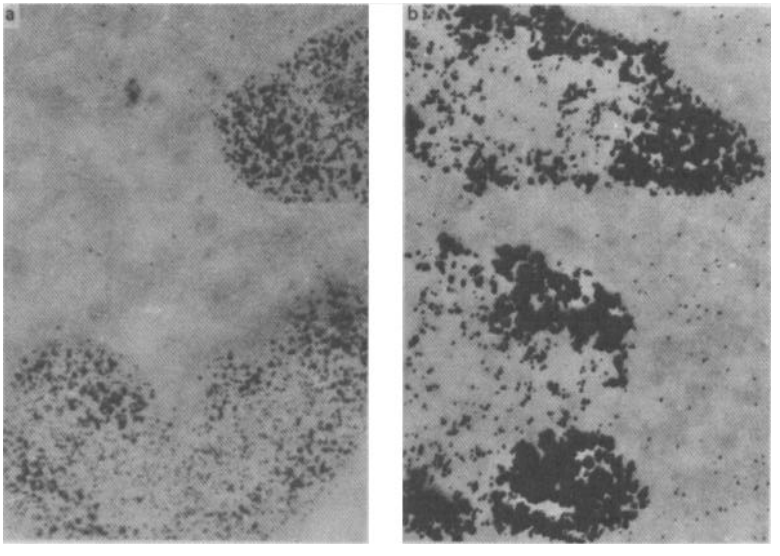
In the LM study of the thick sections of leucocyte pellets the following observations were made. In the group of controls the nuclei of about 55 percent of small lymphocytes were stained black, while the rest of lymphocytes were stained brownish. The remaining population of leucocytes (neutrophils and monocytes) were stained yellow. In the group of chronic users the pattern of histone reactivity differed from that of controls in all subjects and in all cells except for the monocytes. The nuclei of 57 percent of the lymphocytes appeared orange-brown with large black masses while the nuclei of the remaining lymphocytes appeared yellow.

These results indicate a lower concentration of arginine-rich histones in the lymphocytes of users. By contrast to lymphocytes the nuclei of neutrophils in the same group of users appeared brown, an indication of arginine-rich histone preponderance. We would thus summarize these results by saying that cannabis affects the nucleohistones differentially so that arginine-rich histones decrease in lymphocytes and increase in neutrophils.

This differential effect is more clearly shown in studying in the EM thin sections of the same blocks used for the LM study. The ammoniacal silver reaction method (58), which was used for the EM study is based on the specific interaction of silver with reactive centers in the arginine content and it can thus be used for revealing selectively arginine-rich histones (H3 and H4) and protamines.

In our study a consistently more intense reaction was found in neutrophil nuclei of users compared to controls. This is illustrated in figure 3. Conversely, a distinctly weaker reaction was noted in the heterochromatin of roughly half of the lymphocytes of the chronic users.

FIGURE 3



Electron micrographs of neutrophil nuclei from control subject (a) and user (b). Ammoniacal silver reaction (From Stefanis and Issidorides 1976)

Sperm Studies

The cannabis effect on arginine-rich proteins was more strikingly shown on spermatozoa. During maturation of the sperm in the testis spermatozoa become increasingly elongated in shape (56) and replace their somatic histones with arginine-rich protamines (26). It is their content in this protein that renders the spermatozoa heads a very useful cell system to study drug effects on arginine-rich nucleoproteins. The results we obtained by using four controls and four cannabis users have shown that the spermatozoan nuclei of all four users although not different in shape compared to controls give a spotty reaction to arginine, i.e., they have an appearance indicating that replacement of somatic histones by protamines has been impaired. This is illustrated in figure 4, which shows that spermatozoa from controls give a dense black reaction on the entire nuclear area, indicative of high arginine content, while spermatozoa from users give a spotty punctate reaction with particulate precipitates and unreactive areas in between (85).

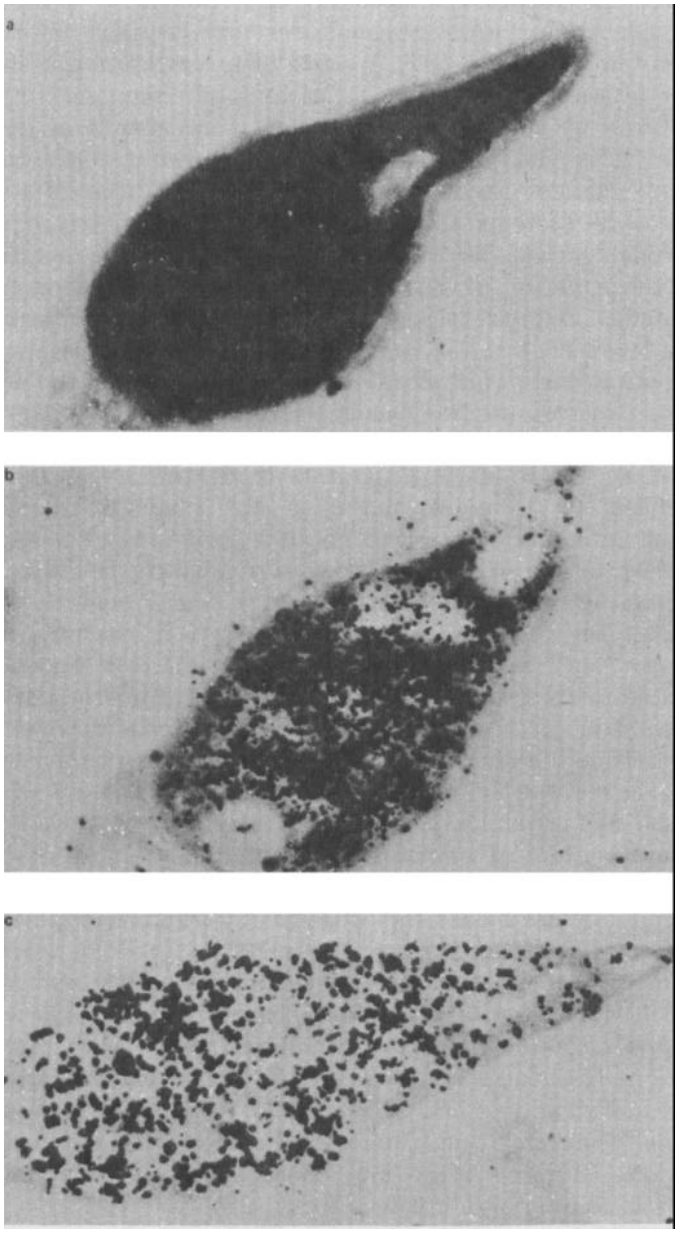
Membrane Histochemistry

The lipophylic properties of THC are well established in animal work (25). It is generally agreed that the affinity of THC molecules for membrane lipids is an important factor accounting for its biological action (7). In order to study the effect of cannabis on membrane lipids in human users we applied the LFB-PAS technique (47) after which phospholipids stain blue and glycolipids stain red.

Thirty-four users and 18 controls were investigated. The results have shown that the two groups differ substantially in that the ratio of phospholipids to glycolipids is altered in the neutrophils of users. This change in ratio was found to be due to a loss of phospholipids from the membrane of the cortical cytoplasm and an increase in glycolipids in the cytoplasm. Such an action of cannabis on the membrane structural constituents is to be considered in evaluating its clinical effects.

In summary, results obtained from the morphological histochemical investigation of blood cells and sperm clearly demonstrate that cannabis use in man leads to changes in nuclear metabolism, indicative of an alteration in the state of chromatin. In our previous publication (85) several suggestions were made regarding the mechanism by which these changes are brought about. The assumption of a direct inhibitory action of cannabis on the

FIGURE 4



Electron micrographs of spermatozoa from control subject (a) and two users (b and c). Ammoniacal silver reaction (From Stefanis and Issidorides 1976)

template either by interrelating with nucleic acids or by affecting nucleohistone metabolism would be consistent with observations of other investigators on tissue cultures that cannabis inhibits RNA and protein synthesis (37, 40, 65, 83). However, the alternative interpretation of an indirect action of cannabis on nuclear metabolism by affecting hormonal levels has also to be considered in view of the fact that hormones are known to be required for inducing changes leading to maturation and differentiation of a variety of all systems. Characteristically testosterone is required for protamine synthesis during sperm maturation (82), a fact calling for particular attention in view of the current controversy on the effect of cannabis long-term use on gonadal function and testosterone plasma levels (13, 31, 51, 61, 75). Our findings on membrane lipid composition changes in chronic users may also raise the possibility that the observed nuclear changes may be indirectly triggered by a primary cannabis effect on the cell membrane.

What seems to be of significance is that regardless of the mechanism of cannabis action in the nucleus, the necessary cell-drug interaction to bring about the observed changes has to take place at the level of the tissue of origin of the affected cells and while they are still at their early stage of differentiation.

In fact the nuclear appendages observed in the neutrophils of users can only be formed in the bone marrow since they are associated with the reconstitution of the chromatin immediately after mitotic division (5). Similarly, decrease in the arginine-rich protamine in the sperm of users can only be explained by a drug action during the spermatid stage, when replacement of somatic histones by protamines is taking place. Finally, the observed differential effect of cannabis on the arginine content of the blood cells' nuclei (increase in neutrophils and decrease in roughly half of the lymphocytes) speaks for drug effect during haemopoiesis in the bone marrow.

We may now discuss our histochemical findings with regard to their functional significance and to the individual's physical health. The appendages in males are usually associated with pathological conditions (5) but their presence may not be accompanied by any known abnormality (77). This is also true for the acidic phosphoproteins. They are found increased in neoplastic and regenerative conditions (80), but they may merely indicate induction of the chromatin to altered template activity (98).

The fact that in our cases the increase of phosphoproteins paralleled a decreased reactivity of basic groups signifying a condensation of the nucleus may indicate that phosphoproteins are

increased in order to compensate for a primary repressing effect of cannabis on the template. If so, this would be consistent with the finding that Δ-9-THC added in tissue culture results in condensation of the nucleus (37, 38); it would further imply that prolonged cannabis use may result in the development of compensatory mechanisms to counteract functional repercussions arising from a primary repressing effect on nucleohistones or from any other drug effect deranging cellular homeostatic state. This would be consistent with our essentially negative results from the clinical and diagnostically orientated laboratory investigation of our group of users. In fact, despite the histochemical findings in their blood cells no overt hematological abnormality was detected. Similarly, despite the low protamine content the sperm head's species specific shape was not affected signifying normal condensation and unimpaired reproductive capacity (57).

Lack of positive clinical findings should not, though, mislead us to disregard the potential functional significance of changes in such cell constituents as nucleohistones which are mainly responsible for regulating gene expression and template activity (41). Compensatory mechanisms may develop in some cell systems and not in others, and even when such compensatory mechanisms are established they may still steal away part of the organism's initial functional capacity, rendering it more liable to internal and external stressors.

Biochemical Investigation of Cannabis Acute Effects on Chronic Users and Controls

It is known that drugs causing euphoria and stimulatory effects in man (opiates, amphetamine, ethanol) do affect central catecholaminergic, serotonergic and acetylcholinergic synaptic transmission by a variety of mechanisms. It would thus be expected that cannabis and Delta-9-tetrahydrocannabinol (THC) in particular would affect central biogenic amine activity. Several studies in this area conducted mainly in animals yielded results which are far from clarifying the mode of THC action that brings about the well-known central and peripheral effects. Ho et al. (32) reported a biphasic effect of THC on biogenic amines: low doses caused an increase in noradrenaline (NA) with a concomitant decrease in serotonin (5-HT), while high doses caused the reverse effect.

Schildkraut and Efron found that THC decreased the retention of ^{3}H-THC injected intracisternally and increased the O-methylated

and deaminated metabolites of NA (76), while others found an attenuation of the disappearance of radioactive NA from rat brain (97), i.e., a slowdown of the turnover of the injected amine. Presynaptically, THC was found to inhibit the depletion of 5-HT by reserpine while the NA depletion was not affected (22). In synaptosomal studies, THC was shown to inhibit the uptake of 5-HT (78). Another group has reported an inhibition of the dopamine uptake and a small release of dopamine by THC (36). By fluorescence methods it was shown in rats that administration of cannabis sublimate increases the NA content of the terminal axonal varicosities of the hypothalamus (16). In its presynaptic actions, THC given chronically caused an induction in tyrosine hydroxylase, while tryptophan hydroxylase remained unaffected (33). Daily injections of 20 mg/kg THC in rats, a rather high dose, after seven days caused a decrease in serum dopamine-ß-hydroxylase (DBH), while in rats subjected daily to immobilization stress, THC potentiated the stress-induced increase in the enzyme activity (69).

The effect of THC on brain acetylcholine appears only at high doses. The drug causes an elevation of ACH content and a reduction of its utilization (19). In this sense, THC acts like a sedative.

It has been proposed that THC acts by changing the balance at the antagonistic dopaminergic-acetytcholinergic system in the striatum by reducing dopamine transmission (27), although the effects of the drug on dopaminergic system are not established. It could be expected that THC generally acts on the mechanisms of amine depletion, releasing them from their storage. This has been shown for 5-HT (34): THC causes a shift of 5-HT from the particulate fraction to the supernatant, that is from the bound to the free form. If THC releases 5-HT and at the same time has a slowdown effect on the turnover of NA (32), then, depending on the predrug state, the balance between NA and 5-HT could be affected and the overall action of the drug could be either depressant or antidepressant.

Yet, all the above findings from animal experiments, however informative they may be, cannot be extrapolated and used to explain the experimental responses of man to cannabis. Since studies on the effects of cannabis smoking on biogenic amine metabolism in man are scarce (35) and fragmentary, our group has recently attempted to systematically investigate biogenic amines in chronic users and to correlate their changes with changes in a variety of other clinical, behavioral and biological parameters. Work in this area is still in progress, and only preliminary findings

obtained by dopamine-b-hydroxylase (DbH) and cyclic AMP determinations will be presented.

Serum DbH Studies

Dopamine-b-hydroxylase is an enzyme that is localized in noradrenergic neurons and is responsible for the final step in NA biosynthesis by converting dopamine to norepinephrine (1). It is thus a logical target of cannabis investigation, since it may serve as an index of the drug's effect on the sympathetic system and its activity can be linked to noradrenergic activation of reward centers in the lateral hypothalamus.

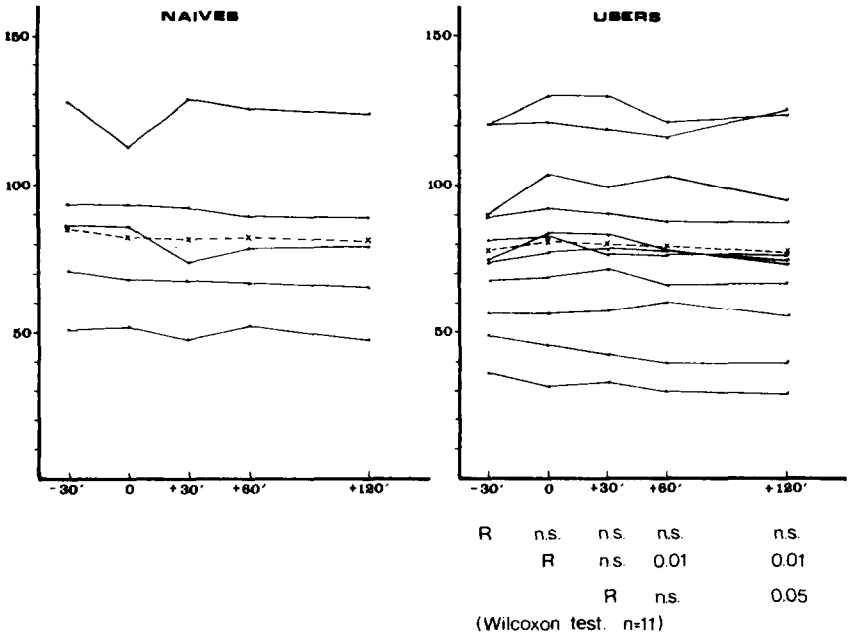
Serum DbH activity was determined at fixed time intervals before and after cannabis smoking in 11 chronic users and 5 naive subjects. In their single smoking experiment users consumed an amount, of cannabis oil equivalent to approximately 120 mg THC-Δ-9 while naives consumed less than l/5 of the same material. The results obtained by this preliminary study are shown in figure 5. Despite the small number of subjects and the wide dispersion of individual values, a progressive decrease of DbH activity is clear in both groups after smoking. In the group of users the decrease has reached levels of statistical significance at the 60 and 120 minutes post-smoking testing intervals. These results indicate that THC exerts a stress-relieving sedative effect on the sympathetic system which is contrasted with its immediate stimulant effect on pulse rate (55, 84). Similar effects on DbH have been observed with antipsychotic drugs (59) and are consistent with experimental findings (32) indicating that by slowing down the exocytosis process THC slows the turnover of NA and increases slightly its concentration in brain tissue.

Plasma Nucleotides Studies

Closely related to biogenic amine investigation and to our histochemical findings on nucleoproteins (85) is our study on the cannabis effect on the cyclic adenosine 3', 5'-monophosphate (CAMP) levels in the plasma of chronic users. It is known that levels of CAMP are affected by catecholamines such as NA and dopamine as well as by 5-HT, Ach and prostaglandins. It is also known that dibutyryl CAMP increases the levels of a variety of enzymes including those which are involved in metabolic pathways of

FIGURE 5

SERUM DOPAMINE-β-HYDROXYLASE



neurotransmitter synthesis (46). Moreover, cAMP levels in animal brain homogenates were found to be affected by psychotropic drugs which interfere with either adenylate cyclase or phosphodiasterase activity (29, 39, 49, 54, 70). In man, urine (68) and plasma (93) cAMP levels were found to vary with mood states in affective disorders (68). Plasma cAMP levels were also found to be decreased following treatment with antipsychotic drugs (92).

With respect to cannabis effects in nucleotides, information derives so far only from animal and tissue culture experiments. Golby and Kleinsmith (see 34) studied the effect of THC on brain levels of cAMP in mice. They found that THC-Δ-9 in low doses caused a significant increase whereas high doses caused a definite decrease of cAMP concentrations. This diphasic effect was correlated with changes in biogenic amine concentrations. Askew and Ho (see 34) failed to reveal a significant effect of THC-Δ-9 on brain nucleotide levels in the rat. A definite elevation of cAMP was only found by these authors in response to THC-Δ-8 administration.

Huot (37) in neuroblastoma cultures has noticed a significant increase in cAMP due to stimulation of adenylate cyclase. This

increase paralleled an inhibitory effect on ATPase activity. It was postulated that a THC stimulating action on adenylate cyclase activity may be involved in the cannabis psychodysleptic effects in man.

By using the protein-binding assay method of Tovey et al. (96), cAMP levels were investigated in the same material (11 chronic uses and 5 naives) and under the same experimental conditions as for the DbH study. The results which were obtained by this preliminary investigation have shown that there is a slight and slowly progressive rise of cAMP levels following hashish smoking by subjects of both groups (users and nonusers). This rise in the group of users reached statistical significance at the 30 minute post-smoking interval. The results indicate that the effect of cannabis on cAMP plasma levels simulate the effects that were observed in depressed patients treated with tricyclic compounds (93). Whether this effect may be due to phosphodiesterase inhibition or to adenylate cyclase stimulation is a question that needs to be further investigated in conjunction with determinations of biogenic amine conditions in body fluids.

SUMMARY

In this paper the results of a multidisciplinary long term and controlled study on chronic cannabis use are critically reviewed. The first part of the study consisted of: (a) standardization of methods and identification of the experimental sample of chronic cannabis users and matched controls; (b) comparison of the two groups on a number of variables following administration of a battery of medical, psychiatric, neurophysiologic, and psychologic tests; (c) acute cannabis inhalation experiments during which the effect of cannabis preparations of various strengths and of THC-delta-9 were studied in relation to behavioral, psychologic, neurophysiologic, and psychophysiologic responses; (d) identification of possible withdrawal symptoms during a 3-day abstinence period and reintroduction of hashish use.

The second part of the study consisted of: (a) a controlled histochemical and electron-microscopic investigation of blood cells and sperm, aimed at revealing changes produced by cannabis at the molecular level, particularly in the cell-nuclear area; (b) a biochemical investigation of changes in biogenic amines and substances related to their metabolism and function during cannabis presmoking and postsmoking periods.

Our findings from the first part of the study failed to distinguish users from nonusers on most of the investigated parameters. However, they provided useful information on a variety of controversial issues and revealed methodological limitations which should guide future research. Our findings from the second part of the study, although still preliminary, clearly indicate that cannabis use affects cell-nuclear metabolism and produces changes on the molecular level potentially significant for man's biologic functioning. Furthermore findings from this part of this study indicated that cannabis' acute effects in man are correlated with changes in metabolism directly related to biogenic amine biosynthesis and function. It is concluded that despite advances in recent years cannabis research has still a long way to go before providing the definitive answers to the very important questions arising from its habitual use by man.

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CHAPTER 14

Drug Dependence Studies in Laboratory Animals

Tomoji Yanagita, M.D.

Drug dependence studies in laboratory animals are usually conducted for such purposes as: (1) analysis of dependence-producing properties of a drug (dependence potential); (2) evaluation of the possibility that a drug is likely to be abused by man (abuse liability); (3) prediction of the possible harm that might be produced by abuse of a drug; and (4) studies on dependence-producing mechanisms. In this paper the progress related to all of the above problems with the exception of the last will be discussed.

DEPENDENCE-PRODUCING PROPERTIES

The dependence-producing properties of a drug can be divided into psychological and physical aspects.

Psychological Dependence

In laboratory animals the psychological dependence-producing property of a drug can be studied by observing their drug-seeking and drug-taking behaviors when the drug is made available to them (1, 11, 14). Behaviorally this effect of a drug will be called its reinforcing effect (8). Most of the principal drugs of abuse in man, except hallucinogens, were found to possess this reinforcing effect in animals as studied by self-administration techniques (1, 8, 18).

Table 1 summarizes the results obtained by continuous self-administration experiments with various types of drug in rhesus monkeys. The monkeys were allowed to self-administer drugs by pressing a lever switch around the clock for several weeks without time or dose limitations. The animals self-administered these drugs at high daily dose levels and manifested overt signs of drug effects (1, 15, 16, 18). With such drugs as morphine, codeine, demerol, pentazocine, pentobarbital, and alcohol, a gradual increase in self-administration was observed in the first 4-5 weeks. Thereafter, for most animals the daily doses reached a plateau. The gradual increase appears to reflect tolerance development, since the severity of the drug effects remained constant or even diminished in spite of the dose increase. The drugs of this group are also known on the basis of other evidence to be tolerance-producing. By contrast, lack of increase in the self-administration of nicotine or benzodiazepines may be attributable to rapid or weak tolerance development.

The daily intake pattern was erratic in self-administration of some stimulants and volatile anesthetics (16). The reinforcing effect could not be observed in the self-administration of LSD-25, mescaline, STP, nor with nalorphine. While many studies of THC were not successful in demonstrating its reinforcing effect, one study found evidence of self-administration of THC in rhesus monkeys following its substitution for cocaine (7). Reinforcing effects can also be demonstrated by short term cross self-administration experiments using a prototype reinforcing drug and saline as reference agents (4, 13, 18).

In animals the evidence of a definite reinforcing effect and the overt signs of drug effects at self-medicated dose levels are similar to those known in man. Thus it can be said that psychological dependence on certain types of drugs has been experimentally reproduced in animals.

Physical Dependence

Physical dependence-producing properties of a drug can be studied in laboratory animals by withdrawing the drug after repeated administration for a fixed period. The major withdrawal signs observable in morphine dependent monkeys are hyper-irritability and aversive autonomic manifestations (table 2) (9). On the other hand the withdrawal signs observable in barbital or alcohol dependent monkeys are hyper-irritability, convulsive disorders, and occasional delirium-like behavior (table 3) (17).

TABLE 1

Continuous self-administration in Rhesus monkeys (iv)

Self-administration positive				
Stable daily intake		Erratic		
Gradual increase	No increase	Frequent intake	Infrequent	Negative
Morphine	Nicotine	Cocaine	Caffeine	LSD-25
Meperidine	Diazepam	Amphetamines		Mescaline
Codeine	Chlordiazepoxide[a])	Volatile anesthetics[b])		STP(DOM)
Pentazocine				THC?
Pentobarbital[a])				Nalorphine
Alcohol[a])				Saline

a) Both intravenous and intragastric
b) Inhalation

In the development of physical dependence on these drugs, dose regimen is a crucial determinant. If the route of administration, the size of each dose, and the time interval from one dose to the next are sufficient to produce strong and continuous drug effects in the animals, physical dependence can be developed in as short a period as 2 weeks or even less. This has been confirmed in rhesus monkeys with morphine, pentobarbital, or alcohol (17, 18). Some investigators have observed a rapid development of physical dependence on morphine or alcohol within 24 hours in small animals by using a continuous infusion or vapour exposure technique (2, 12). The lower the dose level or the longer the dosing time interval is, the slower the development of physical dependence.

Cross physical dependence as well as cross tolerance is a well known phenomenon among certain drugs. These fall into two major groups: a morphine group which includes natural, half-synthetic, and synthetic narcotic analgesics (table 4) and a barbiturates group which includes many sedative-hypnotics and alcohol (table 5) (19). Within each group each drug mutually supports physical dependence on other drugs of the same group. Experimentally, cross physical dependence can be demonstrated by substituting one drug for a preexisting drug on which physical dependence has previously been developed and maintained.

Some drugs which produce physical dependence by repeated administration and are antagonized by naloxone, may, however, not

TABLE 2

Withdrawal signs in morphine dependent Rhesus monkeys (M. H. Seevers 1936)

Grade	Withdrawal signs
Mild	Apprehension, Continual yawning. Rhinorrhea, Lacrimation, Hiccup, Shivering, Perspiration on face, Chattering, Quarrelling and fighting
Intermediate	Intention tremor. Anorexia, Pilomotor activity, Muscle twitchings and rigidity, Holding the abdomen
Severe	Extreme restlessness, Assumption of peculiar attitudes. Vomiting, Severe diarrhea, Erection and continued masturbation, Inflammation of the eyelids and conjunctiva, Continual calling and crying, Lying on the side with eyes closed. Marked spasticity
Very severe	Docility in the normal excitable animal, Dyspnea, Pallor. Strabismus, Dehydration, Weight loss, Prostration, Circulatory collapse, Death

TABLE 3

Withdrawal signs in barbital dependent Rhesus monkeys (Yanagita and Takahashi 1970)

Grade	Withdrawal signs
Mild	Apprehension Hyperirritability Mild tremor Anorexia Piloerection
Intermediate	Aggravated tremor Muscle rigidity Impaired motor activities Retching or vomiting Weight loss (10%)
Severe	Convulsions Delirium (Hallucinatory behavior, Nystagmus, Dissociation from environment) Hyperthermia (>1.5°C)

TABLE 4

Physical dependence potential of several potent analgesics and related drugs tested in Rhesus monkeys
(Yanagita 1973a)

Drug	Cross physical dependence			Physical dependence-producing property
	Suppression of morphine withdrawal**	Precipitation of morphine withdrawal	Complete suppression (mg/kg)**	
Morphine	+	—	3.0 sc	+++
Methadone	+	—	3.0 sc	untested
Oxymethebanol	+	—	3.0 sc	+++
Meperidine	+	—	10.0 sc	+++
Codeine	+	—	16.0 sc	+++
d-Propoxyphene	+	—	16.0 sc	++
Thebaine	—	+		++
Azabicyclane	—(+)*	+	++	+++
Propiram	—(+)	+		++
Pentazocine	—(+)	+		+
Naloxone	—(—)	+		—

*( ) = Suppression in monkeys dependent on low dose of morphine and withdrawn (0.3mg/kg x 4 per day sc)
** = Tested in monkeys dependent on morphine and withdrawn (3mg/kg x 4 per day sc)

TABLE 5

Physical dependence potential of several sedative-hypnotics tested in Rhesus monkeys (Yanagita 1973b)

Drugs	Cross physical dependence*		Physical dependence producing property
	Suppression of barbital withdrawal	Complete suppression (mg/kg)	
Barbital	+	75 po	++
Pentobarbital	+	>25 iv	++
Alcohol	+	4,000 po	++
Chloroform	+		untested
Meprobamate	+	>200 po	++
Diazepam	+	5 po	++
Chlordiazepoxide	+	20 po	++
Oxazolam	+	20 po	+
Chlorpromazine	+	—	—
Perlapine	+	—	—

* = Tested in monkeys dependent on barbital and withdrawn (75mg/kg x 2 per day po)

support morphine dependence because of their antagonistic properties. These drugs are called "partial antagonists." Whether these drugs support physical dependence on morphine or precipitate withdrawal signs depends on the balance between the loss of the agonistic effect of morphine and the gain of the agonistic effect of the partial antagonist. In man and animals it has been demonstrated that pentazocine will support physical dependence maintained by low doses of morphine but will not support physical dependence maintained by high doses of morphine, and it will precipitate withdrawal (6,18).

EVALUATION OF THE ABUSE LIABILITY

The history of drug abuse demonstrates that not all drugs with substantial dependence potential are necessarily abused by man. While some drugs have continuously drawn abusers' attention, others have been of only transient interest. For example, while the abuse of opiates and alcohol has been continuous and popular, abuse of codeine and ether has been limited to either a small population or to a relatively short period of time in their histories (3, 5). Marihuana smoking and organic solvent inhalation are also

worldwide epidemics of relatively recent onset, compared to the long term availability of these agents. Thus, it is obvious that for evaluation of the abuse liability of a drug, one has to consider not only its dependence potential but also individual and social factors related to susceptibility to the drug. Therefore the prediction of human abuse potential is a comprehensive evaluation of the interaction among the drug properties, individual differences, and the social environment. However, there is no doubt that the dependence potential of drugs plays an essential role in the onset, maintenance, or exaggeration of abuse incidences. An important property of a drug in evaluating its abuse liability is its reinforcing effect. The mere fact that a drug has been self-administered by animals, however, may not be sufficient evidence to predict a high abuse liability for the drug. For prediction of high abuse liability, it is necessary to demonstrate a potent reinforcing effect comparable to those of the principal drugs of abuse.

Table 6 is the result of a progressive ratio test conducted by intravenous self-administration of morphine, pentazocine, and alcohol in rhesus monkeys for determination of the reinforcing potencies of these agents. In this experiment the ratio of lever presses versus drug injection progressively doubled after every 4 doses beginning from 100:1, and a breaking point at which monkeys extinguished the drug-seeking behavior was observed. As a result, substantial potencies of reinforcing effect have been demonstrated with these agents. If the reinforcing potency of a drug is found to be equal to or even higher than those of other abused agents, there is good reason to believe that the abuse liability of the drug may be noteworthy.

Contrary to the long-held view, however, physical dependence has only limited significance for the evaluation of abuse liability; it is significant only when the withdrawal manifestation is very aversive, since the drug-seeking behavior is then likely to be intensified in an attempt to avoid the aversion. Under these conditions, physical dependence becomes very important. In fact; this appears true with many morphine-like drugs. Experimentally this intensification has been demonstrated in the above mentioned progressive ratio test (table 6). In the table, ratios of 3 subjects at the breaking point for morphine were much higher when physical dependence on the drug had already been developed prior to the test (pretreated) than when had it had not (untreated). On the other hand, this intensification was less marked with alcohol and was not observed with pentazocine. It may be fair to say that the

TABLE 6

Progressive ratio test on morphine, pentazocine and alcohol in intravenous self-administration in Rhesus monkeys (Yanagita 1975)

Agent	Unit dose (mg/kg/inj)	Monkeys	Ratio at breaking point[a]	
			Pretreated[b]	Untreated[c]
Morphine	0.5	#174	1,600	1,600
		#234	12,800	1,600
		#248	12,800	6,400
		#254	6,400	200
Pentazocine	0.25	#171	3,200	6,400
		#364	3,200	3,200
		#412	3,200	6,400
Alcohol	800	#171	3,200	3,200
		#425	6,400	6,400
		#466	6,400	1,600
		#485	6,400	3,200

a) Ratio of lever presses versus injection for the last dose before extinction
b) Pretreated with the test agent for 4 weeks by programmed administration at previously self-maintained dose levels
c) Pretreated with saline

physical dependence potential of pentazocine or alcohol does not contribute as much to its abuse liability as does that of morphine.

PREDICTION OF THE POSSIBLE HARM CAUSED BY DRUG ABUSE

The harm caused by drug abuse is the basic issue from which the whole problem of drug abuse derived. The possible harm can be classified roughly into two categories: the harm to the public and that to individuals. The immediate causes of harm are mainly: (1) drug-seeking behaviors, (2) drug-taking behaviors, (3) pharmacological effects, (4) physically toxic effects, and (5) withdrawal. Compulsive drug-seeking behaviors may result in economic and legal irresponsibility with regard to families and society. Drug-taking behavior itself may also involve procedures possibly hazardous to health. Pharmacological effects may result in psychotic and/or antisocial behaviors in addition to death. The physically toxic effects imply subacute and chronic toxicity which produces such morphological and functional disturbances as the liver injury by barbiturates and alcohol, gonadal atrophy by opium alkaloids, and respiratory disturbance by glue sniffing. Withdrawal may also be harmful to both society and the individual since it may involve delirium and be life-threatening from dehydration or convulsions.

In predicting harm, animal studies can provide information about the following, which may or may not relate to the dependence-producing properties of drugs:

(1) Potency of the reinforcing effect of a drug to produce compulsive drug-seeking behaviors.
(2) Potency of the pharmacological effects of a drug to produce behavioral disorders on self-medicated dose regimens.
(3) Potency of the physically toxic effects of a drug to produce biohazardous changes on self-medicated dose regimens.
(4) Severity of the withdrawal manifestations in terms of aversiveness and mortality.

Laboratory procedures to assess the reinforcing potency have been discussed previously, so will not be repeated here. With regard to pharmacological effects, the basic information can be obtained through general pharmacological studies in various animal species. Crucial information, however, is obtainable only through continuous self-administration experiments as described in the first part of

this paper. These experiments will reveal to what extent the animals seek a drug and its effects. Thus, it is known that monkeys may seek and take pentobarbital, alcohol, and volatile anesthetics, up to the point that they are self-anesthetized. They will take cocaine to the point of convulsions; amphetamines to extreme excitation, and morphine to severe depression. Death due to overdoses of cocaine or morphine and by suffocation when self-anesthetized with pentobarbital or volatile anesthetics is not uncommon. On the other hand, animals will never self-administer nicotine or caffeine to the point at which excitation is demonstrated.

Similarly, the basic information on physical toxicity can be obtained through subacute or chronic toxicological studies in various species of animals, but crucial information is dependent on the continuous self-administration experiment, since toxicity at the self-determined dose regimen is in question. For example, it has been known for some time that some monkeys will take high doses of alcohol daily, become emaciated, eventually develop severe liver and renal injuries, and finally die several weeks after the initiation of self-administration (19). In contrast to alcohol, monkeys self-administering morphine for longer than 6 months at daily doses of more than 60 mg/kg show no serious organ injury except for gonadal atrophy. However, some infection and thrombosis attributable to long-term catheterization have been observed (1).

A rough idea of aversiveness and possible life threat of a drug can be obtained through observing withdrawal. Among analgesics, withdrawal appears to be most severe with morphine-like drugs, less severe with some synthetic narcotics, and minimal with pentazocine. Withdrawal symptoms are substantially milder with barbiturates or alcohol than with morphine.

It is, however, known in man that the convulsions developed in barbiturate withdrawal can be life-threatening, and the risks in abrupt withdrawal are even higher with this class of drugs than with opium alkaloids (5). In animals, regardless of species, convulsions are one of the most characteristic signs observed in barbiturate or alcohol withdrawal. It has also been found in some monkeys that while maintaining physical dependence on morphine or demerol by frequent self-administration of these drugs, an abrupt withdrawal resulted in death (15). Such severe physical dependence on narcotics, however, seems to be very rare in man.

CONCLUSION

In any extrapolation of animal findings to man, it is necessary to consider the problems of species differences. Major differences exist in the pharmacodynamic and pharmacokinetic susceptibilities among the various species of animals and man. Clinical pharmacological considerations such as the drug's bioavailability (e.g., differences in the preparation forms) and the conditions under which drugs are delivered to subjects are also important. Careful consideration of al! these biological and situational differences between the animals in laboratories and man in society makes animal studies a valid approach of practical value for the prediction of abuse liability of drugs and their potential harm.

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III.

Psychobiology of Drug Abuse and Affect Disorders

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CHAPTER 15

Endorphins, Lithium, and Naloxone: Their Relationship to Pathological and Drug-Induced Manic-Euphoric States

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Cocaine and amphetamine induced states and naturally occurring manias appear similar clinically and can be blocked by lithium (32, 69, 83, 98). Although it has become fashionable to think of acute amphetamine induced states (19, 28) as a model for paranoid schizophrenia, clinically these states bear a close resemblance to spontaneously occurring mania (30, 65). Behavioral similarities and lithium blockade link the drug induced and naturally occurring euphoric states. Unfortunately, it is difficult to approach the question of the neurochemical mechanism of euphoria by deductions from lithium's presumed mode of action. Lithium is known to influence many physiological systems (17, 20, 24, 35, 50, 60, 69, 86, 88, 89, 90, 99) and while there have been a number of speculations (38), no specific mechanism has been identified for its efficacy in treating either acute mania or manic-depressive illness (86).

Although its mechanism of action remains elusive, lithium is an effective therapeutic agent in the treatment of the manic phase of manic-depressive illness and in prophylaxis of both mania and depression (1, 3, 10, 14, 34, 38). It is an antagonist of the hyperactivity, catatonia, increased pressure and production of speech, sleeplessness, grandiosity, and euphoria characteristic of naturally occurring manic episodes and some drug induced states (32, 98). Lithium has been reported to ameliorate amphetamine induced motoric effects in rats (36, 88). Lithium pretreatment has also been found to reduce the jumping, fighting, stereotypes, and

hyperactivity induced by d-amphetamine (9). Lithium antagonizes the amphetamine induced changes in the serotonergic (62) and noradrenergic systems (4) in rodent and man, respectively. Supporting the suggestions of these data regarding lithium's antagonistic effect in amphetamine induced euphoria and hyperactivity in man are a case study (32) and double blind placebo controlled study (98) reporting that lithium attenuates the euphoriant and activating effects of amphetamine. There then appears to be both research and clinical data consistent with the notion that lithium attenuates stimulant-response, euphoria and mania. Lithium also appears to be effective in the treatment of naturally occurring pathological euphoric manic states and catatonia associated with mania and primary affective illness (1, 3, 10, 14, 34, 38). But how?

Mandell and Knapp (69) suggest a serotonergic mechanism for the blockade of cocaine by lithium as lithium antagonizes behavioral effects of other drugs that, like cocaine, reduce the biosynthesis of 5-HT in animals. On this basis they suggest a place for lithium in the treatment of compulsive stimulant users as a subject for further study. An alternative proposal attributing the blockade of stimulant drug effects as well as mania to lithium's cationic activity has been suggested by Byck (13).

ENDORPHINS

The discovery of the endogenous substances with opioid activity, the endorphins, in man and other species (45, 53, 66, 79) has stimulated recent investigations attempting to delineate the role of these substances in euphoria and human behavior (8, 12, 55, 64, 87, 93). Opiate receptors, through which opiate alkaloids and peptides exert their pharmacological effects, have receptor density profiles in brain (66, 77, 91) which make them prime candidate structures for the mediation of emotionality, drive, motor behavior and pain perception (45, 64). Since "pure" narcotic antagonists are known to block and *reverse* the effects of opiates and displace endorphins at opiate receptor sites in the brain (45), the administration of the antagonist naloxone has recently been employed as a strategy for investigating behavior and mood effects mediated by endorphins (2, 5, 49, 74, 78). The reversal or attenuation of behavior or mood effects by the opiate antagonist naloxone, therefore, appears to provide information about the pharmacological substrate of the behavior or mood effects which can not be derived from data with

lithium pretreatment. Demonstration of an effect for naloxone alone, as well as reversal and attenuation of opioid agonist effects, would lend considerable support to the hypothesis that opiate receptors are involved in a particular phenomenon. Naloxone has recently been found to attenuate the amphetamine-induced increases in continuous avoidance responding and locomotor activity in the rat (51) and reverse the effects of both morphine and d-amphetamine on intracranial self-stimulation in the rat (52). These data support the hypothesis that at least some of the effects of stimulant drugs might be mediated by the endorphin system (13, 87).

We report a case of lithium carbonate blockade of cocaine and amphetamine effects in the same person. This blockade occurred only at high plasma lithium concentrations. This report adds to the body of evidence that indicates that stimulant induced euphoria may be impaired by pretreatment with lithium. This case provides clinical evidence which lends support to hypotheses regarding the neurochemical mechanism of drug-induced and naturally occurring euphorias (13, 70, 57).

CASE REPORT

James, a forty-year-old former heroin addict maintained on methadone (30 mg/day) for three years in the Yale Substance Abuse Unit, is the subject of this report. The patient had been referred repeatedly by the staff of the unit to the psychiatric consultants for "hyperactivity" and episodes of "suspiciousness associated with hyperactivity and grandiosity," as well as for one episode of depressed mood. It was suggested that the use of amphetamine or cocaine could be responsible for these abrupt changes in his behavior. Although he was frequently seen in the company of known cocaine dealers and users, and fresh antecubital scars were seen on occasion, he had only two urines positive for cocaine metabolites during the three year period. No positive amphetamine urines had been reported.

While James had no psychiatric hospitalizations unrelated to his heroin addiction, an aunt and cousin were hospitalized for "acute psycho tic episodes." There was no personal or family history of alcohol abuse. His developmental history was unremarkable.

In August of 1976 the patient presented with hyperactivity, pressure of speech, and flight of ideas. A presumptive diagnosis of manic-depressive illness was considered and treatment with lithium

carbonate was begun. Two months passed without a "hyperactive-euphoric" episode.

Shortly afterwards the patient complained that he had "a blood disease." On further questioning, he gave a detailed history of four unsuccessful attempts to "get off" on cocaine. He reported, "I'd wait for a rush and I wouldn't get a rush at all so I just kept bootin' but I wouldn't feel anything." Four days prior to this presentation, he stated, "I bought $20 worth of cocaine and didn't get anything. I went back and I got another $20 worth . . . he gave me another spoon for nothing and I did that and I didn't get anything . . . I knew I had a hit . . . I got absolutely nothing; the other kids were all getting speedy . . . getting off . . . they told me there's something wrong with you, J . . . I thought it might be because there were little bubbles in my blood." He then added that, "about a month ago I tried to shoot it [cocaine] . . . and got absolutely nothing," but that over the "last week I tried to get off three separate times . . . all I did was blow $150 bucks . , . I usually get off on $10 or at the most a spoon ($20) [but I] didn't get all speedy or get a rush . . . as a matter of fact, the last time I got more depressed."

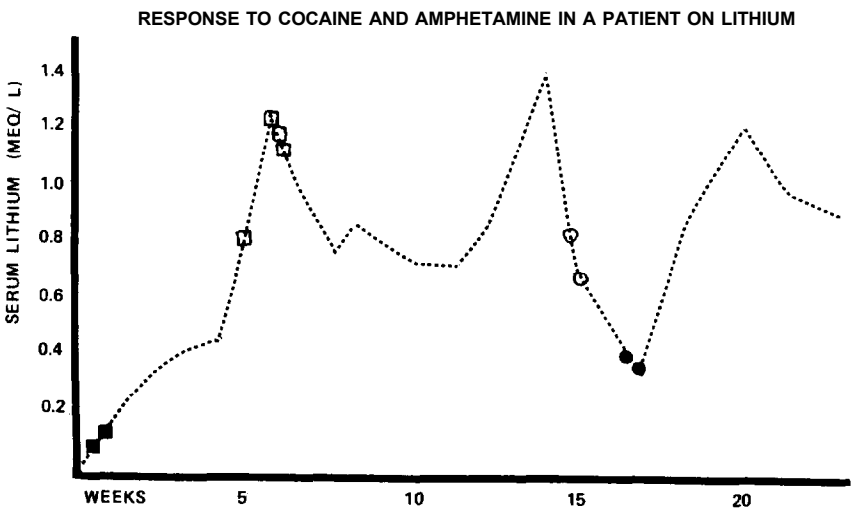
The patient's known lithium levels and account of successful and abortive attempts to "get off" on intravenous cocaine and amphetamine are presented in figure 1. The figure shows the weekly serum lithium levels which resulted from the patient's intermittent compliance on a prescribed program of 1800 mg each day. It can be seen that both cocaine and amphetamine produced euphoria at lower lithium levels, but no effect was reported at lithium levels above .6 mEq/1.

The patient was reassured that he did not have a blood disease and informed that the lithium might be responsible for the change in his response to cocaine. He was nonetheless encouraged to continue taking his lithium regularly. He discontinued attempts to "get off" on cocaine as "it was a waste of money." Then, after an unsuccessful attempt to obtain effects from amphetamine, he stopped taking his lithium. He began taking his lithium regularly only after his urine was found to be positive for amphetamine since he wanted to "avoid a speed run" and remain in good standing in the drug program. He was thus using the lithium as a self treatment regime to prevent the consequences of his impulsivity.

FIGURE 1

The effect of serum lithium on subjective response to cocaine and amphetamine in P. over time. Serum lithium levels above 0.6 mEq/1 were necessary to "block" the effects of intravenous cocaine or amphetamine.

Key
■ Positive response to cocaine
□ No response to cocaine
● Positive response to amphetamine
○ No response to amphetamine



Discussion of Case Report

This case clearly demonstrates blockade of cocaine and amphetamine euphoria by lithium carbonate treatment. Retrospcc-tively, it is probable that this patient did not have endogenous manic-depressive illness. The patient later reported that the previous episodes of euphoria and hyperactivity were all associated with stimulant usage. The pharmacological demonstration of lithium blockade may be confounded by the concurrent administration of methadone, but there was no block of stimulant effects by methadone alone. However, the interaction between chronic opiate agonist and chronic lithium administration could be responsible for the reported blockade. As with all street reports of drug usage, the identity of the specific stimulant used in each instance must remain in doubt. The patient's account, confirmed by the positive urines for benzoylecgonine (97), is assurance that cocaine was used in at least two instances. The positive responses of his companions

suggest that an active compound was used. Double blind studies are necessary to confirm this case report and determine whether the euphoric effects of cocaine were truly blocked or modified to the extent that J. did not experience the desired effects of the drug.

ENDORPHIN-EUPHORIA/MANIA: LITHIUM CONNECTION

The clinical similarity between cocaine and amphetamine-induced and naturally occurring manic states and their blockade by lithium, link the drug-induced and naturally occurring euphorias. Unfortunately, because of its actions on many physiological systems, it is difficult to approach the neurochemical mechanism of euphoria or pathological euphoric states by deductions from lithium's mechanism of action. Byck has proposed a hypothesis (32) which suggests that endorphins are inextricably involved with hedonic and anhedonic feelings. He suggested that endorphin binding is modified in drug-induced and naturally occurring euphoric states and may explain the action of lithium in preventing and treating these states.

Opiate agonist and antagonist binding to receptors is markedly influenced by sodium. Except for lithium, whose hydration radius is similar to that of sodium, monovalent cations do not change this affinity (93). Agonists and antagonists compete for the same receptors, but the affinity of these receptors at the physiological extracellular sodium concentration is greater for antagonists than for agonists; *increasing the sodium concentration enhances this difference.* While long term changes in sodium balance do not occur in lithium-treated patients (probably because any alteration in sodium excretion is rapidly corrected by homeostatic mechanism), the therapeutic use of lithium may produce a long-term modification of total cationic concentration in various body compartments. The effect of added lithium would thus be equivalent to increasing the sodium concentration. If lithium administration produced an increase in the cationic concentration which acted in a manner consistent with opiate binding studies, we could expect increased antagonistic binding and decreased binding of euphorigenic agonist compounds. By this logic, lithium should be anti-euphorigenic in endogenous pathological states as well as in exogenous drug-induced states as a result of modification of peptide receptor systems. The demonstrated actions of lithium in the treatment of manic states and naloxone in reversing behavioral effects of both morphine and d-amphetamine (51, 52) are consistent with this hypothesis. Data

using naloxone effects and opioid reversal or attenuation to link affective and behavioral effects of amphetamine-induced and naturally occurring catatonic and other pathological manic states to actions at endogenous opiate receptor sites may be a more promising strategy when employed in humans for separating the relative contribution of endorphin and adrenergic systems to euphoria and psychomotor activation and inhibition.

However, naloxone has been reported to be without effects of its own in a variety of behavioral, neuroendocrine, and neurochemical model systems in mammals (6, 7, 33, 45, 48, 63, 84). There are no reports of physiological or behavioral effects of naloxone in primates or humans (25, 29, 46, 47, 49). In addition, lithium blockade of euphoria seems to be partial, and occurs with certain exogenously or pathologically induced ego-dystonic feelings of well-being. The involvement of other transmitter systems, particularly aminergic, in an interactive manner is likely in stimulant-induced and endogenous mood state changes. A full discussion of aminergic theories of euphoria and mania (11, 69, 70) and possible relation to the neuromodulatory influences of the endorphins (94) is pertinent but beyond the scope of this paper. However, a brief discussion of the suggestion that dopaminergic mechanisms might play an important role in mania is required because of the clinical effects of L-Dopa in manic-depressive patients (11, 75), known actions of d-amphetamine and opioid agonists at dopaminergic synapses (15, 23, 26, 27, 39, 40, 82, 92), and data that dopamine receptor blocking antispsychotic agents are antimanic (37).

Haloperidol and pimozide action as antimanic and known dopamine receptor blocking agents seemingly supports a dopamine hypothesis (37). However, Creese et al. (21) have demonstrated the substantial affinity of some butyrophenones for the opiate receptor in brain. This observation provides a biochemical rationale for the known influences of these drugs on opiate addiction in animals and abstinence in man (59, 81, 96). In fact the butyrophenones used clinically are analogues of the opiate meperidine (56). Some of the more potent butyrophenones examined for opiate receptor binding activity were found to have a greater affinity for the receptor than opiates like meperidine and propoxyphene. Benperidol and pimozide were the most active of these drugs and have a binding profile similar to opiate antagonists (21, 80). Haloperidol produces some behavioral effects (e.g., catelepsy) which mimic some of the effects of opiate agonists. Haloperidol can potentiate analgesia and the development of tolerance and dependence to morphine when both drugs are given concurrently (27) and produces some degree of

cross tolerance with morphine (27, 82). Haloperidol also antagonizes morphine-induced hyperactivity very effectively (15). These data suggest that opiate receptor activity might be responsible for at least part of the butyrophenones' antimanic and antieuphoric effects.

ENDORPHINS AND PSYCHOSIS

Opiate agonist receptor activity may contribute to antipsychotic activity as well. Support for this hypothesis comes from data which suggest that, like the traditional antipsychotic medications, morphine and other narcotic agonists interfere with the post-synaptic action of dopamine (23, 26, 27, 39, 40). Opiate agonists, as does haloperidol, increase dopamine metabolites HVA and DOPAC in rat brain as well as inhibit the enzyme dopamine stimulated adenylate cyclase (40). These actions of opiate agonists are consistent with the prediction of antipsychotic efficacy (41) on the basis of current theories of psychosis (92) and the antipsychotic action of the neuroleptics (54, 92).

The involvement of dopamine in the tonic inhibition of prolactin secretion (71) and the known action of the neuroleptics at dopaminergic receptors (54, 92) have led to the suggestion that antipsychotic medications can be identified by their stimulation of prolactin secretion (16, 72, 73). Potent antipsychotic phenothiazines, butyrophenones, but not structurally-related drugs without antipsychotic potency, block dopamine receptors (54) and stimulate prolactin secretion (16, 67, 72, 73). These and other data have led to the hypothesis that tuberoinfundibular dopamine blockade, as assessed by elevations in serum prolactin, might be the best model system for screening new antipsychotic compounds (16, 72, 73). However, morphine, methadone, and endorphins have recently been found to increase prolactin secretion through opiate receptor stimulation as assessed by naloxone blockade (31, 68, 95). Gold et al. (43-44) have recently found that 0.4 mg/kg of morphine sulfate produces significant three-fold increases in basal serum prolactin while 0.4 mg/kg of a synthetic d-alanine m-enkephalin derivative (85) produces significant sevenfold increases in serum prolactin in primates. These m-enkephalin-induced increases in serum prolactin are similar to those produced by the potent antipsychotic haloperidol in this species (42). These prolactin data are consistent with animal data suggesting that opioid agonists interfere with the post-synaptic action of dopamine (23, 26, 27, 31,

39, 40). Opiate agonists may, through opiate receptors, modify dopaminergic impulse flow and release (41) to act as a neuromodulator of dopamine receptor activity. In this way, opiate neuromodulatory mechanisms could bias dopaminergic systems to be involved in motor behavior and mood as well as in antipsychotic effects (18, 55, 76) and psychosis (8). But what about the "pure" opiate antagonists? If endorphins function in the brain to modulate dopaminergic impulse flow, then naloxone should have an opposite effect on biological measurements which correlate with dopaminergic activity.

NALOXONE-PROLACTIN: A MARKER FOR CENTRAL ENDORPHIN BLOCKADE?

Naloxone has generally been found to have no effects of its own other than to block or reverse the effects of opioid agonists (6, 7, 25, 29, 33, 46-49, 63, 84). There are no reports of physiological effects reported for naloxone in nonhuman primates or humans. These and other negative data have been difficult to interpret due to a lack of any central and measurable effect of naloxone which could be measured concurrently and provide a marker or evidence of a central effect of naloxone at a particular dose. However, these negative data have led to the suggestion that the endorphins are secreted episodically and do not have a tonic neuromodulatory role in the brain. We have recently investigated and described an effect of naloxone on serum prolactin which suggests at least one tonic neuromodulatory function of endogenous opioid peptides (44).

Naloxone hydrochloride (0.25 mg/kg) administered intravenously caused significant and sustained decreases in serum prolactin in five *Macaca arctoides*. Each experimental session lasted 5 h with the last 4 h involving blood-sample withdrawal and either naloxone or saline administration by means of an intravenous cannula without handling or confrontation. All samples were prepared for radioimmunoassay as previously described (41, 42). Naloxone produced a marked and significant fall in serum prolactin from 23.0 ng/ml +/– 2.9 S.E.M. to 3.5 ng/ml +/– 0.9 S.E.M. at 60 minutes after drug infusion ($p<0.01$). Serum prolactin concentration was significantly decreased from baseline levels at each time point from +30 to +180 minutes after naloxone. There were no significant effects on serum prolactin after saline administration. These naloxone-induced decreases in basal serum prolactin are similar to those produced by the dopamine receptor stimulating drug apomorphine.

These data on naloxone and prolactin may be useful in studies where naloxone is administered to investigate behavioral and other effects of endorphins by allowing the administration of a dose of naloxone which produces a measurable effect. With this central marker data. negative data in naloxone studies may be more meaningful and support an episodic rather than tonic role of endorphins in a particular behavior or psychopathological state. Alternatively, positive data in naloxone studies may be more likely if higher, prolactin-lowering, doses of naloxone are employed.

These naloxone data indirectly support the hypothesis that antipsychotic drugs can be identified by their stimulation of prolactin secretion (16, 72, 73), since naloxone decreases serum prolactin and has not been found to have antipsychotic activity in psychotic humans (22). Higher doses of naloxone given in a chronic treatment protocol may be necessary to support these data. Exogenous and endogenous opioid agonists are potent stimulators of prolactin secretion and may have antipsychotic activity in man (41, 61, 76). The opioid agonist-induced increase in prolactin can be blocked by concurrent or pretreatment with naloxone or the dopamine receptor stimulating drug apomorphine (31, 68, 95). These and other data reviewed above suggest that dopaminergic neurotransmitter systems are involved in an interactive manner with peptide neurotransmitters. This interaction may be involved in the generation and pharmacological treatment of complex mood and behavioral states.

CRITIQUE

There are several weak links in this chain of reasoning. For example, the effects of lithium on opiate receptor binding have been determined with this ion alone, and so results of adding small amounts of lithium to sodium are as yet hypothetical. The ionic environment of the receptor must be known before the magnitude of the lithium and sodium effect can be measured. In addition there is evidence for both opioid agonist and antagonist activities of "specific" dopamine blocking agents. Whether prolonged opiate agonist and antagonist activity contributes to antipsychotic and antieuphoric effects, respectively, remains to be demonstrated. Tuberoinfundibular dopamine blockade as assessed *in vivo* by increases in serum prolactin may not be a viable model for the antipsychotic locus of action of the neuroleptics. Naloxone may be a more potent morphine and exogenous opiate than endorphin

antagonist. Finally, there is the suggestion that opiate agonist activity may produce euphoria, provide the pathophysiological substrate for acute mania, and also act as an antimanic agent. One possible explanation for this apparent paradox is suggested in the recent acute vs. chronic effects of heroin study of Mirin et al. (74). In contrast to acute effects, chronic exogenous agonist administration (or chronic endorphin excess in mania) may, through modification of dopaminergic or other aminergic systems, cause the opposite—dysphoric, antimanic—effects. A similar phenomenon may explain the euphoria followed by depression in manic-depressive disease.

Our hypothesis, which attempts to provide a mechanism of action for lithium and a neurohumoral substrate for euphoria, is readily testable. Naloxone, or related but more potent endorphin antagonists, should be found to be an effective antagonist to drug-induced and naturally occurring euphoric states. These antagonists could be useful in the treatment of bipolar affective illness and manic states associated with catatonia. A test of the lithium effect on the postulated opiate-euphoria system is possible in a number of physiological systems and in each instance the effect of lithium should in part be similar to that of opiate antagonists. Similarly, anti-euphoric antipsychotics might be expected to act like lithium or naloxone in amphetamine- and cocaine-induced states, naturally occurring euphoric states, and opiate receptor binding systems. Finally, chronic administration of endorphins should be antieuphoric and antipsychotic in man.

Recently lithium has been reported to have no effect on the euphoriant action of large doses of morphine (57). This endorphin hypothesis would predict only a partial antagonist action for lithium against the effects of morphine and so the failure to block large doses does not markedly affect the status of that hypothesis. The same authors reported a dysphoric effect as well as a sensation of sluggishness and tiredness in normal subjects treated with lithium. These are, in effect, the opposite sensations to those produced by the stimulant drugs. The effects of lithium can be summarized as universally opposite to those of stimulants, i.e., dysphoria, tiredness and sluggishness (58). These are not dissimilar to the effects of the antipsychotics given in acute doses to normals or chronic heroin administration (74). Since all these are the opposite to symptoms of mania, it may be that either a dopaminergic or peptidergic mechanism, or both, is involved in mania and the action of stimulants.

CONCLUSION

Biological psychiatrists have for the most part centered their interest on the relationship of abnormalities in brain dopamine to amphetamine psychosis and schizophrenia. It is probably more appropriate to consider that acute administration of stimulants provides a model for euphoria and mania. The hypothesis that amphetamine psychosis is a model for mania with psychosis could thus be investigated in humans by cumulative administration of amphetamine after lithium pretreatment. Lithium pretreatment would be expected to block or attenuate this experimental amphetamine psychosis.

We have presented a case which represents a clear clinical example of a specific lithium block of two stimulant drugs. This case is compatible with an endorphin hypothesis for drug-induced and naturally occurring euphoric states. We have also suggested the possibility that an opioid peptide mechanism might have pathophysiological significance in manic-depressive disease. If this hypothesis is viable, naloxone should block the euphoria of drug and naturally occurring manic states. We have also reviewed recent data on the effects of exogenous and endogenous opioid agonists as well as the opioid antagonist naloxone on serum prolactin levels. These prolactin data offer theoretical support for clinical trials of prolactin stimulating endorphins in psychosis and naloxone in catatonia and possibly parkinsonism. These prolactin and other animal data suggest that the endorphins are potent tonic modulators of dopaminergic activity in brain. It may be necessary to invoke a peptidergic-aminergic mechanism to adequately explain complex, drug-induced and pathological manic-euphoric states. These prolactin data may be helpful in determining appropriate doses of naloxone and opioid peptides for clinical trials.

Direct experimental investigations are necessary in most cases but expecially in response to our speculative hypotheses.

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CHAPTER 16

Drug and Mood State-Specific Encoding and Retrieval of Experience

Herbert Weingartner, Ph.D., Dennis Murphy, M.D., and Richard C. Stillman, M.D.

Many psychoactive drugs produce neurochemical changes which are both discriminable from an undrugged state and are reinforcing for the drug user. Such discriminable and reinforcing properties are clearly pertinent in accounting for the subjective drug experience. These two properties may also help to explain the potential of some drugs for abuse and the interactive situational and personality-related factors that would determine idiosyncratic individual or group drug effects. Dramatic alterations in mood such as seen in depression or mania in bipolar and unipolar affective disorder appear to share some of the behavioral and biological features that characterize the response to abusable drugs.

In this report we contrast some of the cognitive changes that occur in mood altered states with those seen in the drug intoxicated state. We have observed that the changes in state and their cognitive components such as those seen associated with depressed and/or manic phases of unipolar or bipolar illness share much with responses to drugs that induce euphoria, sedation, stimulation, activation, or arousal. Likewise some of the neurochemical events associated with disturbances in mood also appear to be relevant to the understanding of the biology of the drug altered experience (7).

In our laboratory we have designed information processing systems that might be particularly effective in exploring some of the cognitive characteristics of state change in response to a variety of psychoactive drugs. We have used similar methods of approach for the study of cognition as it relates to disturbances in mood in bipolar and unipolar affective illness. One major focus of this

approach has been to use state dependent learning designs to interrelate the storage and retrieval of experience (11, 13). The major feature of this research has been to relate biological and psychological processes that might be involved in experiencing and encoding events in one state and retrieving experience in either the same or some other state, as for example an altered mood, a drug altered change in brain function, or a change in neurochemical activity in the brain.

FEATURES OF STATE DEPENDENT LEARNING (SDL)

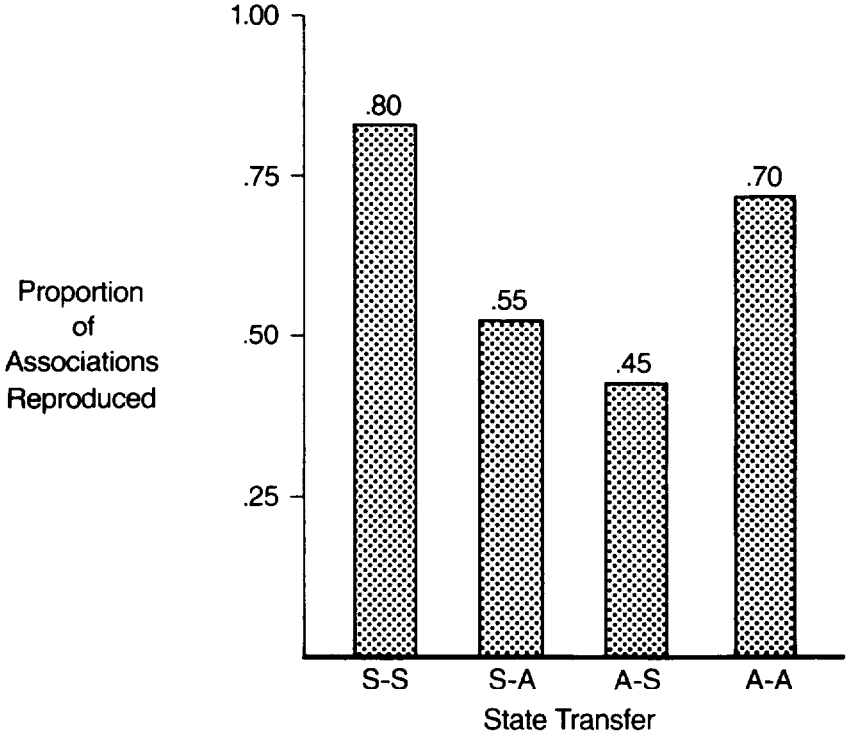
A growing number of studies have demonstrated that under some learning and test conditions information acquired in some altered state is most effectively retrieved in a similar altered state as compared to retrieval in a different or disparate state. This phenomenon was first studied in animals and then in man. In most of these studies state change was accomplished through the use of a drug manipulation either at the time of learning or at the time of retrieval or at both times. We have studied this phenomenon not only under drug altered conditions, such as in the alcohol or marihuana intoxicated state but in patients who, over time, manifest robust changes in mood state as in depressed and manic phases of bipolar illness. The studies reported have suggested that drug induced dissociations of learned information stored in one state and recalled in a different state may share much in common with similar effects seen in patients as they evidence changes in mood state and attempt to recover experiences acquired in some earlier but different mood state.

In an alcohol SDL study we had 10 normal subjects each consume 3.5 ounces of 190 proof alcohol mixed in 3.5 ounces of orange juice. Twenty minutes later we obtained Breathalyzer measures as estimates of blood alcohol level (mean values were .081 mg%). Following this we asked these subjects to generate 20 verbal free associations to each of 2 standard stimuli, a method previously found useful for measuring cognitive responses to psychoactive drugs (14). This same task was also accomplished, at another time, in an unintoxicated state. Five hours later subjects were asked to reproduce their self-generated associative responses. Reproduction of associations was accomplished under two different conditions. In one, subjects were sober at the time of recall. In the other condition they accomplished this retrieval 20 minutes after consuming the same quantity of alcohol, producing about the same state of intoxication. The four conditions were then:

	Generate In formation	*Retrieve In formation*
(congruent) conditions)	sober	sober
	intoxicated	intoxicated
(disparate conditions)	sober	intoxicated
	intoxicated	sober

The findings from this study showed that when information is generated and retrieved in the same state, the reproduction of patterns of associations is more complete than when this occurs in disparate generation-retrieval conditions ($F(3,27) = 5.41$; $p<.01$).

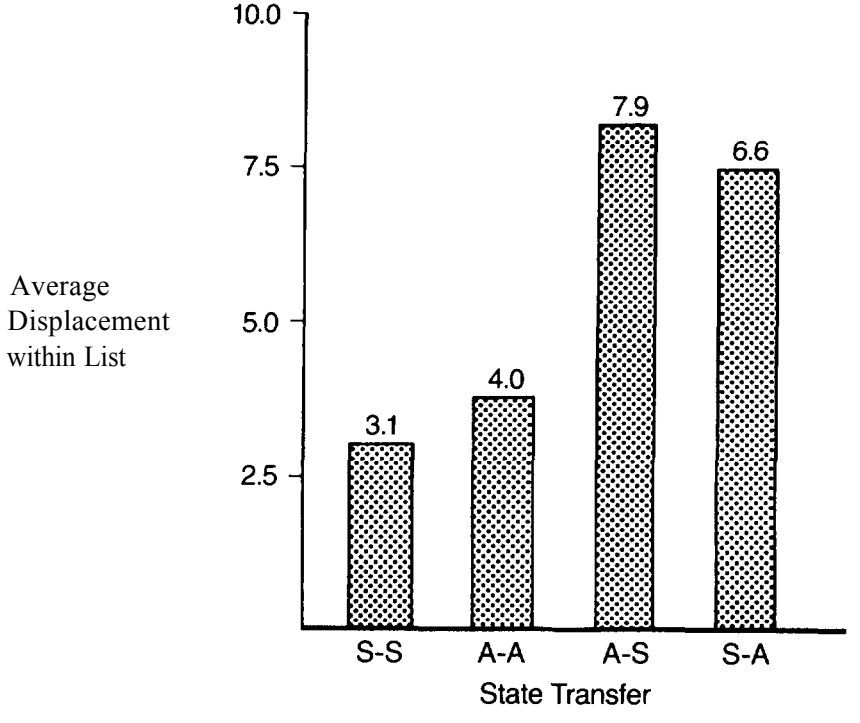
FIGURE 1



Reproduction of Associations in Congruent and Disparate State Recall

This experiment was repeated in a different 10 subjects using the same design and alcohol dose. Unlike the first study we required subjects not merely to regenerate their associations but to do so in the same order or sequence in which they were initially generated in response to the same stimuli. The retrieval of episodic events (e.g., *A* occurred, then *B,* then *C)* was thought to better reflect how we in fact experience, encode, and retrieve events than merely recapitulating what word events were thought to have previously been related to some stimulus. Such episodic time-sequence tagged information is also a closer match to how we store biographically relevant events. Again, in this study, we saw a robust dissociation of information when recall of episodic events is attempted in some disparate retrieval state ($F(3,27) = 11.84$; $p < .001$).

FIGURE 2



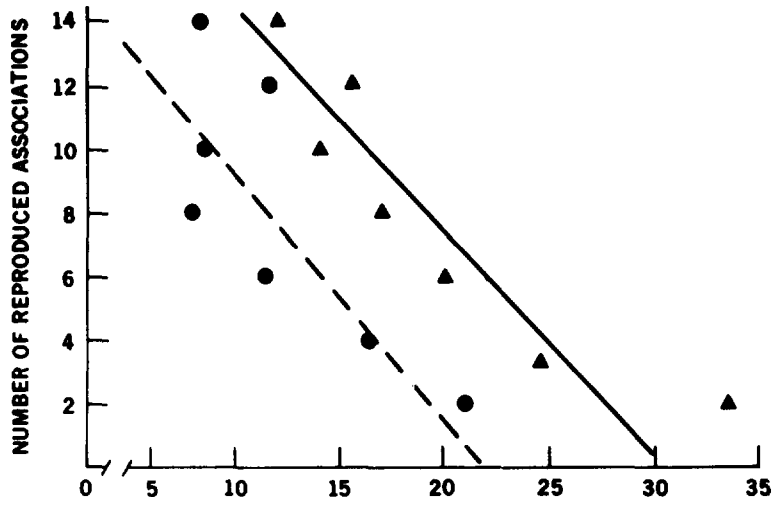
Reproduction of Episodic Associative Information in Congruent and Disparate State Recall

A similar strategy for examining SDL effects was used in a study in which we systematically studied 8 patients with bipolar affective illness over a period of many weeks. Patients would generate 20 free verbal associations to different word stimuli and four days later they would try to regenerate their responses. This was repeated for different word stimuli over and over again. At the same time we had trained clinical staff rate and measure the patient's mood-clinical state using previously designed and validated mood rating scales (6). We then examined the relationship between reproducibility of patterns of associations with the absolute change in mood-clinical state. There emerged a consistent pattern of significant negative correlations, each showing that reproduction of associative responses was dependent on the similarity between mood state at the time these associations were generated and mood at the time of reproduction of associations (retrieval). Analysis of data on all patients as a group, and individual patient data both showed that retrieval is most effective if mood state is similar at the time of response generation and response regeneration. These findings are summarized in figure 3, which describes the composite pattern of relationships using all data generated from the 8 patients studied: 186 pairs of generated associative patterns and their reproduction ($r=-.45$; $df=185$; $p<.001$).

ENCODING CHANGES THAT ACCOMPANY CHANGES IN STATE AND THE SDL PHENOMENON

The studies described above illustrate that the SDL phenomenon occurs in the context of states of alcohol intoxication and altered mood. Three studies which we have completed also suggest that states that are associated with SDL dissociations also induce qualitatively unique strategies for processing input which would cognitively differentiate such states from the "normal" state. In one such study we have been able to demonstrate that the kind of associative responses that are produced while manic are qualitatively different from the patterns of associations produced by these same patients in the non-manic state (5). That is, as patients become increasingly manic they produce an increased number of rarer, more idiosyncratic associative responses at the expense of more commonly elicited associations. The relationship between the kinds of associations that come to mind in response to word stimuli is an important determinant of how subjects think about events, encode events, organize information, and remember information (2,

FIGURE 3



Mood State-Dependent Retrieval of Verbal Associations

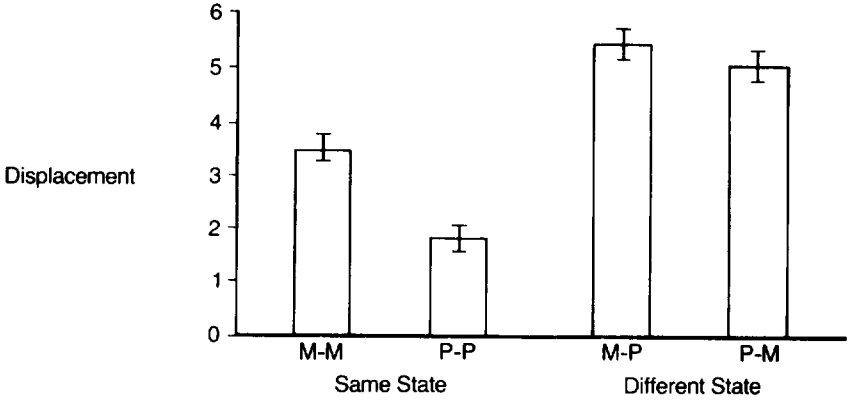
10). Thus, changes in associative patterns that occur during mania are, in part, responsible for changes in how events are interpreted in a mood state specific manner. These changes ultimately affect how a stimulus would also be used in reproducing associative word responses in a same or different mood state.

Similarly, we have begun to explore the kinds of eye scan strategies that subjects use in examining visual displays in an undrugged state as compared to a marihuana intoxicated state. Our preliminary data seems to indicate that subjects looking at pattern information in a marihuana intoxicated state tend to exhibit scan paths that focus on the fine detail of displays. Normally these same subjects tend to "look" at fields of information using wholistic processing strategies evidenced by eye fixations that sweep over larger fields of visual information. This detailed scanning while intoxicated as compared to gestalt processing in the unintoxicated state may also have implications for brain lateralizing effects of marihuana as perhaps reflected in such state specific differences in visual scan strategies. Other recent findings from our laboratory are

consistent with such a notion. We noted consistent changes in the speed of processing simple letters, displayed either in a block upper case form or as a lower case letter display, when presented to the left vs. right hemisphere, which would indicate that marihuana produces somewhat different effects in the dominant vs. non-dominant hemisphere (8). Thus, marihuana-induced shifts in the cognitive strategies used to transform, process, and encode experience may reflect lateralizing effects of marihuana in the brain. As such, it represents one kind of expression of qualitative differences in state specific information processing strategies.

In another study we asked subjects to impose organization on sets of pictures which were each random displays of texture, line, and form. These displays were deliberately constructed, pretested, and selected so as to make them difficult to encode with some verbal label. Subjects while either marihuana intoxicated, having smoked marihuana cigarettes assayed to contain 12 mg THC, or in an undrugged state, examined equivalent sets of these stimuli and imposed subjective organization by sequencing these 20 stimuli, presented as 2" x 4" pictures, in some order which made sense to the subject and which he felt he could reproduce at some later time. Later, in either a congruent or disparate state, subjects attempted to reorder these same stimuli. Under congruent conditions the reordering of these stimuli was a significantly better match to the original sequential ordering (encoding) than when ordering and later reordering occurred in disparate state (see figure 4 below).

FIGURE 4



Reproduction of Pattern Sequencing in Congruent and Disparate State Recall

All of these studies seem to suggest that where SDL appears it involves qualitatively different encodings or strategies for dealing with experience or recovering experience from memory.

MECHANISMS OF SDL

Some of our recent research efforts have focused on the structure and mechanisms of SDL, including defining the characteristics of stimuli and conditions at the times of storage and retrieval that might modulate SDL related dissociations. We have designed a number of experiments in which the induction of SDL could be assured, given a particular manipulation of storage and retrieval state, and then have superimposed conditions which might attenuate or potentiate dissociations of memory. The purpose of these studies was specifically focused on possible mechanisms and determinants of SDL and their implication for understanding state specific encoding and retrieval operations.

In one of these studies we had subjects listen to categorized lists of words after either smoking placebo material or active marihuana (containing 15 mg THC). Later, subjects tried to remember these words in either a congruent or disparate state. As expected, recall in a disparate retrieval state was significantly less complete than congruent storage-retrieval state recall. Subjects who attempted recall in the disparate state appeared to "lose" whole categories of information. For example, they would forget that names of flowers, vegetables, and cities were read to them. If a category name was recalled, however, they were no less able to recall category exemplars than when recall was attempted under congruent storage-retrieval state conditions. That is, whole categories of information dissociate rather than the fine detail within previously experienced structured events. If subjects are provided with the names of presented categories as cues or prompts at the time of recall, then SDL dissociations are erased. Such external cueing allows subjects to access information stored in some disparate state which was previously available but inaccessable under free recall retrieval conditions (4). This same effect of cueing at the time of retrieval erasing dissociations of memory has also been seen using physostigmine to induce state change (13).

The retrieval test conditions can also be altered by what the subject does in attempting to remember information. If a subject begins to recall previously stored words by starting with the information which was presented first, then dissociations are less

likely to be evident than if the subject starts the process of remembering with some event other than the first. The first recalled response by the subject effectively acts as a cue or prompt for recalling other information, and some cues, because of their learned relationship to other events that follow, provide a kind of context that can effectively surmount the state specific and disparate retrieval condition (3).

Some characteristics of stimuli can also modulate the likelihood of inducing dissociations in information processed in disparate state. For example, if subjects are presented with a mix of words some of which are more saliently encoded than others, then it appears that the least effectively encodable events are most susceptible to dissociation in a disparate state (12). Another way of altering how well an event is encoded is merely to repeat that event at the time of storage. That is, when events are presented just once, encoding is shallow, and they are more vulnerable to dissociation than when these same events are repeated, leaving a more salient, deeply processed trace event (3).

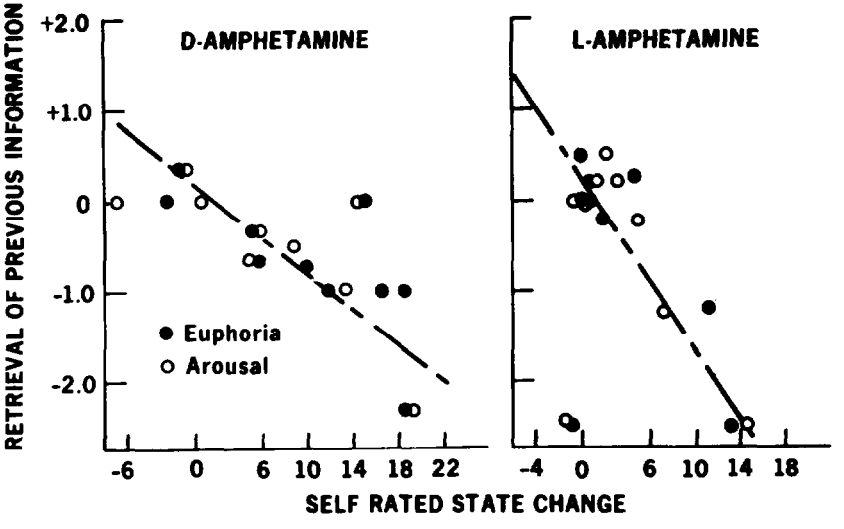
It therefore appears that striking or saliently encoded events are less vulnerable to dissociation. Regardless of encoding depth, if the subject's self-generated retrieval strategy for searching memory for information stored in the disparate state is not used, but instead the subject utilizes strong, effective search strategies provided by the environment (e.g., the experimenter), then dissociations are not evident. Dissociations involve the loss of subtle characteristics of experience that tie episodic, biographical events together. The recovery of such events requires that if the key to recall is lost, it must be provided for effective access to such previous experience.

THE SUBJECTIVE EXPERIENCE OF STATE CHANGE AS A NECESSARY CONDITION FOR SDL

We have noted in a number of studies that occasionally subjects would rate themselves in some state as particularly high, even if that state happened to follow placebo treatment. Recall might then occur in a disparate state with respect to their rated high, even if this occurs after again smoking placebo material but not experiencing an intoxicated state. These subjects show some of the same kinds of dissociation in recall as can be seen when, for example, learning takes place following marihuana treatment and retrieval follows smoking of placebo material.

We systematically explored this phenomenon by treating with amphetamine a group of depressed patients similar to those who had evidenced mood related dissociations of memory. Patients learned a sequence of words one hour following treatment with d-amphetamine, on another occasion following l-amphetamine treatment, and after placebo treatment. These three conditions were repeated after pretreating and maintaining patients on lithium. We found that amphetamine does induce SDL dissociations of information recalled in a disparate state. However, the most robust finding was that the extent to which dissociations of previously learned episodic events were evident was a function of the extent to which mood was lifted following amphetamine treatment and the disparity in mood that differentiated the storage state and retrieval state (see figure 5). The drug treatment was a necessary condition for the expression of SDL, but it also required a pronounced subjective drug response, lifting of mood and then return to baseline mood state (15).

FIGURE 5



Amphetamine Mood State-Dependent Retrieval of Previously Learned Responses

A similar finding was observed by behaviorally manipulating the mood of depressed patients and normal controls. Here we manipulated success or failure on tasks preceding the acquisition of information and/or just prior to the recall of information. We found that the success-failure manipulation produced a much stronger mood altering response in the depressed patients than in normal

controls. If mood as a result of the success-failure manipulation at the time of storage was disparate with mood at the time of retrieval, then SDL retrieval dissociations were evident. Normal controls, who were less mood response sensitive to these same success-failure manipulations, showed no evidence of a dissociation at the time of recall. Again the state difference could not merely be defined by a manipulation of state with drug or some behavioral context but required the experience of a strong subjective response. This may, in fact, merely reflect the larger phenomenon which defines a response, be it to a drug or some other stimulus, in terms of a behavioral and biological history which helps to induce the milieu in which that stimulus is "read" and "interpreted."

DISCUSSION AND CONCLUSIONS

It has been clear to us that one potentially rich research framework within which it appears possible to pursue some of these basic issues which might relate the biology of altered brain states with its psychology involves the use of information processing frameworks to define and describe changes in how experiences are appreciated, understood (encoded), stored (acquired, learned) and later retrieved either in terms of performance which requires access to previous learning or in remembering previous experience. Using the now numerous models and related techniques that have emerged from the study of how non-drug or mood-altered learning and memory proceed, it has been possible to begin to define some of the cognitive and other behavioral changes that characterize disturbances in mood as in depression and mania and similarly to use such schemes to examine the drug altered states such as are produced by alcohol, marihuana, and amphetamine. Most of the findings that have emerged from these research efforts have been limited to issues of the efficiency of cognition or behavior in some altered brain state, rather than on the qualitative changes in information processing that characterize how events are experienced and retrieved differently, rather than less well, in one state vs. another. Furthermore, almost none of such state specific information processing changes have been related to concurrent biological events. The studies reported here illustrate how one might systematically explore this set of issues, namely the qualitative changes in information processing that would differentiate one state from another.

Qualitative changes in how experiences are attended, stored, and later retrieved should also be reflected in a pattern of biological changes that would characterize brain as a unique context for the occurrence of state specific cognition. To accomplish this we have used and developed state dependent learning (SDL) paradigms as research strategies for framing pertinent questions that would differentiate cognition in one state from that in another state. The most important concepts that are basic to our approach include the following: Experienced events are those which have been selected out from a larger field of information on the basis of stimulus structural characteristics, as well as pertinent structured histories of previously stored experience (information) in memory. These structures define the strategies which are used to search fields of information, e.g., as in scanning a field or visual display of information. Some events are processed further, and are held in a short term memory store for further analyses. The extent to which events have been processed, and the elaborateness or depth of processing will, to a large extent, determine the likelihood of later recall (1). Events are also processed in some informational context which determines how they will be encoded. The specific encoding of events also determines the retrieval strategies which must be generated and used to search memory store if some event is likely to be recalled at a later point in time (9). Retrieval occurs in some context, in much the same way as information acquisition and encoding. An information context determines how information is encoded or what retrieval strategies are generated to search memory, and similarly a drug or mood-altered brain state can define a unique context for searching an information field, interpreting, organizing and encoding information, or inducing or biasing strategies for searching and accessing previously experienced events.

Using such a framework, it is possible to ask, first, whether a given state is discriminable from some other state, not only in terms of whether it "feels" different, but whether it induces a unique context for interpreting and storing events or for recapitulating past experience. Is information experienced in one state effectively recoverable in some different or disparate state? That is, are experiences that have occurred in one state dissociated at the time of recall when retrieval is attempted in some disparate state? Second, what are the unique transformations of events that occur in such an altered state? What is the unique context for processing events in a given state? Third, what are the mechanisms that determine, modify, and alter state specific strategies for encoding and retrieving experience? Finally, what are the interrelated

biological and psychological determinants that characterize such state specific encodings and retrieval of experience? The research accomplished to date has represented some of the bare beginnings of an exploration of these issues, which we believe to be a powerful vehicle for understanding the psychological and biological factors that are necessary to appreciate drug- and mood-altered states in man.

We would propose that a euphoriant, stimulant, or depressant drug, or some altered mood state forms a kind of biological and psychological context for processing and encoding events. Such a context may uniquely determine how we understand the meaning of events, how these are related to one another and to past events, and their interrelated relevance to the stream of ongoing events that precedes and follows some experience. Such a context also serves to determine and limit how we search for previously experienced biographical events in memory. The structures of these search strategies are intimately linked to the structures that were used to encode events. These contexts can be quite different from one another, and some happen to feel good while others represent a milieu for dealing with events which are dysphoric and to be avoided. Part of our behavior is motivated so that we might find effective contexts that permit events to be interpreted in a manner that permits positive evaluations. When the events around us look bleak we might seek out some alternative context for altering experience, and one vehicle for accomplishing this is with drugs of abuse.

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IV.
Treatment

CHAPTER 17

Multimodality Treatment of Narcotic Addiction: An Overview

George E. Woody, M.D., Charles P. O'Brien, M.D., Ph.D., and Robert Greenstein, M.D.

A major commitment of time and resources has been made in the treatment of narcotic addiction during the last fifteen years. This contrasts with addiction treatment prior to the 1960's when long-term therapy at Lexington, Kentucky, or Ft. Worth, Texas, or detoxification in a local hospital were the only treatments available. In those times, many hospitals excluded addicts, and there was little interest from most of the medical community in applying its expertise toward developing effective treatments for addiction. The more recent efforts and the current high level of interest have produced great changes, and many options are now available. As a result, treatment is easier to obtain, and the outlook for this once discouraging condition has been improved. Pharmacological treatments and therapeutic communities have provided the backbone of the present-day therapeutic approaches, but interest is growing in outpatient psychological therapies. This paper will discuss the treatments being used now and will present an overview of the field.

PHARMACOLOGIC THERAPIES

Narcotic substitution

The single therapy that has had the greatest impact on narcotic addiction appears to be methadone maintenance. Unlike drug-free approaches, it is acceptable to a large number of addicts (9). It is medically safe, has minimal side effects and no toxicity when given to tolerant individuals, even for long periods of time (29). Though

the results of methadone treatment vary among programs, there is strong evidence that it provides a way to control narcotic addiction. Most patients who remain in methadone treatment have a marked decrease in heroin use, an increase in employment rates, and demonstrate improved personal adjustment (12). At present there are approximately 80,000 people being treated with methadone in the United States (45), but despite methadone's wide applicability and effectiveness, it leaves much to be desired. It has been controversial since the beginning, and many aspects of methadone programs have been criticized (7, 13).

One problem has been an inability to demonstrate that methadone treatment increases the long term cure rate for addiction. This is a disappointment, as many had hoped that the social rehabilitation obtained via methadone maintenance would lay the groundwork for successful detoxification. In retrospect, this disappointment is probably natural and has precedents in other areas of medicine where new treatments are accompained by hopes which are not realized.

A second problem is the inability of methadone programs to attract and retain more addicts in treatment. Early experiences led to hopes that the majority of addicts within a given area could be enrolled and retained in programs. This has not happened. Enrollment usually includes much less than 50 percent of the addicts in any immediate area, and dropout rates are usually high (42). Program variables may account for many of these difficulties, and improvements in program quality may produce better results. A rapid evaluation and prompt initiation of treatment is one such quality that may increase program retention (66).

Another problem with methadone is diversion. Unless programs require daily attendance, "take home" doses must be given. A portion of these are almost always diverted. This may result in accidental ingestion of methadone by children or other nontolerant individuals, or in the sale of legitimately-prescribed methadone to other drug abusers (56, 61). On the other hand, the inconvenience of the requirement for daily attendance may reduce the attractiveness of treatment. Unfortunately, this may be particularly true for patients who are working and showing other indications of progress.

A fourth problem is that methadone is highly addicting, and some patients have complained that it is harder to detoxify from than heroin. This observation probably relates to dosage level and not to the drug itself (38). Most street heroin is of low purity, and thus physical dependence is low (2). Because of these differences, many patients being treated with methadone may develop a greater

degree of physical dependence while receiving methadone than they had prior to entering treatment. This may be necessary in order for some addicts to benefit from methadone treatment, particularly in cases where high levels of tolerance are desirable, but it should iead to caution in prescribing high dosages.

In spite of these problems, however, it is probably accurate to say that prior to the development of methadone maintenance there was no outpatient treatment that could demonstrate positive results for significant numbers of addicts. Methadone treatment, though far from perfect, seems to have added an important and positive element to the treatment of narcotic addiction.

The current development of methadyl acetate (LAAM), a derivative of methadone that prevents withdrawal symptoms for forty-eight to seventy-two hours, shows promise for correcting the diversion problem. Currently this drug is in a developmental phase, but it is undergoing widespread clinical trials. LAAM has effects that are similar to methadone and appears to have no serious toxicity when used properly. Its major advantage is that people taking it need come to clinic only three times per week. This is especially beneficial for patients who must travel long distances and for those who have irregular schedules or who work long hours. It is also desirable from a public health standpoint because its use almost eliminates the need for take-home bottles. Some think that it also tends to lessen dependency on the clinic and is a step toward becoming drug free (15). Studies done to date show that results for those who remain on LAAM compare favorably with those on methadone (31). However, LAAM may be less acceptable to addicts than methadone, as initial dropout rates are higher (3). This is difficult to evaluate because it is a new drug, and anxiety or other psychological factors related to its newness and investigative status probably influence some patients to discontinue it. If LAAM meets the safety and efficacy standards of the U.S. Food and Drug Administration (FDA) and is approved for general use, all clinics could use it, and most programs then would be in a position to offer patients either LAAM treatment three times per week or daily methadone. This system could lead to a marked reduction in methadone diversion and would be much easier for patients than coming to clinic for daily methadone treatments.

Propoxyphene napsylate, a drug with weak narcotic effects, has been tried with an eye to developing a maintenance drug that will produce less physical dependence than methadone. Propoxyphene can suppress abstinence symptoms in patients who have low degrees of physical dependence, and open clinical trials have shown that

some addicts can be maintained on it (21, 58). However, double blind studies comparing low doses of methadone (maximum 36mg/day) with high doses of propoxyphene (maximum 1200 mg/day in divided doses) have shown that propoxyphene is not as well accepted as methadone. Preliminary data from these studies show that dropout rates and frequency of street drug use are considerably higher in patients maintained on propoxyphene. It seems that propoxyphene, therefore, is not as effective as methadone for maintenance treatment (34). Since a few patients do well on propoxyphene it might be useful as an alternative to methadone for selected patients who have low levels of physical dependence, who do not fulfill FDA requirements, or who want maintenance but are opposed to taking methadone. Detoxification from propoxyphene produces less discomfort than detoxification from methadone and therefore it may be useful as a transitional drug that can bridge the gap between a low dose of methadone and abstinence. At the present time, however, propoxyphene does not have FDA approval for the treatment of opiate addiction.

Detoxification

Detoxification has never resulted in very much social rehabilitation or long-term abstinence (8), as patients usually relapse within the first two months after release from a detoxification program, sometimes even on the day of discharge. Many patients leave against medical advice before detoxification is finished (16). Most patients in a three-week outpatient program relapse to illicit drug use before they stop receiving methadone. Behavior problems are common during detoxification, and patients can become very disruptive, with adverse effects on other patients and staff. Several investigators have found recently that more addicts complete detoxification with fewer behavior problems if they are permitted to alter their own dose within limits set by the treatment team (48, 49). This method should increase the short-term success of detoxification. Its long-term results may be improved by following it with narcotic antagonist treatment.

Narcotic antagonists

Antagonists have been used for many years to treat narcotic overdoses. Nalorphine was the first in clinical use, but it was used

only with caution as it had agonistic as well as antagonistic effects. It was replaced by naloxone, an excellent antagonist with essentially no agonistic effects. Neither of these drugs is useful for the treatment of addiction per se, as they are short-acting and ineffective when given orally unless used in very high doses (39). However, two antagonists, cyclazocine and naltrexone, have been developed recently for use in outpatient treatment programs. Both appear to be safe and effective when administered to detoxified addicts (50, 51). They are given orally and completely block or markedly attenuate the effects of narcotics for twenty-four to seventy-two hours (16). Naltrexone is the superior drug, as it appears to have no agonistic effects other than occasional gastric irritation, and it is considerably longer acting (up to 72 hours). These drugs can be used as "insurance" against relapse, and they are effective in well-motivated patients. On the basis of favorable experience with antagonists in selected patients, some treatment programs are recommending that they be used for two to six months following detoxification.

Though antagonists are effective pharmacologically, their clinical usefulness for the majority of patients is uncertain. Most addicts are not interested in taking them, and most of those who start drop out within the first month (16). Naltrexone produces no euphoria or physiological dependence, so it does not have an immediate reward, nor does it motivate patients to continue in order to prevent withdrawal symptoms as methadone does. Depot forms lasting 2 to 4 weeks are being developed, and they may result in more compliance with antagonist treatment. Some programs are experimenting with behavioral reinforcers that may encourage patients to stay in antagonist treatment longer.

Pharmacologic Treatments for Concurrent Psychiatric Problems.

Another area of current interest is the treatment of psychiatric problems that often accompany addiction. Some believe that psychiatric problems are a prerequisite for the development of addiction (10, 14, 46, 68, 69). Others feel that narcotic addicts have minimal inherent psychopathology and that much of the psychopathology noted is a consequence rather than a cause of addiction (43, 44). Wherever the truth may lie, many studies and clinical observations indicate that addicts have an assortment of psychiatric disorders (17, 18, 19). The degree of psychopathology is probably

related to the addict's cultural background. Those individuals who come from an environment where there are great social pressures against drug abuse are more likely to have serious psychiatric problems than are those coming from a background in which drug abuse is viewed less negatively (22, 23).

One common problem is depression (59). There is considerable evidence that addicts have a higher incidence of depression than nonaddict peers. The depression, when present, is probably greatest at admission (27), but it remains high even after stabilization on methadone. Some studies have shown that 20 to 40 percent of patients on methadone maintenance are depressed (52, 60). The depression is typically mild to moderate, and not the severe, psychomotor-retarded and delusional type seen on inpatient psychiatric units. If untreated, it may contribute to the severity of the addiction, since self-medication for depression (or other psychiatric problems) may be a reason that addicts relapse or continue to use drugs while being treated with methadone (24). Effective antidepressant treatment may improve outcome, and two pilot studies have shown that depressed, methadone-treated addicts will respond to tricyclic antidepressants (53, 65). In one double blind study comparing doxepin with placebo, patients treated with methadone and doxepin had less anxiety, less depression, reported less drug craving and less amphetamine use than patients treated with methadone and placebo (65).

Many addicts have significant anxiety and may request tranquilizers, especially diazepam and sedative hypnotics. Though these drugs are effective in reducing anxiety, there is considerable risk that they will be abused. Addicts not infrequently take 30-80 mg of diazepam in one dose and say that it creates a peaceful, euphoric sensation which they describe as a "high." Continuous use of high doses of these drugs can produce physiological dependence; we have observed several instances of this, including three patients who had grand mal seizures after high dose diazepam was abruptly stopped (63, 64). Because of its frequent abuse by patients in drug treatment programs, diazepam should be prescribed with great caution. It is probably more appropriate to prescribe small amounts of oxazepam, chlordiazepoxide, doxepin, phenothiazines, or haloperidol for patients who request medication for anxiety. At least one of these usually works, and none has been noted to be abused by addicit patients to any significant degree.

Neuroleptics are useful for addicts with psychosis or borderline personality disorders. Psychoses probably are seen more commonly in patients who come from high socioeconomic groups (22).

Patients with these problems can be very disruptive to their families, employers, and the treatment program when they are overtly psychotic or when expressing intense affects such as anger or acute depression with suicidal behavior. Often, they can be treated by combining neuroleptics with methadone. Brief hospitalization may be necessary. We have been impressed by the ability of low doses of haloperidol to attentuate the intense outbursts of anger or aggression seen in paranoid schizophrenics and borderlines. It has been noted by clinicians for a long time that methadone aione appears to have some antipsychotic action (28), but this is enhanced by adding haloperidol.

Another area of interest is the treatment of alcoholic narcotic addicts. Alcoholism has been reported in 20 to 80 percent of narcotic addicts (70), and is a problem among patients on methadone maintenance. Some workers feel that methadone treatment increases the severity of alcoholism (11). However, a recent study has shown that methadone neither increases nor decreases its severity (1). Some pilot work has shown that disulfiram (Antabuse) can be used safely with methadone and may improve treatment outcome (4, 30). At present the Veterans Administration has started a collaborative project to study the effectiveness of disulfiram when used as an adjunct to methadone in the treatment of addicts who are also alcoholic.

Therapeutic Community

Some of the most intensive efforts to treat addiction have been made by therapeutic communities. These are iong term residential programs, some lasting for more than two years. They rely heavily on group therapy and use intense confrontation techniques. Selectivity in referral is essential in order to screen out those patients who cannot tolerate the anxiety that is generated. Studies have shown high rates of rehabilitation in patients who complete treatment in therapeutic communities (47). Recent work has demonstrated that positive changes occur in patients who complete even a portion of the entire program and that those patients who stay longest tend to improve the most (6). However, all studies of therapeutic communities are difficult to interpret because there are self-selection factors operating in those who enter and those who graduate. Controlled studies are needed to differentiate what part of outcome is due to treatment and what is due to patient factors.

The practical and ethical problems inherent, in random assignment of patients to a therapeutic community or a methadone program make controlled studies of therapeutic communities difficult. They are four to five times more expensive per patient-year than methadone programs, and consequently their cost-effectiveness relative to methadone programs is an area that must be considered.

Outpatient, Psychotherapies Used With Methadone Maintenance

There is growing interest in studying the effect of outpatient psychotherapy when combined with methadone maintenance. Some feel that psychotherapy is one aspect of treatment which, if improved, wouid lead to better results (32). Family therapy as an approach has been studied, and some preliminary results show that it can have a positive effect. In a controlled study completed recently in Philadelphia, a group receiving structural family therapy plus methadone did significantly better than control groups receiving only methadone and routine counselling. The family therapy patients detoxified more frequently and successfully and had higher rates of employment than controls (54, 55). At this time no other controlled studies of family therapy in addiction have been done, and more work in this area seems indicated.

Individual psychotherapy is another area to be explored. Traditional psychiatric and psychoanalytic teaching has indicated that analytically oriented psychotherapy is not appropriate for addicts (67). However, clinicans with experience working in maintenance programs have expressed the belief that analytic psychotherapy or a modification of it may be helpful if used in addition to methadone. It is not clear what type of therapy is most applicable, but participants in a recent NIDA conference suggested that it should combine support, structure and self-expression (32). No controlled studies on the effectiveness of psychotherapy have been done at this time, and positive results from psychotherapy studies could have a major impact on the organization and staffing patterns of methadone treatment programs.

BEHAVIORAL THERAPIES

Contingency Contracts

Contingency contracts are written agreements between a patient and his therapist which stipulate that certain behaviors must be produced within a specified time if the patient is to remain in good standing. These contracts are used most often for patients who do not respond to methadone and routine counselling. Some feel that they may provide the extra push that is necessary to make something happen (57) and may lead to positive results in as many as 60 percent of cases (37). Initiating such a contract commits one to suspending the patient if he does not respond, so it should be done carefully and selectively.

Deconditioning

Deconditioning techniques aim to diminish the intensity of drug-seeking behavior. Some patients have been observed to develop signs and symptoms of narcotic withdrawal following detoxification when they return to their old neighborhood (62). This has occurred following months or years of abstinence, such as after release from long-term incarceration. These withdrawal reactions appear to be conditioned to environmental stimuli that were associated previously with drug use. Recently, signs and symptoms of conditioned withdrawal have been reproduced under controlled laboratory conditions in patients being treated in a methadone program (35). Conditioning of euphoria and other agonistic effects has also been observed (41). The significance of these phenomena under clinical conditions is uncertain. They may account for only a small part of the tendency to relapse to drug use. Nevertheless, a program to locate and extinguish these responses in individual patients seems feasible. A series of experiments is now underway to see whether extinction of conditioned responses contributes to improved treatment results (36, 40). In these studies, patients undergoing treatment with naltrexone are exposed to drug-related stimuli and gradually desensitized to their effects. Eventually they are permitted to self-inject narcotics while on naltrexone. The antagonist blocks the rewarding effects of opiates, and the absence of this reinforcement leads to extinction of the conditioned responses

associated with drug injection. This procedure or variations of it may decrease the intensity of drug-seeking impulses and improve outcome.

Biofeedback

EMG biofeedback may be useful, especially for the reduction of anxiety and depression associated with addiction. It has special appeal because it is a nonpharmacological treatment which offers the promise of teaching patients techniques which they can use safely and independently. Several pilot studies have shown that biofeedback may reduce anxiety and depression (26); however it is not clear whether these results are treatment effects or nonspecific (placebo) effects. A recently completed controlled study of biofeedback has shown that both treatment and control groups improved significantly and equally (25). More controlled studies are necessary if actual treatment effects are to be demonstrated.

Milieu Therapy

Certain aspects of the treatment milieu, such as structure, support, staff quality, doctor time per patient, physical facilities, staff to patient ratio, and staff cooperation probably affect outcome (33). Milieu qualities may influence who applies for therapy, who stays, and how patients respond. Very little work has been done in examining the treatment milieu of drug programs. Moos has developed scales to measure environment in general psychiatric treatment facilities, and his scales may be adapted for use in addiction programs. It is not known what elements of milieu are helpful, but structure and support are probably important qualities. Studies in this area may identify aspects of programs that influence outcome. This area is complex since the milieu itself is most likely a result of interactions between the program and patients enrolled in it. However, it may be possible to identify qualities of the milieu and relate them to outcome in specific groups of patients. For example, it may be found that psychopathic personalities do best in settings that use intense and frequent confrontation, whereas neurotic patients do poorly in such a setting and have a better outcome in settings that are less intense and more supportive.

ENDORPHINS

The recent and exciting discovery of endorphins (5, 20) may lead to a significant breakthrough in understanding and treating addiction. Endorphins are naturally occuring peptides which have narcotic-like effects. Important basic research is now going on which may clarify a biological basis for opiate addiction. Interestingly, the hypothesis of such a biological basis for addiction originally led Dole and Nyswander to propose methadone substitution therapy. The possibility that the strong drug-seeking behavior of chronic opiate addicts may be influenced by biochemical deficiencies in endorphins is one of many potential clinical applications of this line of research.

SUMMARY

In closing, it seems important to add that, when viewed longitudinally, addiction resembles a chronic medical disease. Rehabilitation may take several years and improvement rather than cure may be the most reasonable goal. Disappointment at the lack of success in finding an effective cure is common, but a relapsing and remitting course does not necessarily imply failure. Return to treatment may signal continuing efforts and progression toward abstinence. Improvement in current techniques may make remissions longer and relapses shorter. Current work on endogenous opiates (endorphins) may lead to tests which will identify those patients who can achieve drug-free status and those who can function only when maintenance opiates are applied.

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IV.
Treatment: LAAM

Walter Ling
Chairman

CHAPTER 18

Levo-Alpha-Acetylmethadol: New Drug for Old Habits

Walter Ling, M.D.

INTRODUCTION

Welcome to the symposium on ℓ-alpha-acetylmethadol (LAAM). This symposium deals with the clinical aspects of the development of LAAM as a pharmacological therapeutic surrogate for the treatment of chronic heroin addiction. It will review a group of individual and cooperative studies completed in the past decade, report on the progress of several ongoing studies, draw some conclusions on the safety and efficacy of LAAM as a maintenance treatment agent, and offer some perspective about the future development of LAAM and its eventual role in the treatment of narcotic addiction.

Perhaps a good place to begin the story of LAAM is with methadone maintenance. The idea of a pharmacological approach to heroin addiction is, of course, not new and has been used in England for many years.

In the United States, however, for many years before the introduction of methadone maintenance it was generally believed that chronic heroin addicts were primarily mentally ill, and that their craving for narcotics was an epiphenomenon which would automatically disappear with successful psychological rehabilitation. Treatment was focused on long-term psychological intervention in institutions. The results of these therapeutic approaches were generally disappointing, because of frequent relapses.

In 1965, Drs. Vincent Dole and Marie Nyswander of the Rockefeller Institute, New York City, introduced the idea of methadone maintenance. They believed that the craving for narcotics exhibited by chronic heroin addicts was based on some

physical, biochemical changes resulting from repeated exposure to the narcotics and proposed that this aspect of the addict's problem can be treated independently and quite apart from other aspects of social rehabilitation, much like treating diabetics with insulin. In practice, addicts were maintained on a stabilizing dose of oral methadone given once daily which relieved them of their ever-present narcotic hunger and thus enabled many of them to become socially rehabilitated.

Over the next several years, methadone maintenance rapidly gained popularity, and by the early 1970's it had become one of the most widely accepted treatments for heroin addicts in the United States.

The widespread use of methadone maintenance, however, has not been without problems. For although its 24-hour duration of action may seem a vast improvement over the situations with heroin, this is really too short for the purpose of social rehabilitation. Daily clinic attendance often interferes with such rehabilitation efforts as job training, school attendance, and actual employment. Allowing addicts to take methadone home partially alleviated this situation but created some serious problems of a different kind. Medications taken home were sold on the street and became the major commodity of a new black market for drugs. Reports of primary street methadone addiction and deaths from accidental poisoning soon began to appear. The need to find a longer acting methadone-like drug that will reduce this need for take-home medication in particular and improve the maintenance treatment of heroin addicts in general led to renewed interest in LAAM.

LAAM, a congener of methadone, was first synthesized in 1948 and underwent early clinical testing as an analgesic. However, the delayed onset of action and its prolonged time course, leading to culminative toxicity, limited its clinical usefulness as an analgesic for acute pain. In the early 1950's, Fraser and Isbell and their colleagues (1) had demonstrated that a single oral dose of LAAM could suppress the symptoms of narcotic withdrawal for up to 72 hours. However, they felt this was not an advantage over methadone, since at that time major medical interest was in detoxification rather than in maintenance. In 1968, Jaffe and coworkers (2) first used alpha-acetylmethadol in a narcotic addict treatment program in Chicago, Illinois. They substituted d-l-alpha-acetylmethadol (DLAAM) three times weekly in a small group of patients maintained on daily methadone and showed that these patients did about equally well on acetylmethadol as they did on methadone. Since the L-form of acetylmethadol was largely responsible for the

observed clinical effects, subsequent investigations have been focussed on LAAM.

Many investigators, individually and in collaboration, have contributed to the clinical development of LAAM in the past decade. Except for some early individual studies, various members of this panel have been personally involved in one way or another in much of this effort. Dr. Jack Blaine, who is the project officer for LAAM at the National Institute on Drug Abuse (NIDA), will review the early clinical studies which provided the first indications of safety and efficacy for LAAM. Most of these were results of investigations by individual investigators or several investigators working together at a single site.

By 1972 sufficient data had become available for the safe conduct of a multihospital large-scale trial. Dr. Jerome Jaffe, Head of the Special Action Office for Drug Abuse Prevention (SAODAP). Dr. Samuel Kaim, Chief of the Veterans Administration (VA) Alcohol and Drug Dependency Service, and Dr. C. James Klett, Chief of the VA Central Neuropsychiatric Research Laboratory, at Perry Point, Maryland, were instrumental in the planning of this 12-hospital double blind cooperative study.

As a member of the Executive Committee for that study and as one of the principal investigators, Dr. Charuvastra is intimately knowledgeable of the study and will review for this audience the results of this effort which has been from time to time called pivotal in the development of LAAM.

Another large scale multicenter study, an open trial designed to complement the VA study, was initiated in 1973 by SAODAP. Dr. C. James Klett not only served as the principal investigator and sponsor for the project but also coordinated the collections and analysis of the research data, as he did in the VA study. The success of the two multicenter studies owes much to the untiring effort on Dr. Klett's part, and his patience with the investigators and coordinators has earned him the title "Shepherd of LAAM" among some investigators. Dr. Klett will review the results of the SAODAP study. I suspect in his usual relaxed manner he will make the project sound simple and straightforward, whereas in fact it was clinically and administratively most complex and complicated.

We believe that the VA and SAODAP cooperative projects, taken in conjunction with some earlier studies, provide substantial evidence of safety and efficacy for LAAM. However, at the conclusion of these studies the number of investigators having experience with LAAM remained relatively small. In an effort to bring this experience to a larger number of clinicians and to gather

further safety and efficacy data on this drug, several thousand patients are being treated in some 60-70 clinics across the United States under a common protocol sponsored and administered by Whysner Associates under a contract from NIDA. Dr. John Whysner, whose involvement in LAAM research dates back to the earlier SAODAP study, having served as its first project officer at SAODAP, is head of Whysner Associates and will report on the progress of this most ambitious undertaking.

The development of LAAM is unique in one other important respect. I have asked Dr. Pierre Renault to be the final speaker in this presentation because of his present position as Chief of the Clinical/Behavioral Branch at NIDA, within which resides the responsibility for the current efforts on LAAM. Ordinarily, a pharmaceutical company becomes interested in a certain drug and undertakes to develop it through various phases of preclinical and clinical trials until sufficient data on safety and efficacy have been gathered. It then applies to the U.S. Food and Drug Administration (FDA) for approval to market the product. In so doing, the company commits its resources as a developer and hopes for a return in profit through sales under a patent. The government has only the role of a regulatory agency. Because LAAM has been in the public domain for many years and therefore was not patentable, there was no particular incentive for drug companies to become interested in its development. The government was thus put in the peculiar position of having to undertake the major effort to develop the drug and at the same time to regulate its development. Through the formation of an Interagency Pharmacological Task Force, several government agencies have been able to work cooperatively but maintain their separate and distinct responsibilities. The eventual approval of LAAM for general use remains with the FDA. NIDA has more or less assumed the task of assembling the scientific data to satisfy the FDA's requirements. Dr. Renault's office is that branch of NIDA directly charged with this latter responsibility. The emphasis of his presentation will be on the current status and the future perspective of LAAM.

There remain a few loose ends. Much of the clinical data on LAAM have been gathered in adult male heroin addicts. Little information is available in females. More work obviously will be needed here. The pharmacokinetic data on LAAM remain somewhat incomplete. There may be time for us to report on some of the ongoing work between Sepulveda VA Hospital and the Center for Human Toxicology at the University of Utah, Salt Lake City. Several investigators working as a consortium are examining several

methods of induction and detoxification. For the purpose of this introduction, I have chosen to share with you the relative advantages of LAAM in comparison to methadone. Whereas the bulk of this symposium is focused on how LAAM is being developed, the examination of its relative merits in comparison to methadone hopefully will provide some insight into why this work is of clinical interest. I shall examine this from the standpoint of the patients, the clinics, and the community at large.

As was alluded to earlier, the 24-hour duration of action of methadone really is too short for purposes of social rehabilitation. Many hours have to be spent in traveling to and from the clinics daily to receive methadone. This interferes with school attendance, job training, actual employment, and homemaking. Moreover, many addicts actually feel enslaved by this rigid ritual; they feel tied down and "hooked" in a new way.

This in turn leads to resentment and anger. Not infrequently, harsh criticism and charges were made against methadone maintenance treatment as a result of these feelings. Given three times weekly, LAAM allows the addict more time for other rehabilitative efforts; it breaks the daily ritual of methadone ingestion, deemphasizes the issue of medication, and may also decrease the degree of psychological dependence.

For some addicts, a moderate dose of methadone does not suppress abstinence for the full 24 hours. Many patients arrive at the clinic on the verge of suffering from withdrawal. They describe themselves as feeling "icky," and are irritable, impatient, and easily provoked. Many confrontations occur between patients and clinic personnel under these circumstances. On the other hand, at higher doses, some patients become oversedated soon after receiving their medication and are at times arrested for being under the influence of drugs. The longer time course of LAAM eliminates or minimizes this psychological seesaw phenomenon.

The major problems of street diversion and accidental poisoning with take-home medication have already been noted. In addition, patients are sometimes harassed because of their being in possession of a narcotic even though it was dispensed by a clinic. Occasionally, genuine loss or thefts of medication also occur, and this may lead to the patient's coming under suspicion of selling his methadone. Usually the patient is unable to prove such losses, and clinics generally refuse replacement of such medication. The result is that the patient often feels that his efforts have been futile, that nobody would trust him no matter how hard he tries.

Many addicts, after being on methadone, find it very difficult or impossible to discontinue treatment. There is some suggestion, though hard data remain lacking, that it might be easier to detoxify from LAAM than methadone. If this proves to be the case from several ongoing studies, it alone would make LAAM a superior drug to methadone as far as the patients are concerned.

Perhaps the biggest beneficiaries of LAAM are the clinics. A three-time-per-week dispensing schedule simplifies the logistics of drug handling, storage, and bookkeeping, and improves accountability. It gives the clinic staff more time to spend with their patients in other therapeutic activities and may expand the clinic's total treatment capacity.

More importantly, a three-time-per-week dispensing at the clinic with no take-homes will eliminate the dosage games altogether. In methadone clinics where take-home medication is allowed, staff and patients spend an enormous amount of time engaged in dosage bargaining, because methadone is such a sellable commodity on the street. It is often impossible to tell whether a complaining patient genuinely needs more medication or whether he is trying to convince his doctors to give him more methadone so that he can sell part or all of it. Consequently, clinic staff try their best to hold the dosages down, and patients through various means try to increase them. All this takes time but has little therapeutic value. Moreover, since take-home privileges often depend on the patient's ability to give a urine free of illicit drugs, urine games and tricks, including bribery, are an integral part of the clinic's daily routine. Eliminating take-home medication would remove the incentive on the patient's part to obtain more drugs and give the physician more flexibility in his dosage considerations.

The fact that LAAM has a slow onset of clinical effect makes it much less likely to be abused by addicts, since there is no immediate gratification, which is what most addicts are after when they "fix."

Predictably LAAM will not totally replace methadone, but its availability with concurrent modification in clinic practice should give clinics added flexibility and improve the general strategies of the pharmacological approach to narcotic addiction.

Improvement in treatment strategies ultimately means cost saving to the community as a whole. The risk of accidental poisoning will be vastly reduced, and the methadone black market will hopefully disappear.

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CHAPTER 19

Early Clinical Studies of Levo-Alpha Acetylmethadol (LAAM): An Opiate for Use in the Medical Treatment of Chronic Heroin Dependence

Jack D. Blaine, M.D.

INTRODUCTION

For many years, heroin-dependent individuals were treated by abrupt or gradual discontinuation of heroin, leading to abstinence. Resulting withdrawal symptoms were often treated palliatively with non-opiate medication. The failure of medically controlled heroin detoxification alone to achieve the goal of long term continued abstinence has been voluminously documented in the United States. The reduction of human suffering and freedom from the compulsive search for and use of heroin do have value as a first step in rehabilitation by permitting a shift to more constructive pursuits. Efforts at treatment by maintenance of heroin-dependent individuals on legally dispensed heroin also appear to be an inadequate and impractical treatment approach.

Methadone, a synthetic developed as an analgesic opiate, has a pharmacological profile similar to morphine. Methadone retains its activity when taken by mouth and is slowly inactivated (22). Thus, one oral daily dose of methadone can substitute for several intravenous doses of heroin.

Dole and Nyswander (9) demonstrated that heroin-dependent persons could be "stabilized" for extended time periods on a single daily oral dose of methadone. Dose is gradually increased as tolerance develops, starting from the dose which relieves the abstinence syndrome. As dose is raised, a level is reached which relieves the individual's craving or "hunger" for heroin but is not

intoxicating itself. As the dose level is increased, sufficient tolerance is induced to block the euphoric effect of intravenous heroin. Thus, stabilization on methadone frees the individual from heroin-oriented hustling and allows participation in a comprehensive treatment and rehabilitation program. Data generated by several clinical researchers in the ensuing years indicated the safety and efficacy of this form of treatment under good medical supervision (13, 26).

While methadone was an effective agent, several investigators (4, 24, 25) realized in the late 1960's that a longer-lasting medication would offer several practical therapeutic advantages. Chemical (6, 38, 42, 10) and pharmacological (11, 12) data already available suggested the potential clinical usefulness of levo-alpha acetylmethadol (LAAM), a methadone derivative developed two decades earlier.

CLINICAL PHARMACOLOGY OF LAAM

Extensive investigations of the clinical pharmacology of LAAM were carried out at the Addiction Research Center, Lexington, Kentucky (11, 12, 22, 23), using subjects formerly dependent on opiates and withdrawn. Single doses of LAAM produced morphine-like physiological and subjective effects.

However, Fraser and Isbell (11) commented that "the results were very peculiar," based on the time-effect curves by the parenteral and oral routes of administration. When 10 to 30 mg of LAAM was given by the subcutaneous and intravenous route, no objective manifestations of opiate-like action were noted for four to six hours after injection, after which time the opiate-like effects slowly became apparent over 12 to 16 hours. The opiate effects after a single dose were extremely long lasting compared to other opiates. These effects were always detectable 24 hours after injection, usually seen at 48 hours, and occasionally persisted for 72 hours. After oral administration of 30 to 40 mg of LAAM, definite, more intense, morphine-like effects were observed much more rapidly, within 90 minutes, reaching maximum effect in 4 hours, and had similar persistent action to the parenteral route. Subcutaneous doses of LAAM given twice daily for several days resulted in cumulative opiate toxicity including respiratory depression, mental confusion, altered consciousness approaching coma, and severe nausea and vomiting.

Fraser and Isbell (11) further demonstrated that single oral doses of 30 to 60 mg of LAAM rapidly abolished all signs of abstinence in

patients who had been stabilized on 400 mg of morphine daily and abruptly withdrawn 28 hours previously.

Substitution of LAAM for morphine was completely adequate when 1 mg daily of oral LAAM was substituted for each 6 to 8 mg of parenteral morphine given four times a day. No withdrawal signs appeared when the interval between LAAM doses was increased to 72 hours. Definite, but mild, abstinence symptoms developed in all patients 84 hours after administration of the last oral dose of LAAM. Following abrupt discontinuation of LAAM, a mild abstinence syndrome appeared which was quite similar in time course and intensity to methadone. Gradual reduction of LAAM dose over a period of seven days did not appear to alter the course or intensity of abstinence after the last dose.

Thus, LAAM was found to be approximately equally as efficacious as l-methadone in alleviating abstinence from morphine by the oral route, but the drug was inconsistent by the parenteral route of administration, due to the slow onset but persistent activity.

Interestingly, Fraser and Isbell (11) suggested LAAM may possess advantages over methadone and other narcotic analgesics if the drug's analgesic effect has as great a duration as the physical dependence-supporting and miotic actions. They cautioned that "if the drug is used clinically, it should be given orally in small dose and at widely separated intervals in order to prevent cumulation of the toxic effects."

EVALUATION AS AN ANALGESIC

Early clinical investigation did focus on the usefulness of LAAM as an analgesic in chronic pain. As predicted, LAAM was less effective than morphine when administered subcutaneously, and the onset of analgesic activity was delayed for about 90 minutes. Delayed cumulative toxic effects of opiate overdose were noted when larger doses of LAAM were given more than once daily to nontolerant chronic pain patients (1, 35). Effective analgesia with extended duration was noted with lower doses of orally administered racemic alpha acetylmethadol (7, 8). The LAAM metabolite, nor-LAAM, was shown to be a more potent analgesic than morphine or LAAM, and toxic side effects were less when taken by mouth (16). Analgesic effects were equivalent with a similar time course to morphine when nor-LAAM was given parenterally (18). However, the delayed onset of action, prolonged time course, and

cumulative effect limited the clinical usefulness of LAAM and nor-LAAM for analgesia, and its development was not undertaken by the pharmaceutical industry.

CLINICAL PSYCHOPHARMACOLOGY OF LAAM

Irwin, Blachly and co-workers (20, 21) compared in double blind, randomly controlled studies the psychopharmacological profiles of 0.1 to 0.2 mg/kg doses of oral methadone and LAAM in nontolerant subjects. Peak effects occurred after three to four hours for both drugs. Durations of action were similar for both drugs at lower doses, but at higher doses the action of methadone lasted less than 12 hours, while LAAM persisted over 24 hours. The higher dose of LAAM produced similar but somewhat less intense subjective effects than the lower dose of methadone.

Biphasic effects were noted for both drugs, with early activation, elevation of mood, and liking for the drug, followed by a later depressant effect and dislike for the drug. The effects of LAAM were primarily activating, including slightly increased capacity for functioning; increased arousal, drives, energy, speed, and durations of movement and expressiveness; and slightly improved mood. In contrast, depressant effects predominated with methadone, including impaired arousal, focusing, and psychomotor activity; distorted perceptions; and worsened mood. Methadone and LAAM were quantitatively equipotent in many other effects characteristic of opiates, including causing ataxia, unusual body sensations, distortion of sensations, impaired memory, reduced impulse control, mild headaches, itching, nausea and vomiting, facial pallor, slowed respiratory rate, and miosis.

EVALUATION OF CROSS TOLERANCE TO INTRAVENOUS OPIATES

Several investigators have studied the development of cross tolerance by LAAM to the effects of intravenous opiates. Irwin and coworkers found that LAAM was usually effective in providing blockade to 30 mg of morphine sulfate in subjects stabilized on a variety of LAAM doses. Occasionally, a slight high was reported, usually within 8 hours or after 48 hours of LAAM consumption. Subjects could distinguish morphine from placebo and experience a slight rush (20).

In studies by Zaks and Fink (45), LAAM provided complete blockade to 25 mg of intravenous heroin for 24 hours after last dose in subjects rnaintained on low doses (30 to 40 mg twice weekly and 50 mg on Friday), while 50 mg of heroin produced mild, transient euphoria. LAAM provided complete blockade to 25 and 50 mg of heroin for 24 hours in subjects maintained on high dose LAAM (80 mg Monday, Wednesday, and Friday) or methadone (100 mg daily).

In another study (37), a dose-response curve was established for the dose of LAAM and blockade of 25 mgm of intravenous heroin given 72 hours after the previous LAAM dose in maintenance patients. At dose levels of 30 mg of LAAM given Monday, Wednesday, and Friday, some effects of heroin were experienced. At 50 mg levels, no effect of heroin was perceived by the subjects, but slight pupillary constriction was detected. At dose levels of 70 mg and above, blockade was complete. Interestingly, this approximated the dose-response curve of LAAM to produce sustained maximum pupillary constriction (miosis): 20 mg for 24 hours; 30-50 mg for 48 hours; 80-90 mg for 72 hours.

METABOLISM AND PHARMACOKINETICS

The recent development of methodologies for identifying and quantitating levels of LAAM and its metabolites in human biofluids (31) has stimulated interest in the metabolism and pharmacokinetics of LAAM. The delayed onset, long duration of action, differences by oral and parenteral routes of administration, and cumulative effects of LAAM have, in part, been attributed to the biotransformation to two active metabolites, nor-LAAM and dinor-LAAM by the n-demethylating enzymes in the liver (2). Several studies indicate that the opiate-like effects of LAAM may be determined primarily by these metabolites rather than the parent compound (3, 14, 17, 30). Because of the potential clinical usefulness of this information for clinical management, further studies are currently going on in this area.

CLINICAL TRIALS AS A MAINTENANCE DRUG FOR TREATMENT OF HEROIN DEPENDENCE

Jaffe and co-workers in Chicago (24, 25) initiated in the late 1960's the first clinical trials of acetylmethadol based on the

indications of human safety and efficacy as a long-acting opiate maintenance drug suggested by the earlier clinical pharmacological studies at the Addiction Research Center. In a series of well-controlled, double-blind studies (24, 25, 27, 28, 29, 40), these researchers investigated the safety and efficacy of LAAM and racemic acetylmethadol compared to methadone in chronic heroin-dependent persons. Subjects already stabilized on methadone were randomly assigned to LAAM or methadone. The experimental groups received LAAM on Monday, Wednesday, and Friday, and dextramethorphan placebo on alternate days, while the control group received methadone daily.

Generally, these controlled clinical trials revealed few differences between LAAM and methadone patients on outcome measures of use of heroin and other illicit drugs, illegal activity and arrests, employment, education, clinic attendance, patient acceptance, or dosage changes. They confirmed earlier findings that LAAM can be administered at 48 to 72-hour intervals without the development of an opiate abstinence syndrome.

Few unusual reports of toxicity or side effects were noted. These adverse reactions which did occur were particularly associated with excessive dosage. Similar reactions were not uncommonly reported with methadone and would be considered common to all opiates. Results of hematology, blood chemistry, urinalysis, and physical examinations revealed few differences between LAAM and methadone patients. Most results have been within normal limits, and treatment commonly produced an improvement in some abnormal pretreatment laboratory values. The isolated deaths which occurred during the study were not related to LAAM or methadone. Although there were several reports of anxiety and nervousness in an earlier study with racemic acetylmethadol, these were not present using LAAM. No occurrences of confusion, unpleasant subjective states, or psychotic symptoms caused by LAAM were reported. Several instances of nightmares and anxiety and one report of a dissociative state with bizarre behavior were reported (41).

In the years following the reports of the initial pilot studies, several additional teams of investigators conducted clinical trials with LAAM (4, 15, 19, 36, 39, 41, 45). Generally, these studies confirmed the findings of comparable safety and effectiveness of LAAM and methadone as maintenance drugs for use in the treatment of chronic heroin-dependent persons. Approximately 750 patients were given LAAM in these studies. Dosages varied widely,

with a mean LAAM dosage of 60 mg three times weekly and a range of 20 to 90 mg.

Most of these investigators found that LAAM given Monday, Wednesday, and Friday prevented the occurrence of withdrawal symptoms equally to methadone given seven times a week. Some reported that increasing the dosage either at each administration or on Friday was necessary to completely prevent abstinence symptoms for 72 hours (36, 45). However, the results of a double-blind controlled study by Goldstein (15) suggest that complaints of LAAM not holding over the entire weekend were psychological rather than pharmacological in origin and arose out of the patient's attitude and concern that the medication would not prevent withdrawal for 72 hours. Great individual variation was noted in the dosage that will prevent abstinence for 72 hours.

Treatment outcome measures were generally found not to show significant differences between LAAM and methadone treatments. The main differences between LAAM and methadone treatment groups noted in all these studies is that a larger percentage of LAAM patients than of methadone patients drop out of the study, although the differences were often not statistically significant. The dropouts tended to occur early in the studies during the stabilization phase. These early dropouts may be partially related to psychological concerns about taking an "experimental" new drug. Thus, any minor symptom experienced by the patient may be attributed to the "experimental" drug and be perceived as proof that it won't work. As discussed previously, LAAM does have a delayed onset because of the time required to metabolize LAAM to its more active metabolites and build up pharmacologically active blood levels. Thus, initial discomfort may occur in some patients dependent on large doses of heroin or methadone who are not given adequate starting doses of LAAM, or for patients who slowly convert LAAM to its active metabolites.

Results of these studies confirmed the absence of significant toxicity or adverse reactions for both LAAM and methadone. Laboratory tests and physical examinations were generally normal and unchanged by the drug. The few adverse experiences which did occur were general opiate effects attributable to excessive dosage of LAAM or administration more frequently than three times a week, with resultant accumulation of active drug.

SUMMARY

Opiate maintenance with methadone has been demonstrated to be an effective treatment modality for many chronic heroin-dependent individuals. However, the many clinical and societal advantages of a longer-lasting medication prompted the development of LAAM, which could be administered three days a week rather than daily. Early Phase II clinical trials of LAAM in about 750 patients have been reviewed and have demonstrated the safety and effectiveness of this drug and confirmed its usefulness for treatment of this chronic disease.

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CHAPTER 20

A U.S. Veterans Administration Cooperative Study on Methadyl Acetate

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Street diversion and accidental poisoning are complications of methadone maintenance, resulting directly from the drug's short duration of action. These problems might be avoided by employing a longer acting, methadone-like drug that could be ingested by patients at the clinic at less frequent intervals, without the need of take-home medication. One such substance is levomethadyl acetate. Methadyl acetate is a derivative of methadone. Early clinical studies by Fraser and Isbell (2) demonstrated its ability to suppress symptoms of opiate withdrawal and its long duration of action. A pilot study comparing methadyl acetate with methadone maintenance of chronic heroin addicts observed that former addicts who had made satisfactory social adjustments while receiving oral treatment with methadone continued to do as well while taking methadyl acetate three times weekly during a five week period of observation (3).

In subsequent studies chronic heroin addicts were treated with either methadone or methadyl acetate. No significant differences in terms of patient acceptance, illicit drug use, employment, criminal activities, frequency of clinic attendance, or medical safety were noted (4, 5). In another study street heroin addicts were randomly assigned, after detoxification with methadone, to a methadone or a methadyl acetate group. No differences were noted in patient acceptance, withdrawal symptoms, response to heroin challenges, or positive urine tests between the methadone group and the high-dose methadyl acetate group (6).

Laboratory findings in these early studies showed few differences between methadyl acetate and methadone patients. In a comparison

study the only statistically significant finding was slight hyperglycemia in the methadyl acetate group (1). Adverse reactions to methadyl acetate were rarely reported.

Although these early studies tend to substantiate the initial observation of the clinical usefulness of methadyl acetate, the number of patients studied was quite small. The present study attempted to maximize subject availability by means of multihospital participation in a common protocol. The goals of the study were to evaiuate the safety and toxicity of a fixed dose of methadyl acetate (80 mg. three times weekly) and to compare its relative efficacy with two doses of methadone hydrochloride, a high (100 mg.) and a low (50 mg.) daily dose. The present study was initiated as a double blind, multihospital cooperative project in 12 U.S. Veterans Administration Hospitals on April 16, 1973; the last patient completed the study on March 21, 1975.

METHOD

Patients

Patients were male, military service veteran heroin addicts who met all of the criteria for admission to methadone maintenance programs as defined by the U.S. Food and Drug Administration (FDA), were not currently enrolled in some other methadone treatment program, and were between the ages of 18 and 60. Patients were excluded for incapacitating or life-threatening conditions, disease requiring regular, repeated medication, frankly psychotic states, epilepsy, current severe alcoholism, and pending criminal charges. Eligible patients who signed an informed consent for voluntary participation in the study were then given a general physical examination, with neurologic and psychiatric evaluations.

Procedure

Patients were randomly assigned to levomethadyl acetate or one of two dose levels of methadone. The two methadone groups received active medication daily, but the methadyl acetate group received active medication on Monday, Wednesday, and Friday, with placebo on all other days. All doses were dispensed in a masking-diluting liquid, such as orange drink or grapefruit juice.

The first dose in all three groups was 30 mg., which was increased by 10 mg. on each succeeding Monday until the patient achieved his target dose of 50 mg. of methadone hydrochloride (M-50), 100 mg. of methadone hydrochloride (M-100), or 80 mg. of methadyl acetate (L-80). All doses were dispensed double blind. Duration of treatment was 40 weeks.

Patients' conditions were evaluated immediately before and every four weeks during their tenure in the study. The evaluation included a brief history, a current status record of their employment activity, legal involvement, interpersonal relationships, and drug use during the preceding four weeks, a supplementary medication record, and a symptom-sign checklist. The complete physical examination was repeated at the 12th week and at the end of the study, with abbreviated physical examinations at all other four-week evaluations. Each patient's adherence to the clinic schedule of visits and details of medication dispensed were recorded. Whenever a patient concluded treatment, an attempt was made to repeat all evaluations.

The first level of responsibility for the safety of patients in the study was assumed by the principal investigator at each participating hospital, who was in a position to make direct clinical observations and who reviewed all laboratory and other data prior to their submission to the data processing center. The second level of review was performed by the study chairman, who was regularly provided with an updated computer listing of laboratory values, vital signs, and symptom-sign ratings of each patient. Every three to six months, the data processing center performed extensive statistical analyses for group differences on all safety variables and prepared data displays to show changes in individual patients. During the trial, emphasis was placed on the evaluation of safety-toxicity. In the early months of the study there was great dependence on clinical monitoring by the principal investigator and the study chairman. However, several additional series of analyses incorporating the hospital as a factor were done to supplement the convariance analyses and the trend analyses. Analysis of symptom-sign data was initially evaluated by X (to the second power) during the monitoring stage, but when sufficient data had accumulated to make it meaningful, the items were factor analyzed.

Several indices of efficacy were monitored throughout the study. In all of these analyses a probability less than .05 was accepted as the level of statistical significance.

RESULTS

Characteristics of Sample

The sample consisted of 430 men whose median length of addiction to opiates was 7.3 years. They were reasonably young and reasonably well educated. Most had been married at one time, but 37 percent were still single. Racially, 46 percent were black, 39 percent white, and 11 percent had Spanish surnames. Employment characteristics were consistent with expectation in an addict group.

The sample cannot be considered to be representative of all addicts in the United States since it was limited to male veterans of the armed forces. Additionally, the regional distribution of the sample is vastly different from the addict population in this country: 44% were admitted to four California clinics, while the East accounted for only 26%.

Program Retention

Only 42 percent of the starting sample completed the full 40 weeks of the study: 69 percent terminated early from the L-80 group, 58 percent from the M-50 group, and 48 percent from the M-100 group. This difference between the L-80 and M-100 group is statistically significant. It has to be concluded that high-dose methadone maintenance (M-100) was superior in retention to the L-80 group. It does not necessarily follow that high-dose methadone is the superior maintenance drug, however, because there are other dimensions of outcome that must be considered.

The average length of stay in the study before early termination was remarkably similar for the three groups: 82 days for the two methadone groups and 81 days for the L-80 group. To summarize, most terminations occurred in the early weeks, and over all there was a greater number of L-80 terminators than M-100 terminators, but this difference is not concentrated in the early weeks. Broad categories of termination were established and the only significant differences between groups for these specific categories of dropout were a greater number of terminations for side effects in the L-80 group than in the M-50 group, and a greater number of “no-shows” in the L-80 group than the M-100 group.

Great variation among clinics is evident in the early termination data. The percentage of terminators was quite low in two California clinics (23 percent and 30 percent), but 75 percent or higher in

seven other clinics. Furthermore, the average time in the study for terminators in these two California clinics was relatively long (151 days and 140 days) compared to most other clinics. As a final contrast, one clinic had 85 percent early terminations, 82 percent of which occurred in the first eight weeks (for an average length of stay of 21 days), while the best record was 23 percent early terminators, 15 percent of which dropped out in the first eight weeks for an average length of stay of 151 days.

Safety

There were no deaths of study patients, nor were any serious adverse reactions reported. There were 11 patients terminated primarily for side effects: Four L-80 patients terminated because of inability to ejaculate, and another L-80 patient who was terminated because of swelling joints listed in addition decreased sexual interest along with heartburn, nodding, and constipation. The other L-80 terminators were a patient who could not keep medication down (nausea and vomiting) and dropped out after 16 days; another who complained of being tired and dizzy with chest and arm pain, and one who experienced jerking of extremities at bedtime as well as some nausea. Of the three high-dose methadone patients who were terminated, one developed a pruritic maculopapular rash on the second day while the patient was still receiving 30 mg., one had abnormally high liver function values, which were present before treatment, but showed only minor trends towards stabilization at a lower level, and the third was an apparent case of bone marrow suppression.

As a general statement, reporting of any symptom-signs was infrequent and those that were reported were not severe. In only three instances was there a significant drug difference: aching bones and joints, for which the M-50 group had a significantly higher frequency of moderate to severe ratings than either of the other groups; insomnia, for which the M-50 group had a significantly higher frequency than the M-100 group, and anxiety, for which the M-50 group significantly exceeded the L-80 group in terms of moderate to severe ratings.

It is worth noting that the L-80 group was equal to or lower than whichever methadone group had the greatest number of severe ratings on 26 of the 31 symptom-signs. Each patient's pattern of symptom-sign ratings was reviewed together with his urine test results, his clinic visit record, his laboratory data, and his record of

adjunct medication. This gave a much clearer idea of the patient's total experience in the study, but did not add to or substantially change the results already presented.

The hematologic tests, blood chemistry studies, vital signs, and weight provided 25 comparisons for each of the ten test periods. Only six of these were statistically significant. Three of these occurred on a single variable, weight. The others represented a difference between groups at one period only: white blood count at week 20, calcium at week 36, and alkaline phosphatase at week 16. Two cohorts of patients were established, to permit investigators to look specifically at changes over time rather than cross sectionally. The 24-week cohort consisted of patients who had a complete set of data on a variable at pretreatment and every test period for the first 24 weeks. There was a single significant finding: the interaction of drug and time on weight. In the analysis of the same variables using the 40-week cohort, there was a significant interaction for total WBC. total red blood count, hematocrit reading, hemoglobin level, and weight. In addition, there was a significant difference between groups for SGOT level when all values were collapsed across time.

In another series of analyses, a cohort of 128 patients from three hospitals who had a complete set of values over a 20-week period were used to provide similar, but somewhat different, information. In these analyses, the pretreatment value was included as a covariate, and all subsequent values were adjusted for initial level. Hospital was included as a factor in the design, which permitted a comparison of hospitals and the various interactions of hospital with drug and time. In these analyses, the only main effects of treatment that reached significance were weight and pulse rate. There were significant interactions between drug and time on hematocrit reading, hemoglobin level, and SGOT level.

A final attempt to gain precision and extract information about any drug group changes present in the data consisted of a series of multivariate analyses of covariance. The following hematologic tests were analyzed simultaneously: WBC, RBC, neutrophils, lymphocytes, hematocrit, and hemoglobin. There were no significant differences involving treatment group in these analyses. The renal tests (calcium, BUN, and uric acid) were analyzed in the same manner and with the same result. In the analysis of liver function tests there was a significant difference between groups at the 16th week only. The multivariate test of vital signs and weight was significant at the fourth week only.

Each of these different analyses supplies somewhat different information and needs to be further examined and integrated. In the hematologic tests, all means at all test points were within the normal range. There is a suggestion that something might have been happening with WBC in at least some patients during the middle weeks, but it is difficult to give clinical meaning to it because it did not persist; all means are comfortably in the normal range, and a review of individual patients' data did not identify anything remarkable about this part of the treatment period. Red blood cell count, hematocrit reading, and hemoglobin level surfaced as possibly significant (in a clinical sense) on the cohort analyses only. The evidence for RBC count is not convincing. There was some initial decline in RBC count which then leveled off. Considering the results of the multivariate tests that included all of these variables as well, it seems reasonable to conclude that the occasional between-groups differences that did emerge as statistically significant have no clinical importance. In no case were the blood changes sufficient to necessitate termination from the study.

The evaluation of renal and liver function tests was similarly clinically reassuring. The level of SGOT was noteworthy for the fact that the means of all three drug groups before and throughout treatment were well above the usual normal range (from a low 56 to 107), and the pretreatment values for many individual patients were high enough to be of serious concern in a nonaddict sample. All three groups show essentially no change across time on SGOT level.

The analysis of vital signs and weight had a generally low yield, except for weight, which is clearly affected by all three drug regimens, particularly methadyl acetate. There is clearly an upward trend in all groups, and somewhat more substantially so in the L-80 group. The average weight gain at week 12 was 1.02 kg for the M-50 group, 1.48 kg for M-100, and 2.86 kg for L-80; at week 24, it was 2.30 kg for M-50, 2.64 kg for M-100, and 5.12 kg for L-80; and at week 32, it was 2.43 kg for M-50, 3.79 kg for M-100, and 5.63 kg for L-80. No morbid obesity was reported. Nothing of interest appeared in the data from routine urinalyses.

There is abundant evidence that both methadyl acetate and methadone hydrochloride will maintain addicted individuals without their having to resort to supplementary (illicit) narcotic use to avoid withdrawal. It seems reasonable to assume efficacy in this sense and turn to the question of the relative efficacy of the three drug regimens.

Urine drug testing data are considered to be the key to evaluation of the results of this study. Not only is this considered the most

important outcome, but it provides a way of evaluating the secondary or contingent variables. The amount of drug use is, of course, important, but the pattern is probably even more so.

An index of illicit morphine use has been derived that takes into account total use and pattern of use. This index was developed completely independently of the study data and was therefore not biased by a knowledge of drug group outcomes (Klett and Ling, personal communication). Using this index to compare the three drug regimens gave the following results: 110 M-50 patients had a urine index of 33.3, 111 M-100 patients had an index of 22.6, and 96 L-80 patients had an index of 20.8. The "F" was 6.19 ($p<.005$). The M-50 group was significantly higher on the urine index than either M-100 ($P<.05$) or L-80 ($P<.01$).

Urine test data were analyzed in other ways as well. For each patient, the number of urine tests positive for morphine was divided by the number of specimens tested. A similar score was calculated for barbiturate positive, amphetamine positive, and "something" positive, the latter being the number of specimens positive for either morphine, barbiturates, amphetamines, or cocaine. The results of these analyses showed the L-80 group less likely to use illicit barbiturates than the M-50 group ($P=.014$).

Another kind of outcome index is program conformity, which was defined as each patient's number of actual scheduled clinic visits divided by his total number of expected scheduled visits for however long he was in the study. The M-50 group had an average of 92 percent attendance; M-100, 95 percent; and L-80, 90 percent ($F=5.34$, $P<.01$). The difference between M-100 and L-80 on this clinic visit index was significant at $P<.01$. However, since the methadyl acetate patients only received active medication on Mondays, Wednesdays, and Fridays, the analysis was redone, comparing the three groups on percent attendance rate. The L-80 group (93.12) had lower attendance than M-50 (94.07) or M-100 (95.69), but the difference is not significant.

Another evaluation of relative efficacy was made, using the global rating of outcome, which was a combined staff judgment made shortly after a patient's termination, taking into account all known information about the patient.

The M-50 group was judged to be significantly less improved than either the M-100 group ($P<.01$) or the L-80 group ($P<.05$). Preliminary review of secondary (contingent) outcome variables, such as number of arrests, hours of employment, income, and others, has not yielded evidence of advantage of any one group over

another, but a conclusive summary of these variables will have to be deferred until more definitive analyses have been done.

DISCUSSION

This study was organized and initiated at a time when there was relatively little clinical experience with methadyl acetate. With a limited amount of information for guidance, some decisions had to be made about the design of the study, which, if incorrectly made, could jeopardize its outcome, or possibly increase the risk to the participating patients. The dose schedule is an example. It was decided to start methadyl acetate patients at 30 mg. three times weekly and increase the dose 10 mg./week until they had stabilized at 80 mg. three times weekly. The methadone patients were inducted according to the same schedule. There is now reason to believe that this was not an optimal induction schedule for either group and that there probably is less patient discomfort and better patient retention if, in the clinical use of methadyl acetate, this schedule is accelerated, if the Friday dose is somewhat larger, or if in the early weeks there is supplementary use of methadyl acetate or methadone on days when the methadyl acetate is not regularly dispensed.

This study also suffers from the same defect that all fixed-dose studies do. Clinical experience tells us that dosage of many drugs needs to be individualized not only during the induction phase but also in the search for the optimal stabilization dose. Undoubtedly, patients that were undermedicated or overmedicated were lost from each group.

Another necessary element of conservatism in the planning led to the decision to conduct laboratory tests every four weeks. This increased the difficulty of acquiring the sample of volunteer participants and led to the subsequent termination of many patients who tired of the procedures involved in drawing blood, taking urine, and the completion of other kinds of evaluation. Similarly, the study had to be double blind to provide meaningful information about efficacy in particular. At least a small group of patients had second thoughts about being in a study where they did not know what they were taking and chose the more familiar methadone experience.

It was pointed out earlier that there was a great deal of variation in clinic performance during the study, more than could be

accounted for by differences in geographical location or by chance. Hence it is inferred that in part, this variation has to be related to patient and staff attitudes towards the study and the three drug regimens.

Additionally, there are differences in addict population that contribute to geographic variation. The clinics' performances are probably a fair sampling of what might be expected of any 12 hospitals within the artificial constraints of the study.

In spite of all these shortcomings, the evidence supports the conclusion that methadyl acetate is as safe a drug as methadone and that it compares favorably with high-dose methadone in terms of efficacy as previously defined. Both methadyl acetate and high-dose methadone appear to be better maintenance regimens than low-dose methadone under the conditions of this study.

Each of these conclusions needs to be qualified. It is conceivable that sample attrition may have introduced bias in the direction of apparent safety of both drugs or selectively for methadyl acetate. Second, laboratory analysis was done locally rather than in a central laboratory, and this, without question, contributed to the variability of measurement and decreased the sensitivity of the statistical analysis.

Finally, the complete story on safety awaits truly large-scale phase 3 testing. There were no deaths, serious adverse reactions, or compelling trends in the laboratory or side effects data, but it is not possible to anticipate what experiences might emerge when thousands of patients are exposed to this new drug or any new drug. The statements about efficacy are obviously limited by the fixed-dose design of the study and shaped by the philosophic position that was taken about evaluating outcome. The conclusions with respect to the high-dose vs. low-dose methadone comparison, if translated into action, do not support a policy of giving all patient 100 mg. of methadone hydrochloride daily, nor do they contradict the known fact that many patients do very well receiving doses of 50 mg/day or even less. It seems hardly necessary to stress the importance of individualization of dosage in actual clinical practice. However, strong advocates of low-dose methadone maintenance might reconsider their position in the light of these findings. Methadyl acetate might be better or worse than it appears in this study if used with other induction schedules or individualized doses.

However, it is believed that this study has established methadyl acetate, used three times weekly, as a suitable alternative to methadone as a maintenance treatment for heroin addicts. In the judgment of the investigators and many of their associates, it is of

the utmost importance to complete the developmental work on methadyl acetate so it can be made generally available for the treatment of heroin addicts. The advantages of methadyl acetate (if it continues to appear safe and effective) are socially important. As an alternative to methadone, it offers a solution to the familiar dilemma of either demanding daily clinic attendance, which imposes hardships on patients and lowers program retention, or permitting take-home doses of methadone with its associated dangers of diversion or death for intolerant individuals. It would seem to be enlightened policy to have methadyl acetate available on a three times a week basis with no take-home privileges and at the same time move in the direction of less take-home use of methadone.

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CHAPTER 21

The SAODAP Cooperative Studies of LAAM: Unblinded Comparison with Methadone

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Two cooperative studies of ℓ-alpha-acetylmethadol (LAAM) were conceptualized by the U.S. Special Action Office for Drug Abuse Prevention (SAODAP) at about the same time as the U.S. Veterans Administration (VA) study, but because of inevitable administrative delays involving the U.S. Food and Drug Administration, the Drug Enforcement Administration, and institutional review clearances, the first patients did not begin treatment until almost nine months after the VA study had started. The first of the SAODAP studies was deliberately designed to be comparable to the VA study in most important respects, e.g., duration of study was to be 40 weeks, and the evaluations were done at the same intervals with essentially the same forms, laboratory tests, and other procedures.

There were, however, two important differences. The patient sample in the SAODAP study consisted of patients currently being maintained on methadone rather than patients newly applying for maintenance. Second, although patients were randomly assigned to either methadone or LAAM, it was decided to conduct the study as an open clinical trial rather than using the double blind control. There was another important difference between the two studies that derived from the first two. Because of the difference between patient types, i.e., street addicts requesting maintenance vs. patients already on maintenance, the dosage problem in the SAODAP study was one of determining the proper cross-over dosage ratio from methadone to LAAM rather than determining an appropriate induction schedule. The induction schedule and ultimate maintenance dose were fixed in the VA study, not simply to make the logistics of double blind unit-dose administration less complex, but

because conservative elements in the planning of this study suggested that dose should be controlled. These constraints were considered less important in the SAODAP study. Since the trial was nonblind, clinicians could begin to adjust the dose beginning with the second visit. In fact, they were encouraged to do so and particularly to consider a higher Friday dose. It was, however, believed to be necessary to standardize the crossover ratio, and after much debate it was decided to use a one to one conversion.

Before presenting any results of the SAODAP study, a few general comments about these two studies may be in order. The goals and the design of both the VA and the SAODAP studies made sense at the time they were planned. In retrospect they still do, but both studies have their strengths and their weaknesses which ought to be clearly recognized so they can be put in proper perspective with the studies that preceded them and the studies that are now in progress or that still remain to be done. Obviously, the double blind control of the VA study has to be considered its main strength from the standpoint of research design. However, it will never be known for certain how well the double blind control worked. There were patients who correctly identified their assigned drug as LAAM, including one who dramatically poured his Tuesday placebo dose on the clinic floor. No matter how imperfect this double blind control was, it did provide greater protection from bias than the open SAODAP trial, as we shall see when I give some comparative results. The fixed induction-maintenance schedule of the VA study was an asset in comparing three drug regimens, but in other ways it restricted the amount of information we might have obtained about LAAM. The first dose might have been too high or too low, dosage was probably increased too slowly, and the fixed maintenance dose of 80 mg TIW was certainly not optimal for all patients. However, the apparent advantage of flexible dosage in the SAODAP study was largely cancelled out either by the conservatism of many of the clinicians in terms of adjusting dosage upwards or by their greater willingness to terminate patients from the study who were known to be on LAAM and who were having real or imagined difficulties in adapting to the new drug.

Both studies suffer from conceptual problems when it comes to evaluating efficacy and this issue has been discussed in the report of both studies (1, 2). At one level, the efficacy of LAAM relates to its ability to substitute for heroin and/or methadone in the prevention of the abstinence syndrome. A somewhat, different question involves the length of time an oral dose of LAAM is effective in this regard either as a single dose or administered on some intermittent

schedule, i.e., every other day, three times a week, or whatever. If this is the level at which the efficacy of LAAM is to be assessed, then the appropriate criterion would seem to be the extent and intensity of withdrawal symptoms reported by patients assigned to LAAM. Unfortunately, this criterion has some defects associated with ways of reliably and validly establishing degree of discomfort. There are alternative ways of approaching this problem, each of which has its own merit, but it is a certainty that whatever solution is adopted, it must be conducted under double blind control. An equally important consideration which limits the usefulness of discomfort, as the criterion of effectiveness is that degree of discomfort will be a function of the dosing pattern, and, until the best induction/crossover schedules are known, there will be more discomfort experienced than there would need to be.

If symptoms of withdrawal are not quickly and adequately brought under control, the patient is likely to do one of two things: drop out of the study or begin supplementing his maintenance dosage with heroin. This suggests two additional criteria of effectiveness: program retention and urine tests positive for morphine. Although program retention would be expected to be depressed if LAAM were ineffective in suppressing abstinence, it is a most unsatisfactory criterion of effectiveness because it is related to so many other factors. Some patients complete the study but complain of withdrawal symptoms throughout and/or consistently supplement with heroin, while other patients apparently do well on LAAM until they terminate for some reason. Termination from the study often has nothing whatsoever to do with the drug to which a patient is assigned. There is good reason to believe that study retention for both methadone and LAAM was reduced by the demands imposed by participation in these studies. Finally, study retention is absolutely worthless as a criterion of efficacy in an unblinded trial. At any time that a patient assigned to LAAM in the SAODAP study experienced real or imaginary distress of any kind, the option was available to terminate him from LAAM and put him on methadone. The reverse option was not available for the methadone patients.

Urine tests positive for illicit drugs is a more attractive criterion of effectiveness, particularly if it is appropriately weighted not only for total use of drug but also for pattern of use. Thus, it might be expected that illicit drug use might occur during induction or following crossover, particularly if these induction/crossover schedules are not optimal. If illicit drug use continues much beyond this period, however, it strongly suggests that maintenance is not

effective. Since another goal of maintenance is to decrease or eliminate illicit drug use by providing an acceptable substitute, the use of urine tests positive for morphine as a criterion of efficacy seems particularly appropriate.

Consumer acceptance may actually be the ultimate criterion of LAAM as a maintenance drug. If the client doesn't like the drug because he is uncomfortable, or doesn't experience his customary high, is afraid of the drug because of something he has heard on the street, or loses income because he has no take home dose to sell, he will be likely to drop out or start supplementing his maintenance drug with illicit heroin. On the other hand, if he likes the idea of not taking drugs daily, feels more alert or less like a junkie, he is likely to do well on LAAM. Unfortunately we haven't measured consumer satisfaction directly and can only infer it by inspecting retention, discomfort, and illicit drug use.

There is another class of criteria that has been suggested as bearing on the issue of effectiveness, and that is the extent to which individual patients' lives are modified in terms of employment, illegal activity, interpersonal relationships, and the like. It seems to me that such criteria are important socially and politically in evaluating maintenance as a concept but are not the ones to use in evaluating the value of a specific drug as a maintenance agent.

It should be clear at this point that the SAODAP study, because of its design, could not provide definitive information about the efficacy of LAAM. However, it did provide some suggestive evidence. Thirteen clinics contributed 636 patients for randomization to either continued treatment on methadone or crossover to LAAM. Of the 308 patients randomly assigned to methadone, 186 (60%) completed the full 40 weeks of the study. Of the 328 patients assigned to LAAM, however, only 128 (39%) completed the full course. Patients assigned to LAAM not only dropped out in greater numbers but dropped out significantly earlier-after an average 72 days in the study compared to 122 days for the methadone patients. Furthermore, there were 62 LAAM patients who terminated because the medication was not warding off abstinence symptoms, another 7 because they didn't like the drug, 14 for psychiatric reasons, and 11 because of side effects. No methadone patients terminated for any of these reasons. LAAM patients also complained much more about symptoms of withdrawal. All of this would seem to be overwhelming evidence that LAAM is not as good a maintenance drug as methadone, and if the study had been conducted double blind, it would be difficult to escape this conclusion. However, there are two additional pieces of

information that suggest otherwise. First, the two groups were comparable in terms of illicit drug use. This evidence would also be stronger if the study had been double blind, but it seems unlikely that urines positive for heroin are subject to quite as much bias as other criteria. Secondly, when the 128 patients who completed 40 weeks of LAAM maintenance were asked to volunteer for another 40 weeks of LAAM to provide a long-term safety profile, 112 (89%) elected to do so (11 did not want to stay in the study at all, and another 5 were willing to do so but asked to be switched to methadone). This seemed to be fairly powerful consumer acceptance, especially when compared to the methadone experience: Only 66% (124 out of 186) of the methadone finishers agreed to stay in the study, 29 declined, and 33 asked to be switched to LAAM. If nothing else, this suggests that for at least some patients, LAAM is an acceptable or even preferred alternative to methadone.

Additional evidence for the acceptability of LAAM as a maintenance drug can be inferred from the second study organized by SAODAP. This was a study at four clinics of 136 patients randomly assigned to methadone or LAAM. The LAAM group received methadone on Monday through Thursday but received LAAM on Friday and no drug at all on Saturday and Sunday. This would seem to be a rather rigorous test of LAAM as a maintenance agent, but remarkably 35% of the LAAM starters completed 40 weeks of this regimen (compared to 52% of the straight methadone controls).

The best justification for conducting these two SAODAP studies was to accumulate more clinical experience with LAAM, particularly experience bearing on safety-toxicity issues. Relatively few patients had been exposed to LAAM in earlier studies. Even in the VA study, because the total sample was distributed among three groups, only 142 patients received LAAM. In the two SAODAP studies, another 393 were added. In this total of 535 patients who collectively were treated with LAAM for almost 300 man years, there were four deaths. Two of these were homicides, one was an alcohol-related death, and the last was a result of (non-LAAM) overdose. There were no serious adverse reactions, and the number and kind of side effects were not very different from those commonly associated with methadone. Extensive laboratory evaluation revealed a number of significant differences between groups in the average amount of change over time, but these differences tended to be either sporadic, i.e., at one or two time periods only, or of such small magnitude that they did not seem to be clinically meaningful. There was no evidence of systematic, progressive

changes in value over time. It was concluded that LAAM and methadone are comparable in terms of safety over extended periods (up to 80 weeks).

In conclusion, these large studies (taking VA and SAODAP together) suggest that LAAM is likely to be an acceptable alternative to methadone as a maintenance drug. It is expected that the two drugs will become even more comparable in terms of reported discomfort, program retention, and illicit drug use as clinicians learn to use the drug more effectively, i.e., to optimize the induction/crossover schedules, and as both patients and staff become more familiar with the drug and are more willing to accept it as an alternative without the suspicion that might be associated with any new agent. The continual accumulation of data strengthens the conviction that the drug is as safe as methadone, at least used by healthy males who were included in these studies and probably also in the less carefully screened patients now being evaluated in the large Phase III trial. Females still remain to be studied, and there are other questions which still need to be answered. One of the most important of these is the relative ease or difficulty of detoxification from LAAM vs. methadone. There were a few LAAM patients in these studies that attempted and/or completed detoxification, but information was not systematically collected on their course. This is now being remedied in ongoing studies. Also underway are double blind evaluations of alternative induction schedules in patients newly applying for maintenance and alternative crossover schedules for patients already on maintenance who will be switched to LAAM. These studies will help to fill in some of the remaining gaps in the total picture of this new maintenance drug.

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CHAPTER 22

Phase III Clinical Study of LAAM: Report of Current Status and Analysis of Early Terminations

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INTRODUCTION

Levo-alpha-acetylmethadol (LAAM) is under investigation for maintenance therapy of persons addicted to opiate drugs. Jaffe et al. (5, 6, 7) reported that LAAM was successful as a maintenance drug when administered by a schedule of three times weekly. Although LAAM is not very active as an opiate, its two major metabolites by N-demethylation have potencies which approximate methadone and morphine. Whereas the time course of the blood concentration of LAAM is similar to that of methadone, the time course of the metabolites shows a substantially longer profile (3, 4).

Two cooperative studies have been completed in which approximately 200 patients gained at least a 40-week experience with LAAM; these studies have not shown significant safety problems for LAAM when compared to methadone (8, 9). Clinical laboratory tests throughout the 40-week period remained within the normal range for the drug-abusing population and did not show any significant clinical differences between LAAM and methadone. Reports of side effects, of opiate type and others, are similar for LAAM and methadone, and no unusual adverse reactions have been reported. The only significant adverse safety findings are an unknown contribution of LAAM in a few incidences of overdose reactions–a problem which has been well described for methadone and heroin.

Efficacy of LAAM maintenance therapy has been more difficult to measure due to the problems in defining efficacy. In double

blind studies, Jaffe et al. (5, 6, 7), Ling et al. (8), and Savage et al. (11) have all found LAAM to be a useful maintenance drug. Although patient dropout rates are higher for LAAM than for methadone, illicit heroin use during LAAM maintenance has been found to be less than with methadone. A number of possible reasons for the higher dropout rate for LAAM subjects may be postulated. Because of the lack of a large amount of clinical experience with LAAM, rigid design of experimental protocols precluded flexible dosing of LAAM, especially during the early induction phase. In open studies, anxiety over taking a new drug which is still classed as experimental, the ready alternative of methadone maintenance, and the lack of take-home methadone which has an economic value may all be contributors to the higher dropout rate observed in the LAAM groups.

METHODS

The current work is a large cooperative clinical trial aimed at obtaining 40-week experience with 2000 LAAM patients and a suitable methadone control group. This report provides a general overview of progress in this Phase III study and specifically examines the question of study dropouts, reasons for such dropouts, and possible remedies to decrease such dropouts. All patients in this study are males, 18 years of age or older, who meet the criteria for methadone maintenance therapy. This is a progress report, and the number of patients in the study depends upon the date analyzed and is indicated in the results section.

Three separate protocols have been utilized in this study. In Protocol I, all patients in the study are assigned to LAAM maintenance. In Protocol II, 60 percent of the patients are randomly assigned to LAAM and 40 percent to methadone on an open basis. In these two protocols, for each 1 mg of daily methadone the patient is given 1.2 mg of LAAM on a three times weekly schedule. For new patients a 20 mg initial dose with 10 mg increments is used. In Protocol III, current methadone maintenance patients are randomly assigned to three different medication schedules described in table 1.

Schedule A is an immediate 1.2 crossover ratio from methadone to LAAM with methadone supplementation for the first two weeks. Schedule B is a gradual crossover with LAAM dosage increasing while methadone dosage decreases until the full 1.2 crossover dose is achieved. Schedule C is a full dose 1.2 crossover ratio from

TABLE 1

Protocol III dosage guidelines

Days	Schedule A		Schedule B		Schedule C	
M	PSM		PSM		PSM	
T	BLD	1/4 PSM	1/4 BLD	3/4 PSM	BLD	
W		1/2 PSM		3/4 PSM		1/4 BLD
Th	BLD		1/2 BLD	1/2 PSM	BLD	
F		±1/2 PSM		±1/2 PSM		±1/4 BLD
S	BLD+10mg		1/2 BLD	1/2 PSM	BLD+10mg	
S		±1/4 PSM		±1/2 PSM	—	±1/6 BLD
M		±1/4 PSM		±1/2 PSM		±1/4 BLD
T	BLD		3/4 BLD	1/4 PSM	BLD	
W		±1/6 PSM		±1/4 PSM		±1/6 BLD
Th	BLD		BLD		BLD	
F		±1/6 PSM		±1/6 PSM		±1/6 BLD
S	BLD+10mg		BLD+10mg		BLD+10mg	
S	—		—		—	
M	±1/4 PSM		±1/4 PSM		—	±1/6 BLD
T	BLD		BLD		BLD	
W	—		—		—	
Th	±BLD		±BLD		±BLD	
F	—		—		—	
S	±BLD+10mg		±BLD+10mg		±BLD+10mg	
S	—		—		—	
M	—		—		—	

PSM — Pre-Study Methadone Dose
BLD — Basic LAAM Dose (1.2 X PSM)

methadone to LAAM with smaller doses of LAAM supplements in between the regular three times weekly medication.

For all patients in the Phase III study, an informed consent is signed by the patient, a complete medical history, physical exam, vital signs, SMA 12, CBC, urinalysis, background information, and urine screen for drugs are obtained. There is regular reporting by investigators of all maintenance medication, all adjunctive therapy, weekly tests for morphine in the urine, and monthly tests for amphetamines, barbiturates, and methadone. Measures of efficacy for the three schedules in Protocol III include the administration of a Medication Index and Symptom-Sign Checklist at pretreatment, 3, 10, 17, and 24 days of treatment. The Medication Index asks the patient to evaluate drug effect on a continuum from extremely undermedicated to extremely overmedicated. The Symptom-Sign Checklist is identical to that used by Ling et al. (8). Since this is a progress report, most of this data has not been completely analyzed and will not be presented here.

The patients in the Phase III study are from approximately 50 methadone clinics across the United States. This paper especially

acknowledges the five investigators participating in Protocol III. They are: Dr. Robert Duplis, St. Lukes Center, Miami; Dr. Henri Moyal, Valle del Sol. Phoenix; Dr. Carl Oestermeyer, Cleveland Treatment Center, Cleveland; Dr. John Renner, Boston City Hospital, Boston; and Dr. Edward Senay, Substance Abuse Services, Chicago.

RESULTS

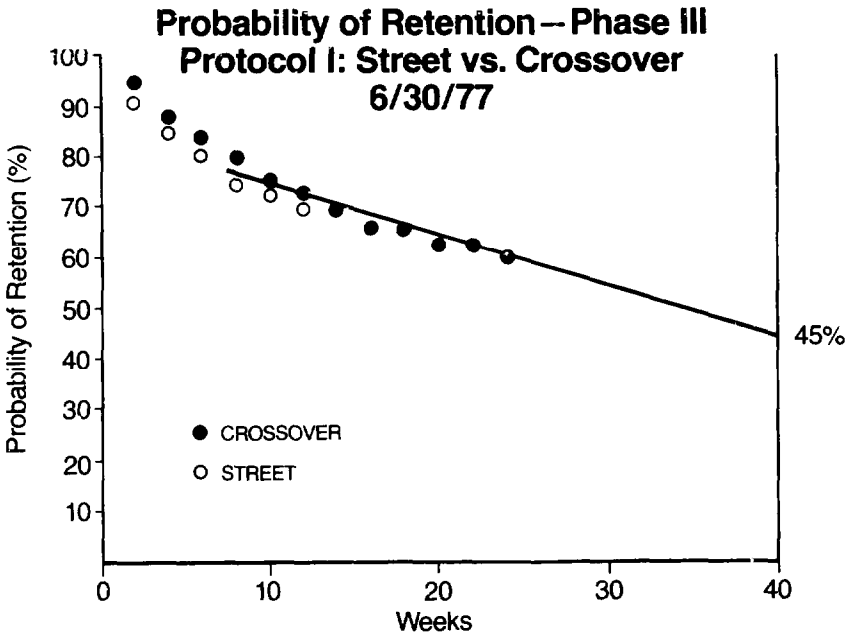
The number of starting patients required to meet the goal of 2000 patients with 40-week experience will depend upon retention rates in this study. By the most recent study census (7/20/77) a total of 2019 patients have been initiated. Of the 1109 patients inducted in Protocol I, 705 are currently in treatment and 404 have terminated. In Protocol II, 910 patients have been started, 634 are in treatment and 276 have terminated. For the patients initiated on methadone 19 percent have terminated, while 37 percent have terminated from LAAM. A more complete description of these terminations follows.

LAAM Terminations

In figure 1 the number of LAAM patients remaining in treatment over time is described by probability of retention. This method of life table analysis computes the probability of survival in the study for a given week (2). Projections from this calculation will give estimates of retention even though very few patients have had the opportunity to complete 40 weeks, Figure 1 shows that street admissions and crossovers from methadone have similar retention rates. Linear projections from the available data indicate that 40-week retention will be about 45 percent. The shape of the probability curve shows an initial high termination rate, but whether or not this curve decreases in slope in the last 10 weeks of treatment remains to be seen.

Reasons for LAAM patients terminating are shown in table 2. Most patients terminate For reasons clearly not related to the study medication. As expected a higher percentage of “No Shows” are from street admissions than from methadone crossover patients. Patients who were already stabilized on methadone before LAAM treatment terminated at higher rates (and presumably went back to methadone) for side effects, abstinence, or overmedication. Overall

FIGURE 1



the differences between the two groups are predictable. Street and methadone crossover initiates do not appear to differ in overall dropout rates.

LAAM vs. Methadone

The probability of retention figures for LAAM and methadone are shown in figure 2. These figures must be considered estimates because of the small numbers; however, there is a distinct difference between LAAM and methadone. Projected estimates show that the 40 week retention for methadone should be approximately 65 percent and for LAAM 45 percent. More data points are shown for LAAM because there is a greater sample size for LAAM data due to the random assignment which places 60 percent of patients on LAAM and 40 percent on methadone. The assignment was designed in this manner because a higher termination rate was predicted for LAAM.

Reasons for termination are shown in table 3. Under "Clearly Not Drug Related," there appear to be differences between drugs, but clinical investigators have determined that these terminations are clearly not drug related. Further analysis of these differences

TABLE 2

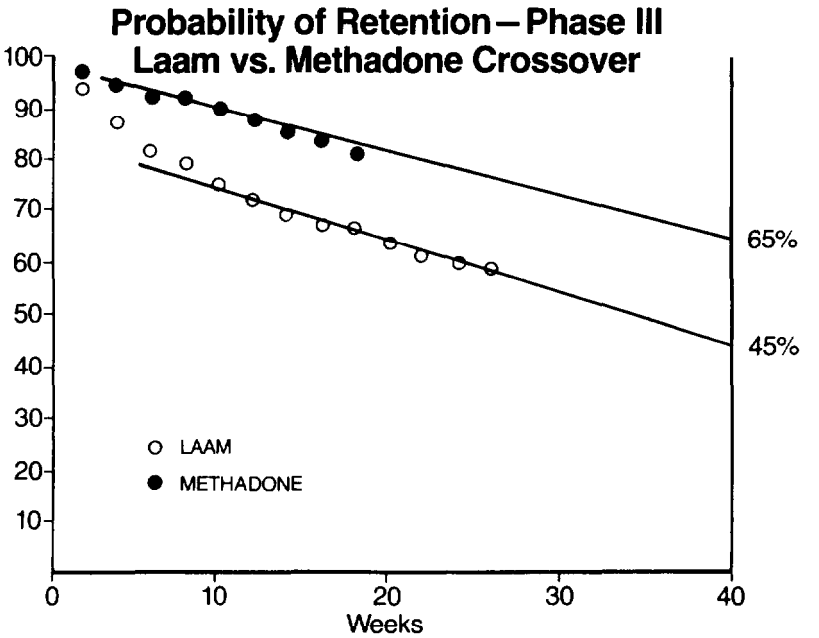
Reasons for early termination: LAAM patients – Protocol I & II

	Crossover	Street	Total
Starters (N)	1031	236	1267
Early terminators (N)	296	77	373
Reasons for early termination (%)			
No show	2.2	11.4	3.9
Clearly not drug related	8.3	4.2	8.6
Possibly drug related	10.7	7.2	10.1
Clearly drug related			
Side effects	1.8	0.8	1.7
Adverse reaction	0.5	0.4	0.4
Med not holding	3.5	1.7	3.1
Feels overmedicated	1 .1	0.4	0.9
No show	0.2	0.8	0.3
Other	0.2	0.0	0.2
TOTAL	28.5	26.9	29.2

will be performed with a greater sample size. Under "Possibly Drug Related," more patients drop out from the LAAM group in all categories. The largest of these categories is possible opiate side effects, which the patient notices more on LAAM (usually when switched from methadone to LAAM). Results show that LAAM patients have been terminated for excessive alcohol and drug use. Methadone patients may be having the same difficulties but they are not terminated because no other treatment is available. The category "Does Not Like Study Medication" is a catch-all for any drug-specific complaints which do not fit any other category. For example, one patient terminated because he didn't like the taste of LAAM. Another patient said that he felt overmedicated on the day on which he ingested medication and undermedicated on the days between doses. This is possibly a variant in metabolism of the drug. Other patients have missed the necessity of coming to the clinic daily. The results also indicate that some patients appear to show increased anxiety or may act out some impulsive behavior on LAAM; these are termed psychiatric discharges.

In the "Clearly Drug Related" category, all dropouts are in the LAAM group as would be expected since the methadone patients have previously been through a stabilization period; the LAAM

FIGURE 2



patients have switched to a new drug, Opiate side effects such as constipation, sexual dysfunction, insomnia, or gastrointestinal upset are experienced by some LAAM patients.

All reported adverse reactions have been investigated thoroughly. None are alarming and these will be reported in a later publication. Dosing problems causing abstinence or overmedication have been lower than expected. Only 3.8 percent of LAAM patients dropped out because the medication was not holding.

Very Early Terminations

In previous studies terminations very early due to undermedication are prevalent (8, 9). In the Phase II study, 8.8 percent of patients dropped out in the first month for undermedication. Table 4 shows the LAAM dropouts in the first month of treatment for the present study and for the SAODAP Cooperative study. As shown, 21.4 percent in the SAODAP study had dropped out by the end of the first month compared to 14.2 percent in the present study; almost all of this difference can be accounted for in the category of "Medication Not Holding." None of the other categories appear to show differences.

TABLE 3

Phase III LAAM Study: Reasons for Early Termination
Protocol II-LAAM vs. Methadone 6/30/77

	LAAM	Meth
Starters (N)	424	280
Early Terminators (N)	130	45
Reasons for Early Termination (5%)		
Clearly Not Drug Related		
Jail	3.1	2.5
Moved	0.5	1.1
No Show	2.4	2.5
Disciplinary Discharge	0.5	1.4
Unrelated Psychiatric	0.5	0.4
Unrelated Medical	1.4	0
Completed Detox on Study Med	0.5	1.8
Does Not Like Study Med	0.7	0
Transferred to Another Clinic	0.7	2.5
Pregnancy	0	0
Eligible for 2-Day Pick-Up	0.2	0
Other	1.4	1.1
Possibly Drug Related		
Possible Side Effects	4.0	0
No Show	1.4	1.1
Excessive Alcohol Use	0.1	0
Excessive Drug Abuse	0.7	0
Medical	0.2	0
Psychiatric	0.9	0
Requested Detox on Nonstudy Med	0.7	0.1
Does Not Like Study Med	1.7	1.1
Other	0	0
Clearly Drug Related		
Side Effects	1.4	0
Adverse Reaction	0.9	0
Medication Not Holding	3.8	0
Feels Overmedicated	1.9	0
No Show	0.5	0
Other	0	0

Protocol III

This substudy was initiated to determine the most effective means of crossing patients over from methadone to LAAM using supplemental medication of either LAAM or methadone (table 1). Where a "±" is indicated the clinical investigators were free to adjust dosage up or down as the patient signs and symptoms

TABLE 4

Comparisons of first month drop-outs: LAAM patients only SAODAP vs. Phase III crossovers 7/18/77

	SAODAP	Phase III
Starts (N)	328	1031
%Drop-outs	21.4	14.2
Reasons for early termination (%)		
Jail	1.5	0.5
No show	0	1.2
Moved	0.3	0.2
Side effects	2.1	2.4
Med not holding	8.8	2.2
Dose too high	0.9	0.9
Didn't like study	1.5	0.7
Didn't like med	0.6	1.3
Detoxification	0	0.1
Disciplinary discharge	0.3	0.2
Excessive drug use	0.6	0.5
Excessive alcohol use	0.3	0.1
Psychiatric	1.5	1.4
Unrelated med	0.6	0.5
Adverse reaction	0	0.6
Other	2.4	1.4

required. No conclusive results can be presented since the study sample is not yet complete and all data have not been analyzed.

A profile of the demographic characteristics of the three randomly assigned groups is shown in table 5. The unequal distribution in cell size is due to misassignment of several patients; these patients have been excluded from the analysis. The demographic profiles of each group show that Schedule A may have contained a slightly older sample with more months in treatment. The prestudy methadone dosage in the Schedule C group may have been higher.

Preliminary results show that Schedule C, LAAM supplementation, has some advantages over A and B in two parameters. First, there were fewer dosage adjustments required for this schedule. The results show that the investigator did not need to change the basic LAAM dose before the third week in this schedule. Second, in table 6 the Medication Index scores showed a superiority in that only 1 percent of patients in Schedule C were overmedicated and none were extremely undermedicated. For all three schedules the number of terminators was almost equal and was 10.8 percent of the starting sample.

TABLE 5

Protocol III demographics

	A	B	C
N	21	18	16
Age			
$\bar{X}$	26.27	27.83	26.13
Range	21-38	20-40	21-36
Years addicted			
$\bar{X}$	6.81	5.72	5.50
Range	2-23	2-20	2-11
Mos current treatment			
$\bar{X}$	10.57	8.78	8.31
Range	1-54	1-36	1-34
Pre-study methadone			
$\bar{X}$	57.62	54.89	46.38
Range	35-95	15-80	10-80

TABLE 6

Dosage schedule changes

	A	B	C
Followed nominal schedule	6 (29%)	4 (22%)	5 (31%)
Changed bld third week	4 (19%)	4 (22%)	1 (6%)
Changed supplement	7 (33%)	4 (22%)	4 (25%)
1 increase	1	0	0
2 increases	1	1	1
3 increases	3	2	3
1 decrease	2	1	0
2 decreases	0	0	0
Changed bld before third week	3 (14%)	4 (22%)	0
Wrong crossover schedule	1 (5%)	2 (11%)	2 (13%)
Miscellaneous deviations	1 (3%)	0	2 (13%)
Not included–did not complete three weeks in study	0	0	2 (13%)
TOTAL	21	18	16

DISCUSSION

The Phase III LAAM study is now well underway, and the preliminary results show that the drug is achieving widespread use and good patient acceptance. Currently the drug is being used in 50 methadone clinics and more than 1% of patients in maintenance therapy are using LAAM.

The dropout rate for LAAM is much better than in the Phase II studies, and a continued improvement in the rate is expected with the development of further experience with the drug. Until the drug is no longer classified as "experimental" any open study conducted to determine the comparative efficacy of LAAM and methadone will be prejudiced against LAAM as will be described below.

The reason for examining dropout rates during LAAM development is to determine whether there are specific problems with the way the drug is used which contribute to dropout. The SAODAP cooperative study had a significant number of dropouts from undermedication. Individual investigators had indicated that the low crossover ratio and restrictions concerning supplemental medication contributed to this problem.

The comparison of dropouts before one month has shown that whereas there was an 8.8 percent dropout rate for undermedication in the SAODAP study, in the current study only 2.2 percent of patients terminated for undermedication. This one factor accounted for almost all of the differences in the terminations before one month between these two studies. In the SAODAP study the initial crossover equivalence was 1 mg of LAAM TIW per 1 mg of methadone daily. In the present study, 1.2 mg of LAAM was used for each mg of methadone. Resnick et al. (10) has shown that after the initial 1.0 crossover ratio patient doses equilibrated from 1.1 to 1.6 times the prestudy methadone dose.

In the Phase III study investigators were urged to treat patients symptomatically for abstinence in the initial crossover period. Since pharmacokinetic results indicated that a period of several weeks may be required for some patients to achieve maximal blood levels of the active metabolites, supplements of methadone were recommended in the present study. In the previous SAODAP study, no provision was made for allowing methadone or LAAM to be used on an as-needed basis. Also other psychoactive medications are allowed in this study, in contrast to the SAODAP study.

The complete sample for Protocol III will be obtained in the future. Preliminary analysis, however, shows that the LAAM supplemental schedule may be superior. The probable mechanism

for such a finding is that the small LAAM supplements add to the total amount of LAAM given in the first two weeks. Since there appears to be a loading dose effect necessary, supplemental LAAM may speed up this process. By the end of the second week, Schedule C patients receive 1 l/4 extra basic LAAM doses. This may be enough to help the crossover process. In distinction, Schedule B patients receive two fewer basic LAAM doses. All of the clinics in the Protocol III study appear to have a lesser dropout rate. This indicates that a prescribed supplement of methadone or LAAM during the first two weeks may be beneficial.

An examination of all other categories in which patients have reported drug-related reasons for termination will be done in the future. In some cases it may be possible to identify specific difficulties with LAAM which can be changed by altering instructions to investigators. However, it is likely that other reasons may be operative which will not change until the drug is no longer experimental.

Most patients are crossovers from methadone or at least have had extensive previous experience with methadone. Patients know those things which methadone can and cannot do. In contrast, any physical, social, or psychiatric problem which arises while a patient is on LAAM is apt to be related to the new experimental drug. The VA Cooperative study was double blind and the SAODAP study was not. All symptoms and signs in the SAODAP study were reported with greater frequency for LAAM, whereas in the VA study only five out of 31 were significantly greater on LAAM (8, 9). This finding indicates that patients may blame the drug for any personal or program failure.

In the early experience with methadone similar problems were encountered. Adams et al. (1) found that 24 percent of patients blamed side effects for their failure on methadone treatment. Yaffe et al. (13) described a very high incidence of side effects from methadone. These side effects are very similar to those of LAAM patients and include constipation, excessive sweating, loss of interest in sex, nausea, sleepiness, drowsiness, insomnia, and so forth.

Another problem related to the open study is the existence of an additional option for those patients randomly assigned to LAAM. The patient who is randomly assigned to LAAM and experiences a problem may choose to try methadone again before dropping out of treatment. The patient. randomly assigned to methadone does not have the option of trying LAAM before terminating from the program.

Patient motivations for entering a treatment program are varied. At one end of the spectrum are patients who are in treatment without having any desire to stop heroin use. These patients will possibly find that a drug which has characteristics close to heroin will have the greatest acceptability. These characteristics may include euphoria, economic value from the sale of take-home doses, and the ability to use heroin after blockade has diminished. For these patients a drug like LAAM which has little euphoria, eliminates take-home doses, and provides a prolonged blockade of heroin will be less acceptable than methadone.

For those patients who look at a maintenance drug for its therapeutic value, however, LAAM may offer advantages. Trueblood et al. (12) in a study of patients at the Addiction Research Foundation (ARF) where only LAAM is provided found that patients reported that LAAM was more acceptable than methadone. Patients felt more comfortable and in better health. Heroin craving was less and heroin blockade was better on LAAM compared to methadone. ARF patients are probably more therapeutically motivated since they are enrolled in a LAAM research clinic.

Higher dropout rates for LAAM will probably continue until the drug can be used outside of a research protocol and until it is not stigmatized by the label "experimental drug." In the present study a continuing effort will be made to examine specific reasons for dropout so that changes in instructions to clinical investigators can be made. However, the most important factor will probably remain attitude toward the drug. Although not reported in the Results section, there is a tremendous variability in dropout rates between clinics. The clinics with high dropouts are always contacted and usually visited. The problems usually include a negative initial staff attitude towards LAAM, which is unfounded, a "bad rap" of LAAM by a few patients, or an unavailable physician, so that patients cannot adequately explore possible medication problems or perceived side effects. Usually it is possible to change these attitudes with the provision of knowledge and interest in the patient's problems.

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CHAPTER 23

The Future of LAAM

Pierre F. Renault, M.D.

Hopefully, in the not too distance future, LAAM will have a major impact on opioid dependence replacement therapy and on programs delivering that therapy. It is anticipated that LAAM will gradually supersede methadone as the major opioid used to maintain opioid-dependent individuals. The advantage of LAAM's longer duration of action should relegate methadone to a secondary role in treating the symptoms of opiate withdrawal syndrome in situations where the flexibility of a more rapidly acting preparation is needed. Therefore, the future of LAAM is interrelated with the future of replacement therapy, with all of its attendant controversy.

The concepts of maintenance or stabilization have been controversial from the time of their inception. Allowing or encouraging an individual to remain physically dependent on a drug, even though that drug is safer and less personally destructive than the drug of abuse, is repugnant to many. Maintenance treatment, since it represents continued physical dependence, appears to forego the concept of "cure of heroin addiction." Although the administration of LAAM three times a week can give freedom from the hazardous use of other drugs as well as from a dangerous and destructive lifestyle to the heroin addict, he remains dependent on a clinic and on those who control his maintenance drug. This apparent lack of cure and the continued dependence on the clinic and the clinicians have been seen by some as representing enslavement, economic control, and cultural domination; yet, paradoxically, for some nonaddicts methadone has symbolized "dogooderism" and the coddling of criminals. For those who would take a hard line, methadone has symbolized ineffectual humanitarianism which flames the fires of social unrest instead of dealing directly with them by decisive suppression.

These controversies surrounding replacement therapy have arisen from an inappropriate expectation that a medication can resolve

major historical and social problems. These expectations have, in turn, arisen from an oversimplification of the problems of drug dependence. Replacement therapy has suffered from the naive belief that all drug-dependent individuals have the same characteristics of personality and social background, and the equally naive belief that one treatment method can be uniformly applied to all drug-dependent individuals, thus putting an end to the demand for drugs.

The future of LAAM and, therefore, the future of replacement therapy itself depends on our ability to improve our selection of patients for specific therapies and to increase and diversify the types of therapies which can be made available to drug-dependent individuals.

The development of LAAM should mark a turning point in our thinking about treatment. LAAM is an ideal maintenance drug, and it represents the epitome of our effort to develop innovative pharmacotherapies for heroin dependence. LAAM is also the product of our preoccupation with pharmacotherapies. Our preoccupation with pharmacotherapy and with pharmacological diagnosis has been the basis for the oversimplifications, in our view, of addicts and treatment and some of the unrealistic expectations of replacement therapy. The controversy over replacement therapy has focused our attention on pharmacology in both diagnosis and treatment. This controversy has made too great an issue of pharmacology, allowing us to neglect the theory and implementation of psychotherapy and rehabilitation. Replacement therapy would not be so controversial if it were not considered by so many to be the basic treatment rather than what it is in reality, simply an adjunct to treatment. Replacement medications like LAAM should be conceived of as agents which can produce symptomatic relief safely and effectively. This symptomatic relief in turn enables individuals to participate in psychotherapy and to follow through with rehabilitative plans. The purpose of psychotherapy should be to help individuals achieve genuine control ever drug taking by identifying and changing critical aspects of their personalities and their environments.

The future of LAAM and the future of replacement therapy depends on our ability to turn our focus once again to the needs of the individual addict. We must develop more sophisticated ways of diagnosing addicts and placing them into diagnostic subgroups, which have genuine relevance for available psychiatric treatments and rehabilitative measures. An excellent example of this important new direction in replacement therapy has been those studies which

have shown that as many as a third of addicts coming for replacement therapy are depressed. There is preliminary data which indicates that psychiatric treatment of this depression not only improves the addict's depression, but also increases treatment compliance and success in treatment for heroin dependence.

In summary, the future of LAAM is the future of replacement therapy. Excellent pharmacologic agents have been developed for replacement therapy, and LAAM is foremost among these. However, the future of replacement therapy depends primarily on our ability to develop accurate diagnoses and specific treatment for individuals who come to treatment over and above the pharmacologic problems which they present. It is time to use LAAM as an adjunct to treatment. It is time to focus on the treatment and to shift the focus away from the pharmacologic adjunct.

IV.
Treatment: Naltrexone

Demetrios A. Julius
Chairman

CHAPTER 24

A History of the Development of Narcotic Antagonists for the Treatment of Narcotic Addiction

William R. Martin, M.D.

The use of narcotic antagonists for therapy had an inauspicious beginning. When I was appointed Director of the Addiction Research Center in 1963, among my responsibilities was the completion of the study of the abuse potentiality of cyclazocine which had been initiated by Dr. H. Frank Fraser. As part of this study, we attempted to make patients dependent on a larger dose of cyclazocine. On the basis of single doses, we estimated that cyclazocine was some 20 times more potent than morphine as an agonist; consequently, we felt that if we addicted patients to around 13 mg/70 kg/day of cyclazocine this would be roughly equivalent to administering 240 mg/day of morphine, a level of dependence which had been well characterized at the Addiction Research Center.

During this study we learned that tolerance developed rapidly to cyclazocine's subjective effects, such as sedation, racing thoughts, dysphoria, and hallucinations. However, with small increments in dose, the subjective effects would reappear, and it was necessary to stabilize some patients for several days before again advancing the dose. When patients who had achieved the stabilization dose were abruptly withdrawn, an atypical abstinence syndrome did become manifest by the fourth day of withdrawal and achieved peak intensity on the seventh day of withdrawal. This was the first indication that cyclazocine had a very long duration of action (6).

Studies were then initiated to determine the duration of action of cyclazocine, and to this end two studies were conducted to determine the duration of (a) signs and symptoms, and (b) the

morphine antagonistic effects produced by single doses of cyclazocine. It was found that signs and symptoms produced by cyclazocine persisted almost undiminished for over 12 hours, and its morphine antagonistic effect was evident for from 12 to 24 hours (8). These data confirmed our speculation that cyclazocine was a very long-acting drug in man, a property not evident in experimental animals.

We had previously shown that chronically administered nalorphine also induces a cyclazocine type of tolerance and dependence, and that when subjects were stabilized on nalorphine they were refractory to the effects of morphine (7). Cyclazocine, administered chronically by the oral route in a dose of 4 mg/70 kg/day, markedly antagonized the effects of single doses of morphine and heroin. One of the patients stabilized on cyclazocine was given 100 mg of heroin intravenously and only minimal subjective effects were produced, probably no greater than those that would have been seen had the same subject received 5 or 10 mg intravenously in the absence of cyclazocinc. We also attempted to make patients dependent on 240 mg of morphine daily while receiving cyclazocine chronically. In this study we were able to escalate the dose of morphine very rapidily. When the subjects were withdrawn from morphine, only liminal signs of abstinence were seen, suggesting that cyclazocine had also blocked physical dependence-producing properties of morphine (8). We suggested that cyclazocine might have utility in the treatment of narcotic addicts.

These studies clearly demonstrated that chronically administered cyclazocine could antagonize both the euphorigenic (reinforcing) and the physical dependence-producing properties of morphine. Further, we knew that chronic cyclazocine would essentially prevent an addict from overdosing himself. We thought it highly unlikely that addicts would attempt to inject more than 100 mg of heroin intravenously, and our studies had indicated that not only was this dose not lethal but produced modest effects at best. We suggested that cyclazocine

> may be of value to therapists and social workers who are treating addicts. If subjects under treatment use narcotics in sprees in an effort to cope with transient stresses, they will not he forced to continue the use of narcotics because they will have become physically dependent. In addition, it would be almost impossible for the nontolerant addict to die from heroin.
>
> There may be other benefits. Wikler stated that two of the important reasons for relapse of the abstinent narcotic addict are conditioned abstinence which may be evoked hy stimuli that

> have been associated with the addict's hustling activity to acquire drugs, and reinforcements of drug-seeking behavior through repeated reductions of abstinence by drug. It is possible in subjects who attempt to readdict themselves while receiving a narcotic antagonist such as cyclazocine, there may be extinction of conditioned physical dependence and drug-seeking behavior.

We further suggested "Cyclazocine could be used for the ambulatory management of former addicts who are highly motivated" (8).

Dr. Abraham Wikler thought the idea that conditioned abstinence and drug-seeking behavior might be extinguished with a narcotic antagonist could have clinical utility, and he communicated his enthusiasm to Dr. Alfred Freedman of New York Medical College. Dr. Freedman and Dr. Sharoff visited the Addiction Research Center where we shared with them our experiences with cyclazocine. In addition, I told Dr. Jerome Jaffe, then in the Department of Pharmacology and Psychiatry of the Albert Einstein Medical College, of our results with cyclazocine and he initiated studies. Dr. Freedman and Dr. Jaffe essentially confirmed our original observations and showed that it was possible to maintain addicts on narcotic antagonists and that the use of narcotics by addicts so maintained was considerably decreased. However, in these studies by Drs. Freedman and Jaffe it became apparent that although tolerance developed to the dysphoric effects of cyclazocine, these effects still had a deterrent effect on acceptance of the drug by addicts (3, 4). There were several reasons for this. Considerable care had to be taken during the induction phase with cyclazocine lest the dysphoric effects deter patients from continuing in therapy. Further, once patients had become stabilized and had developed tolerance to cyclazocine, missing only one or two doses would cause a sufficient reduction in tolerance that a stabilization dose when reinitiated would again produce undesirable and dysphoric subjective effects. Because of these dysphoric effects, cyclazocine acquired a bad name among some addicts.

In 1965 we initiated studies with naloxone with the purpose of determining if it had an abuse potential and whether the sedative, dysphoric, and analgesic properties of this drug could be separated from its antagonistic action in man. With Dr. Thomas K. McClane we also initiated studies in the chronic spinal dog. It was soon apparent that naloxone did not produce either sedation or dysphoria in human subjects (5) nor depress the flexor reflex or constrict pupils in the chronic spinal dog (11). As a matter of fact, an enhancement of the amplitude of the flexor reflex with very large doses of naloxone in the chronic spinal dog was observed. This

enhancement was related at that time to naloxone's convulsant effects. Because naloxone was devoid of agonistic activity, we then initiated studies to determine its duration of action when administered both subcutaneously and orally to determine if it might have potential for maintenance therapy using techniques that we had previously used for determining the duration of action of cyclazocine. We were unable to determine the duration of the blocking effects of naloxone sharply in these studies; however, we did have evidence that indicated that the blockade of naloxone was already diminishing within 5 hours after naloxone had been administered. We then attempted to make patients dependent on naloxone by administering naloxone in dose levels of 15 mg administered six times daily (q. 4 hr). The effects of morphine in patients receiving the stabilization dose of naloxone were essentially blocked except at the time immediately preceding the next dose of naloxone. This further indicated that we had a high level of blockade. When naloxone was abruptly withdrawn, no signs of abstinence emerged. On the basis of these experiments, we concluded that naloxone was devoid of agonistic activity; however, its duration of action seemed too short for maintenance therapy (5).

Drs. Freedman and Fink were more enthusiastic about naloxone, however, and a blockade of heroin of up to 24 hours was observed in patients receiving large oral doses of naloxone (2).

We felt that the long duration of action of cyclazocine was attributable to the methylcyclopropyl substitution on nitrogen, that for some reason the presence of a 14-hydroxyl group markedly reduced nalorphine-like agonistic activity, and raised the question of whether N-allylnoroxymorphone or naltrexone might be a pure antagonist with a long duration of action in man since it had important structural similarities to both naloxone and cyclazocine. Through the cooperation of Drs. Harold Blumberg, Ralph Jacobsen, and Irwin Pachter of Endo Laboratories, they not only made the compound available for clinical studies but conducted toxicity studies. Dr. Blumberg (1) had already shown that naltrexone was a potent narcotic antagonist in animals. Almost all of our expectations of this drug in man have been fulfilled. In the first studies conducted in man, naltrexone proved to be several times more potent than naloxone and to have a longer duration of action. It has a high degree of oral effectiveness and when administered in dose levels of 50 mg/day not only antagonizes the effects of large doses of morphine but markedly attenuates morphine's ability to produce physical dependence (9, 10). Studies conducted under the auspices of the National Research Council indicate that naltrexone is a safe

drug without untoward effects. Further, acute and chronic toxicity studies conducted by the National Institute on Drug Abuse indicate that naltrexone is an especially nontoxic drug.

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CHAPTER 25

Historical Trends in Naltrexone Research

Demetrios A. Julius, M.D.

The development of the narcotic antagonist, naltrexone, has related to and reflected in a fascinating way various medical and psychiatric research trends as well as an array of social and political trends. It has involved innovative cooperation between the clinical community, multiple research groups, various Federal Government agencies, and private industry. Through this cooperative interest in the project, and of course due to the pressing social need to devise new treatment approaches to the problem of heroin abuse, the research effort has yielded what seems to be a most promising and safe chemotherapeutic addition to opiate dependence therapy.

The existence of narcotic antagonist agents has been known since the early twentieth century. Initially, the primary interest in this class of drugs focused on their ability to counteract the effects of opiates in man and on their consequent use in the treatment of acute opiate overdose. This application, of course, was of direct medical life-saving use in hospital emergency rooms across the country. The main agent used for this purpose has become naloxone, which is a potent narcotic antagonist with a short duration of action. However, concurrent laboratory research within the drug industry was and has been constantly seeking out other types of narcotic antagonists.

With the increase of heroin abuse in America during the turbulent 1960's, the interest in new therapeutic approaches also increased. Up until then, heroin dependent individuals had not only been shunned by society in general, but had also been passed along like hot potatoes within the medical and therapeutic professions.

The problem was that no solid therapeutic approaches seemed to have any lasting effect with most of these opiate abuses. There

were, of course, inpatient facilities like that in Lexington, Kentucky, as well as other detoxification centers, but the relapse to heroin dependence was a constant erosion of the therapeutic work of these centers. It was during this upsurge in heroin abuse that the classic work and publication by Dole and Nyswander (2) stimulated widespread interest in their new treatment modality of methadone maintenance. Concurrently, new treatment modalities were being devised and explored at the Government's Addiction Research Center in Lexington, Kentucky.

One such treatment centered around the concepts of classical conditioning theory. Building on earlier theoretical formulations, Abraham Wikler elaborated in the mid-1960's the theory that operant conditioning plays an important role in initiating and perpetuating heroin use. Initially, the euphorigenic properties of narcotics probably act as strong reinforcers of what was called "drug-seeking behavior" in the opiate dependent individual. After this initial phase, tolerance to the narcotic develops and slowly reduces the euphoric effects. Thus in addition to the pursuit of pleasure (i.e., the euphoric effects), there is now a need to avoid pain (i.e., the abstinence syndrome). Therefore, the avoidance of the discomforting opiate abstinence syndrome also perpetuates the "drug-seeking behavior." In addition to this, a hypothesized "conditioned abstinence syndrome" may apparently be precipitated by environmental stimuli that have been associated with opiate dependence in the past. This syndrome has occasionally been reported merely after contact with a previous drug environment. It is characterized by increased reactivity to stimuli, prolonged autonomic responses, and often an intense "craving."

The narcotic antagonist drugs fit in very neatly, of course, with this line of thinking. Pharmacologically these substances have the ability to block the euphorigenic and dependence-producing properties of opiates. It is currently theorized that these drugs have this ability because of their structural similarity to narcotics themselves. Thus antagonists are able to occupy the same presumed opiate receptor sites in the body and thereby produce competitive inhibition of narcotics. It seemed logical, therefore, that a narcotic antagonist could be used to control the above mentioned determinants of drug-seeking behavior. Since the antagonist would block the euphoria and the dependence produced by the opiates, the reinforcement provided by these factors would gradually be attenuated. Thus with the prolonged absence of these reinforcers would come the gradual extinction of drug-seeking behavior.

Now by 1971, the heroin epidemic had reached panic proportions. The number of opiate dependent individuals was steadily rising along with an expansion into almost all sectors of American society. One need only remember all the media reports on heroin use and overdose in the high schools and grade schools to be soberly reminded of the mood of the times. By this time, the Federal Government began formulating action plans to attack this ever-expanding problem. Through Public Law #92-255, a mandate was given to establish within the Executive Office of the President a consolidated agency called the Special Action Office for Drug Abuse Prevention (SAODAP). Among other tasks, SAODAP assumed the lead role in research aimed at the development of new therapeutic techniques. Then SAODAP Director, Dr. Jerome Jaffee, set the development of a safe, long-acting, and effective narcotic antagonist as one of the top priorities for his new agency.

As coordinator for federal drug abuse programs, SAODAP had to work with as many as fourteen different agencies within the Federal Government that were dealing with drug abuse issues at that time. One of the main collaborators with SAODAP was the Division of Narcotic Addiction and Drug Abuse (DNADA) within the National Institute of Mental Health. Conjointly, these two agencies drew up a general development plan for narcotic antagonists. This plan called for concurrent research in the laboratory, in research animals, and in limited clinical use in man in order to develop perhaps more than one usable narcotic antagonist. The criteria set forth by these agencies for an optimal narcotic antagonist were as follows:

1. Ability to antagonize the euphoric high of opiates
2. Absent or low agonistic effects, especially unpleasant ones
3. Does not cause physical dependence
4. Does not exhibit increasing tolerance to its antagonistic actions
5. Absence of serious side effects and toxicity even in chronic use
6. Easily administered
7. Long-lasting or moderate duration of antagonist effects
a. Absent or low abuse potential
9. Reversible effects in case of medical emergency
10. High potency to allow administration of small amounts in a biodegradable vehicle
11. Easily available and inexpensive
12. Therapeutic efficacy in treatment of narcotic addiction

By early 1972 there were several antagonists in existence at various stages of development. The purest antagonist was naloxone. It seemed to be a potent antagonist and showed almost no agonistic

action of its own. Its main drawbacks as a therapeutic agent in opioid dependence were its high cost, the difficulty in synthesizing it, its very poor oral absorption rate, and especially its short duration of action in the body. Naloxone had been approved by the FDA for short-term use in humans for opiate overdose. In spite of its drawbacks, naloxone had met with limited success as an adjunct to treatment by several investigators. This seemed encouraging for narcotic antagonist treatment in general.

Concurrently being developed was another promising and potent antagonist called cyclazocine (3, 6, 7). This drug demonstrated a longer duration of action of up to 24 hours with 4 milligrams of the substance. However, its drawbacks were also recognized. These consisted of strong agonist properties when administered rapidly to individuals. These properties included quite unpleasant feelings described as dysphoria and psychotomimetic effects. Despite the tolerance that develops to these effects, cyclazocine was not well received by the addict volunteers and soon acquired a bad street reputation. However, it was successful in the treatment of some individuals, and these individuals are still, in fact, being treated with cyclazocine in certain clinics in New York City.

Additionally, three other compounds, designated as M-5050, BC-2605, and EN-1639A, were in early animal and human testing at the time. One of these, EN-1639A, seemed to be a potent antagonist and also did not show the dysphoric and unpleasant side effects of cyclazocine (1). It had a good duration, in that 50 mg seemed able to block narcotic action for 24 hours. By late 1972, there was a substantial supply available for testing of this drug, which came to be known as naltrexone. By mid-1973 it became evident that this drug fulfilled the criteria of an optimal narcotic antagonist to a greater degree than any of the other available substances (4, 5, 8, 9, 10).

Besides the research progress being made, there were also administrative changes occurring within the Government. By 1973, the Division on Narcotic Addiction and Drug Abuse was separated from NIMH and expanded into the National Institute on Drug Abuse (NIDA). Thus, from 1973 to 1974, NIDA and SAODAP shared the responsibility for the ongoing development of the narcotic antagonists in general and of naltrexone in particular. By mid-1974, as SAODAP began to phase out of existence, the entire direction and monitoring of the naltrexone research fell to the Division of Research, NIDA.

Under the direction of NIDA Director Dr. Robert DuPont and Division of Research Director Dr. William Pollin, the naltrexone

research project was accorded the same high priority it had enjoyed at earlier times. Meanwhile, the day to day planning, implementation, and monitoring were carried on through a succession of project officers such as Dr. Alan Ramsey, Dr. Joe Silvio, and Dr. Demetrios Julius.

It was NIDA's goal to expedite the development and marketing of naltrexone in the fastest, safest, and most effective way possible. With this goal in mind, an effort was made to interest the National Research Council of the National Academy of Sciences (NAS) in undertaking this development process. The Council agreed to do this in part by developing a well-controlled, double blind clinical trial of naltrexone. A Committee on Clinical Evaluation of Narcotic Antagonists was formed in order to design, organize, monitor, and evaluate the planned research project on naltrexone. Five research clinics were selected to participate in this cooperative study which included among other things standardized and rigid protocols. The Baltimore and New Haven clinics could use only "post-addicts" in their research. The Detroit and Sepulveda clinics could use only "methadone maintenance addicts," while the St. Louis clinic could use only "street addicts." One of the papers to follow–that by Dr. Ling–will deal with the experience of one of these N.A.S. research clinics.

In addition to the controlled cooperative study, NIDA supported from 1573 to 1974 21 other grants dealing with clinical and preclinical research into narcotic antagonists. This support totalled over five million dollars. Researchers in this group were free to use different protocols, to use different treatment settings, to treat different types of dependent individuals, and to pursue any variety of different research questions. These "open" clinical studies added much useful information on the safety, clinical use, and efficacy of naltrexone. Another of the papers that follow–the one by Dr. Resnick–will deal with his experiences in ten years of clinical experience both with cyclazocine and later naltrexone.

A final category of naltrexone clinics dealt with the direct testing out of the original behavioral formulations discussed earlier. The clinic sites were at Camarillo Neuropsychiatric Institute in Ventura, California; McLean Hospital in Belmont, Massachusetts; and the Veterans' Hospital in Philadelphia, Pennsylvania. The experience at the latter clinic will be discussed by Dr. O'Brien as an example of these group clinic studies.

The data from most of these studies has now been collected and has been partially analyzed. The N.A.S. study report has been pulled together and is set for public distribution. At the same time

the remaining data from the NIDA studies are being consolidated for submission to the Food and Drug Administration in order to proceed with Phase III of the drug's development. This will be the widespread and uncontrolled clinical testing of naltrexone.

As for the present, the analysis has shown that although naltrexone has not been proven to be statistically more significant than placebo in retaining subjects in the N.A.S. study and in extinguishing their drug seeking behavior, there certainly is a trend favoring its efficacy in a great number of subjects tested. This trend is most evident in the "post-addict" group. This was the group who were currently drug free following incarceration or participation in a therapeutic program. Furthermore they were often under court pressure in probationary or parole status. Therefore naltrexone seems to be most effective in the externally or internally motivated drug-dependent person.

Naltrexone has also proven to be safe in the population tested, with only occasionally gastrointestinal symptoms of nausea, vomiting, and cramping being reported in some patients. It has also been shown that naltrexone given in a dose of 50 mg per day completely blocks the euphoria and dependence producing effects of narcotics. And quite impressively, the feasibility of doing a well controlled, double blind study of a new chemotherapeutic treatment has been demonstrated even with such difficult groups as street addicts, methadone maintenance addicts, and post addicts. In fact, the naltrexone study, and especially the N.A.S. portion, stands as a model for placebo controlled studies with drug-dependent individuals.

It will be interesting to see what the future has in store for this research. The final Phase III study plan has been formulated and has been offered to Endo Laboratories who hold the patent on the drug. They will be taking the lead on the final development and eventual marketing of naltrexone.

Meanwhile interest in clinical testing of naltrexone continues both in the United States as well as in the International community. Both in Malasyia and in Iran there is strong desire to institute clinical use of naltrexone in their respective opiate dependent populations. With the existing legal pressures to cease the dependence on opiates in these countries, it may well be that naltrexone proves to be a most effective treatment there.

Naltrexone is, of course, not a cure-all for all opiate dependent individuals. There probably is no such treatment, as we have learned through the shortcomings of methadone maintenance. However,

naltrexone seems to be a safe, and in some small percentage of individuals, a most effective new chemotherapeutic treatment.

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CHAPTER 26

Naltrexone: The Clinical Investigator's Dilemma

Walter Ling, M.D.

In the summer of 1974 we became involved in a clinical investigation using the narcotic antagonist naltrexone in the treatment of heroin addicts. The study was organized by the Committee on Clinical Evaluation of Narcotic Antagonists (CENA), U.S. National Academy of Sciences National Research Council (NAS/NRC), under contract to the U.S. National Institute on Drug Abuse (NIDA), U.S. Department of Health, Education, and Welfare. Naltrexone was chosen because of its high efficacy after oral administration, its virtual lack of agonistic properties, and its relatively long duration of action.

The goals of the study were to examine the acceptability of naltrexone at the clinical level and to provide some preliminary assessment of its toxicity and efficacy in this context. Under three separate double blind protocols, three distinct populations of addicts were studied: (1) "street addicts" (patients currently addicted who either could not or would not enter methadone maintenance programs), (2) "postaddicts" (former addicts, typically recently released from incarceration and more or less under external pressure to remain in treatment), and (3) methadone maintenance patients who wished to detoxify and become drug free. Five clinics participated in the study, with St. Louis, Missouri, treating "street addicts," Baltimore, Maryland and New Haven, Connecticut, treating "postaddicts," and Sepulveda, California, and Detroit, Michigan, treating those detoxified from methadone maintenance.

All subjects were males, 18 years and older, free of serious medical and/or psychiatric illnesses. They were randomly assigned,

within each clinic, to either naltrexone or placebo, dispensed as a syrup with similar taste and appearance.

After induction, naltrnxone patients received naltrexone 100 mg. on Mondays and Wednesdays and 150 mg. on Fridays, with no medication for the other days. Placebo patients remained on placebo throughout the study, which consisted of nine months of active treatment with a six-month followup. All other auxiliary services were offered to both groups of patients. Periodic physical examinations and laboratory tests, as well as detailed analyses of early terminations for medical reasons, provided indices of safety. Efficacy was evaluated in terms of program retention, illicit drug use, changes in psychosocial adjustment, and changes in the degree of craving for heroin.

I will not attempt to give a detailed report on the results of the study, since the committee has prepared its own report which will soon appear in print. In general, the study confirmed the extreme difficulties in assessing treatment results in the addict population. Naltrexone appeared slightly better than placebo in terms of retention and use of illicit drugs. Craving for heroin also seemed to decrease with prolonged naltrexone administration. Clinical and laboratory data tended to indicate that naltrexone is safe under the conditions of this study. No serious medical complications or adverse reactions were reported and only minor side effects had occurred.

Undoubtedly the NAS/NRC Committee will draw certain conclusions and make its recommendations to NIDA based on these results. My reasons for describing the study are to provide some background information and to use this study to illustrate some of the difficulties which, as the result of my participation in the project, I have become aware of both clinically and as an investigator. From time to time I shall refer to certain observations made in the NAS/NRC study to aid my discussion. However, the interpretations of these findings are my own and do not represent the view of the committee.

Obviously, the questions about any new drug of greatest interest to clinicians are: (1) Does it work? (2) Is it safe? and (3) Will patients take it? In the case of naltrexone, there are problems in answering each of these questions, but the major problem has to do with deciding what naltrexone is to do. In other words, how does one define efficacy and measure it with some degree of certainty?

The pharmacological property of naltrexone, i.e., its ability to block the euphorigenic effect of narcotics, is already known and is not an issue requiring clinical investigation. The problem in defining

efficacy here is what the clinicians, and ultimately the patients, wish to accomplish in naltrexone treatment. It is essential then first to define the goals of naltrexone treatment in ways that may be measured at baseline and at periodic intervals during and after treatment with naltrexone. In the case of the NAS/NRC study, these were: adherence to a recommended treatment regime (program retention), decrease in the use of illicit drugs (urine test records), less craving for heroin (craving scale), improvement in social adjustment (status interview), and improvement as seen by the clinic staff at termination or completion of treatment (global assessment).

As a measurement of efficacy, adherence to treatment regimen as reflected by program retention is problematic at least in two respects, one having to do with the process of data acquisition and the other with interpretation of the data acquired. With the possible exception of methadone maintenance, retention in drug abuse treatment programs has been generally poor. This undoubtedly relates to the transient nature of the addict's motivation for treatment of any sort, but there are some additional problems peculiar to treatment with naltrexone. For an addict to be started on naltrexone, he must first become drug free. This requires time, especially for patients who are on methadone maintenance. During the course of detoxification, an addict may become disinterested for a variety of reasons. Sometimes he becomes discouraged because of the discomfort, which may be quite substantial for some patients, experienced during withdrawal from methadone. Parenthetically , there is some evidence that successful detoxification from methadone maintenance may require months rather than weeks. The longer the period between the addict's initial interest in naltrexone and the actual dosage initiation, the more opportunity for him to change his mind. Even for those who maintain an interest in naltrexone, successful detoxification may prove impossible for a patient on methadone maintenance.

As for street addicts, since they generally require less time for detoxification, one might expect to have greater success with this group. In actual practice, they proved to be even more difficult because of the tenuous nature of their motivation and the general lack of stability in their lives.

Keeping patients on naltrexone after dosage initiation is also very difficult. For one thing, naltrexone tastes bitter and tends to leave an unpleasant aftertaste which many addicts dislike. Moreover, unlike methadone, which allows patients to feel considerable narcotic effect, naltrexone leaves the patient with no positive subjective

experience to induce him to continue ingesting the drug. Finally, discontinuing naltrexone induces no subjective discomfort to remind patients that they need their medication. All these factors tend to lead to premature termination from naltrexone treatment.

The difficulties in acquiring sufficient program retention data are well illustrated by the NAS/NRC study. Of the 276 methadone maintenance patients who indicated an interest in naltrexone, less than one in five actually received even one dose of naltrexone. Eighteen subjects (less than 1/15) remained in treatment over 60 days, and only five subjects completed nine months of treatment. To put this problem in another way: suppose an investigator is interested in having as few as 50 patients complete a nine-month study, and let us say optimistically that one half of all patients on methadone maintenance are interested in becoming drug free and taking naltrexone. Using the current experience as a guide, this investigator will have to approach some 5,000 methadone maintenance patients in order to carry out his study successfully. This means that each time he approaches a potential study subject his changes of seeing that patient through the nine-month study are only one in a hundred.

For street addicts he could do even worse. None of the 252 street addicts completed the study. Only one out of every 18 street addicts who expressed an interest in taking naltrexone and being drug free remained in treatment for 60 days.

Another problem with using retention to measure treatment effects with drug addicts has to do with interpreting the retention data itself. Many addicts remain in treatment for reasons having little or nothing to do with the treatment they receive. An addict may choose to remain in treatment because the alternative would be going to jail. This can hardly be attributed to any pharmacological efficacy of the drug he receives. For instance, most of the subjects remaining in treatment after eight months belong to the postaddict group (5/7 naltrexone—5/16 placebo) who, as indicated earlier, are often under external pressure to remain in treatment.

A few subjects assigned to a placebo continued to believe they were receiving naltrexone even after "testing." A subject on placebo who "fixed" with his friends but believed that he was protected on naltrexone and therefore not expecting any drug effect, might indeed not experience it if the quality of street heroin was poor.

Some subjects, however, having tested and discovered that they were on a placebo, chose to remain in the study because they could then use illicit drugs without the fear of disciplinary actions against them to which they would be subject in a usual treatment program.

Furthermore, no outcome data are generally available on subjects who dropped out of the study. We really do not know if these people are doing any better or worse than those who remained in the study.

The extent of illicit drug use (as reflected by urine testing) would seem to be somewhat more objective, and elsewhere we have argued that such is the case with LAAM and methadone treatment (1). In the case of naltrexone, even here the situation is a little more complicated. If the rationale for administering naltrexone is based on the behavior theory of extinction, the subjects ought to be encouraged to test it, and one would assume that the more they test the more therapeutic it would be for them. It is at least conceptually difficult to see how the magnitude of this therapeutic effect (degree of testing) can at the same time indicate how poorly they are doing. On the other hand, since there is no subjective sensation that a patient can feel when he is on the medication, until a subject has tested, all the changes may be due to a placebo effect. In the NAS/NRC study, an attempt was made to measure the extent of drug use *after* the subjects have tested and we did find the naltrexone group using less illicit drugs subsequent to their first positive urines.

Changing psychosocial adjustment is meaningful only if there is concomitant improvement in drug-seeking behavior. If a patient is doing better in terms of employment and other social adjustments but continues to use illicit drugs regularly, his social changes may be attributed to the total treatment program impact but can hardly be a direct result of any specific drug action. On the other hand, can a man be considered a failure as far as naltrexone is concerned if he never uses heroin again but continues to be unemployed and makes no other attempts to improve his lot?

One interesting observation from the NAS/NRC study was a decrease in the degree of craving with continued naltrexone treatment. It is not yet clear whether this relates directly to the phenomenon of prolonged naltrexone treatment, or whether the desire for drugs simply decreases with passage of time. As an instrument for measurement of efficacy, it is too early to judge how useful this index will be.

A global assessment on the part of the clinic staff is useful at the end of treatment. However, since the impressions upon which the assessments are made are based on knowledge of the patient during his course of treatment, they cannot be accurately measured at baseline.

Each measurement of efficacy is thus defective in its own way, and efficacy must be measured in some integrated manner. How to approach this depends on the investigator's belief of what naltrexone should do for the patient. Still, there are other ways to consider what efficacy really means. We might, for instance, take the position that since we already know naltrexone will block the effect of narcotics, the major clinical problem is how to deliver naltrexone to the target treatment population: in other words, how to get patients to accept naltrexone. Thus we may reason that in this instance patient acceptance and efficacy are one and the same. Furthermore, knowing that an addict's motivation for treatment is transient, we might develop new means of drug delivery which would make it difficult for an addict to stop taking medication once he is on it. One such approach is the use of a sustained action preparation.

Still another approach to the issue of efficacy of naltrexone is to accept what takes place at the clinical level as a fact of life and attempt to work within these limitations. We know that long-lasting therapeutic effects rarely if ever result from single treatment episodes but from repeated efforts to engage addicts in treatment. (One problem with the NAS/NRC study protocol is the prohibition of reentry once a patient drops out of the study.) It appears to us that one way to look at the clinical effectiveness of naltrexone over time is to allow and encourage patients to undergo treatrnent repeatedly even though the duration of each treatment episode may be shortlived. If naltrexone is beneficial, it should lengthen the time interval between detoxification and the occurrence of physical readdiction for those who receive treatment with naltrexone, as compared to those who do not. This time interval may thus serve as an index of clinical efficacy for naltrexone. And the survival time from initiation of treatment to clinical relapse can be analyzed by means of a life table method and compared to a nontreatment group. This is the direction where our current thinking is leading us.

In summary, I hope this discussion has directed your attention to some of the difficulties that a clinical investigator must consider in studying addicts in general and in conducting clinical trials with naltrexone in addicts in particular. I hope our suggestion of an alternative method to measure the clinical effects of naltrexone will prompt others to give further consideration to still other ways of using naltrexone clinically.

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CHAPTER 27

Update on Naltrexone Treatment

Charles P. O'Brien, M.D. Ph.D., Robert Greenstein, M.D., and George E. Woody, M.D.

Our group in Philadelphia has used naltrexone in the treatment of 201 narcotic addicts in 258 separate treatment episodes as of 1 July 1977. The antagonist treatment program is an important part of our overall multimodality program which includes methadone or propoxyphene maintenance treatment, inpatient detoxification, long-term therapeutic community, family, group, and individual therapies, and a variety of behavioral treatments. Narcotic antagonist treatment, of course, appeals only to those patients who are genuinely interested in becoming drug free. It is not nearly as popular as methadone treatment, but it occupies an important niche–amounting to 5-10 percent of our total patient population at some time in their treatment careers.

Our narcotic antagonist patients are demographically similar to our other patients: mean age 27, 60 percent black, more than 95 percent male, and more than 95 percent veterans of military service. Our methods for detoxification from narcotics and institution of antagonist therapy have been reported elsewhere (2, 4); they are similar to those described by others. We use intravenous naloxone prior to the first naltrexone dose to detect residual physical dependence and thus reduce the incidence of precipitated withdrawal when the first dose of naltrexone is ingested.

RESULTS

Our results will be discussed in four categories.

1. Side Effects and Toxicity of Naltrexone.

Because naltrexone is such an effective antagonist, it will precipitate acute withdrawal reactions in patients who have even

small degrees of residual physical dependence on narcotics. Even in addicts detoxified up to a week previously, some degree of cramping and general aches and pains may occur with the first few doses of naltrexone. Patients with a history of peptic ulcer disease may have severe abdominal pain precipitated by naltrexone. We now exclude such subjects from naltrexone treatment.

Other subjective complaints such as dizziness, nausea, insomnia, or weakness may be related to protracted narcotic abstinence symptoms rather than naltrexone effects. They diminish after the first week and gradually disappear over the next several weeks of treatment.

We found no significant and consistent blood pressure changes in our 201. subjects. Inpatient blood pressure recordings tended to be lower than outpatient measures. But outpatient blood pressure prior to and during naltrexone therapy was not significantly changed. In fact, we have identified hypertensive addicts during our screening, treated their hypertension and then successfully placed them on naltrexone with no adverse effects on their anti-hypertension program.

The only serious toxicity occurring in our series was a case of idiopathic thrombocytopenic purpura while on naltrexone which may have been drug-related and a case of allergic dermatitis or drug rash. The relationship to the rash was established by resuming treatment with naltrexone cautiously, and the rash reappeared.

Overall, we found naltrexone to be a safe drug with minimal side effects–the same conclusion reached by Bradford and Kaim (1).

2. Naltrexone Blockading Effects

We evaluated the degree of protection from narcotic effects afforded by naltrexone by conducting hydromorphone and saline self-injections under double blind conditions. Hydromorphone (Dilaudid) is a narcotic whose subjective effects could not be distinguished from heroin by experienced addicts (3). A variety of hydromorphone dose levels were used (1-4 mg) equivalent to 7-30 mg heroin, and a variety of dose levels of naltrexone (50-200 mg/70 kg) and a variety of time periods after naltrexone ingestion (2-72 hrs) were used. Our results were quite consistent. Naltrexone reliably attenuated narcotic objective and subjective effects for up to 72 hours. The degree of attenuation was proportional to dose of naltrexone, dose of narcotic, and the time since naltrexone was ingested. Thus, the narcotic effects were less than those produced

by a similar dose in that subject prior to naltrexone but reliably more than saline effects. These effects were seen in operant responses, pupillary constriction, and subjective reporting of rush, high, and street value of the injection.

3. Conditioned Responses Associated With Self-Injection

The availability of patients volunteering to take naltrexone provides an opportunity to study some of the conditioning factors associated with the self-injection ritual. The importance of conditioning in the addiction process was first recognized by Wikler (8), and it has been extensively studied in experimental animals. We have described several types of conditioning in human addicts (5, 6).

Conditioned abstinence occurs when the addict is exposed to stimuli which, in the past, have consistently been associated with opiate withdrawal and the obtaining of the next dose. Examples are "copping" area, bags of heroin, "cook-up" rituals, and room in which narcotics are usually injected. After repeated pairing, the stimuli are able to elicit drug craving and withdrawal responses (pupillary dilation, cooling of skin, tachycardia) even when the addict is drug free.

The stimuli which elicited withdrawal responses were all pre-injection stimuli. The act of self-injection usually relieved the withdrawal and craving even if the injection actually consisted of saline. Some addicts reported definite pleasure from the self-injection when saline was received in a double-blind design. This has been described clinically as the "needle-freak" phenomenon.

The pleasure received from the injection itself (either saline or narcotic in the presence of naltrexone) extinguished rapidly. After several trials the pleasure turned to dislike and the patients reported that the self-injection caused their craving to be intensified. Thus some of the conditioned effects of self-injection were modified by unreinforced self-injection in the laboratory. This did not have a discernible effect on treatment outcome. Naltrexone patients who had their self-injection responses extinguished had only a slightly better outcome than those who received naltrexone with no self-injections. Still, the changes in injection behavior were dramatic. It may be more clinically effective to begin by desensitizing the patients to environmental stimuli related to drug procurement and then systematically progress in steps to desensitization to the self-injection procedure.

4. Clinical Outcome

The determination of relative effectiveness of a specific treatment is especially difficult when types of treatment differ radically. In the treatment of narcotic addiction, therapeutic community, methadone or other narcotic maintenance, and narcotic antagonist therapy all appeal to different patients. Thus random assignment of unselected patients to a given treatment is not possible. In our program, all of the above treatment modalities are available, but patients participate in the decision as to which treatment is used. Often they are used sequentially at different stages in a patient's treatment. The result at followup then might be attributed to several treatments rather than just the last one.

We have interviewed naltrexone patients at one month and six months after stopping naltrexone treatment. Social and vocational functioning, drug use, and urine tests were evaluated. We compared naltrexone patients to patients treated in a maintenance study comparing propoxyphene (a weak opiate) and low dose (up to 36 mg per day) methadone. The only differences at intake were that the naltrexone patients reported more different types of drug abuse in addition to opiate dependence, more alcohol abuse, and more attempts at detoxification.

The results at followup showed that methadone patients remained in treatment longer, but there was no significant difference in treatment duration between propoxyphene maintenance and naltrexone. After termination from study treatment, naltrexone patients were significantly less likely to return to methadone maintenance. Nevertheless, naltrexone patients were more likely to be located for followup at one and six months. Naltrexone patients reported significantly more alcohol use at followup, but this difference was present at intake. Naltrexone patients reported significantly more benefits from treatment and more satisfaction with the program than the two maintenance groups. Significantly more naltrexone patients (40%) were opiate-free at one month, but the difference became nonsignificant six months after stopping treatment. Overall, there were remarkably few differences on any outcome measure. These results will be reported in detail elsewhere (7).

SUMMARY

To summarize, then, our work with naltrexone in a multimodality treatment program indicates that it appeals to about 5-10

percent of narcotic addicts–those who consciously want to obtain drug-free status. It does significantly attentuate the effects of narcotics to the extent that they lose their reinforcing properties, and it has minimal side effects. Although we treated a self-selected population, it is noteworthy that about 40 percent of those who remained on naltrexone for more than a week were still opiate free 6 months after cessation of treatment. For some it appeared to be a turning point in their lives. It was the first time in years that they could live in their neighborhood and not be either intoxicated or occupied with the pursuit of narcotics. Our behavioral studies have identified a number of conditioned psychophysiological responses associated with the self-injection ritual. So far, although we have succeeded in extinguishing some of these responses, this has not resulted in an improved clinical outcome. We are currently working on more comprehensive behavioral treatments, but the clinical significance of these conditioned responses is uncertain at present.

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CHAPTER 28

Naltrexone in the Treatment of Opiate Dependence

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INTRODUCTION

At the Division of Drug Abuse Research and Treatment of New York Medical College, we began using naltrexone early in 1973, and studies are continuing at the present time. Over the past four years, more than 400 opiate addicts have been detoxified and inducted onto naltrexone by members of our staff. Our clinic is located in the East Harlem section of New York City, where the incidence of opiate addiction is exceptionally high. The clinic's patient population is comprised of individuals from all levels of society, although most are of low socioeconomic status and have a high incidence of unemployment and use of public assistance. On the average, 38 percent are black, 38 percent are Puerto Rican, and 24 percent are white. Heroin and/or illicit methadone are the drugs primarily abused. Patients are referred to us by community service agencies, by nearby ambulatory detoxification facilities, and by expatients or those continuing in treatment. The clinic's staff includes psychiatrists, internists, psychologists, nurses, social workers, vocational and recreational therapists, students in the mental health professions, and paraprofessional counselors.

This report summarizes the results of four years' clinical experience with naltrexone, in both outpatient and inpatient study groups, and covers the following topics: (a) safety, toxicity, side effects, and duration of opiate blocking action of naltrexone; (b) clinical efficacy of naltrexone in the treatment of opiate dependence; (c) methods for rapid induction onto naltrexone; and (d) future directions.

SAFETY, TOXICITY, SIDE EFFECTS, AND OPIATE-BLOCKING ACTION

Our early work with naltrexone focused primarily on the pharmacology of the drug as a prelude to exploring its clinical efficacy in treating opiate dependence (3, 8, 9). To be clinically useful, a narcotic antagonist should be orally effective, safe, nonaddicting, have minimal side effects, and provide blockade to opiates for at least 24 hours following a single dose. Results of the above studies demonstrated that naltrexone met these criteria. For example, in one study with 37 detoxified heroin addicts (3), daily dosages of naltrexone ranging from 120 to 200 mg were found to produce almost no untoward side effects except for epigastric pain in some individuals, especially when taken on an empty stomach. Basal heart rate and blood pressure as well as blood and urine chemistry were not significantly altered, and no signs of toxicity were detected. Unlike induction onto cyclazocine (1), induction onto naltrexone was accomplished without dysphoric effects, and abrupt cessation of daily naltrexone by placebo substitution resulted in no withdrawal effects. Also, complete blockade of the euphoric and miotic effects of 25 mg experimentally-administered intravenous heroin was found 24 hours following a single naltrexone dose of 50 mg or more, as assessed by subjective rating scales and measures of pupillary diameter. Blockade was also found up to 72 hours following administration of 200 mg naltrexone. These findings were subsequently confirmed (9) in a larger patient group (N=155), although an insignificant elevation of blood pressure was found in some cases.

Since these studies indicated that naltrexone was safe, relatively free of side effects, and acceptable to patients, we directed our attention toward assessing its clinical efficacy in the treatment of opiate dependence.

CLINICAL EFFICACY

Predictive Variables

Our evaluation of naltrexone's clinical efficacy focused primarily upon identifying opiate users most likely to benefit from naltrexone treatment (5). This focus emerged from earlier work with cyclazocine (1) which presented a typological classification of

opiate users based upon patients' self-ratings of the role opiates play in their lives. Briefly, two major groups were identified and shown to have a differential response to cyclazocine treatment. One group appeared to use opiates as a form of "self-medication" to relieve chronic emotional symptoms or stress. They indicated that the drug reduced their inhibitions, anxieties, and painful affects, and perceived themselves to function better with opiates in their system as compared with periods when they were opiate-free. In general, such individuals discontinued cyclazocine treatment prematurely. By contrast, the other group seemed to use heroin as a result of environmental influences: in these individuals disorders of feeling and impaired capacity to function without opiates did not predominate. In general, such individuals remained in cyclazocine treatment for longer periods of time.

Based upon these earlier findings with cyclazocine we hypothesized that patients most likely to benefit from naltrexone would be those with: (a) greater capacity for object relations; (b) higher levels of psychosocial functioning; (c) longer histories of opiate addiction; and, (d) longer opiate-free periods interspersed between periods of addiction. In a group of 81 opiate-dependent individuals, applying for naltrexone treatment over a 10-month period, an extensive battery of information was obtained at intake and then correlated with treatment outcome at 12 months (l-year followup). After meeting all criteria for naltrexone treatment (i.e., male, at least 18 years of age, and no serious medical or psychiatric disturbance), patients were detoxified from opiates, kept opiate-free for 5-10 days, and then inducted onto naltrexone. Naltrexone was dispensed, in the clinic, three times weekly (Monday, 100 mg; Wednesday, 100 mg; Friday, 150 mg). No take-home doses were provided. Each patient was assigned a primary therapist who monitored the course of treatment and provided ancillary services. At twelve months following the first naltrexone dose, patients were categorized as opiate-free or opiate-dependent based upon urinalysis, Narcan Test, and clinical interview with the patient, family members, or close friends.

Results showed that of these 81 patients, 33 percent were opiate-free and 67 percent were opiate-dependent one year following their first naltrexone dose. Consistent with our hypotheses, the opiate-free as compared with the opiate-dependent group, on the average, had been addicted for a longer period of time prior to naltrexone treatment, had longer opiate-free periods interspersed between periods of addiction, had lower levels of opiate dependence at intake according to money spent for opiates during the

preceeding 6 months, and a greater percentage had an ongoing relationship, although none of these differences were statistically significant. The number of weeks that patients stayed on naltrexone did significantly differentiate the two outcome groups: opiate-free patients had taken naltrexone for a mean of 12.1 weeks, whereas opiate-dependent patients had taken it for only 6.8 weeks. Other findings were that: (a) relapsing patients tended to return for treatment and stay for increasingly longer periods of time with each return, and, (b) the proportion of the 81 patients who were opiate-free and opiate-dependent at various points in the study varied greatly during the first 6 months of the study but stabilized thereafter (i.e., the ratio of opiate-free to opiate-dependent patients was approximately the same at 9, 12, and 15 months following the first naltrexone dose).

All 81 patients discussed above stayed on naltrexone for at least one week after receiving their first dose. Another 66 patients who had entered treatment during the same 10-month period failed to complete detoxification and thus received no naltrexone. A comparison of these two groups revealed some striking differences: (1) patients who failed to complete detoxification had used significantly larger amounts of opiates during the 6 months prior to intake; and (2) nearly twice the percentage of patients who stayed on naltrexone for at least one week had been gainfully employed at intake.

Although this study failed to uncover reliable predictors of treatment outcome with naltrexone, an important finding was that time on naltrexone significantly differentiated opiate-free from opiate-dependent patients at 12 months. This finding suggests that naltrexone contributes favorably to treatment outcome as time on naltrexone increases.

Treatment Outcome

Table 1 presents treatment and followup data for 265 patients who were inducted onto naltrexone and then discontinued it within the 29-month period from February 1975 to June 1977. As shown in the column headings, these 265 patients are categorized into three groups, based upon the amount of time they stayed on naltrexone: Group I consists of 62 patients (23 percent of the total N) who stayed on naltrexone 7 days or less; Group II consists of 140 patients (59 percent) who stayed on naltrexone from 8 days to 3 months (mean of 4.8 weeks); and, Group III consists of 63

TABLE 1

Treatment Outcome as a Function of Time on Naltrexone (N=265)

	TIME ON NALTREXONE		
	Group I (N=62)	**Group II (N=140)**	**Group III (N-63)**
	7 days or less	**8 days to 3 months**	**3 to 24 months**
TREATMENT OUTCOME			
Re-addicted:			
within 1 month	82% (51)	63% (88)	24% (15)
within 2-6 months	2% (1)	15% (21)	27% (17)
total	84% (52)	78% (109)	51% (32)
Opiate-free:			
6 months or more	2% (1)	2% (3)	29% (18)
less than 6 months[a]	0% (0)	2% (3)	6% (4)
Other:			
left NYC opiate-free[b]	3% (4)	3% (4)	2% (1)
lost to follow-up	13% (8)	19% (27)	13% (8)

[a] currently opiate-free but discontinued naltrexone less than 6 months ago

[b] left NYC opiate-free from 1 to 5 months after discontinuing naltrexone

patients (24 percent) who stayed on naltrexone from 3 to 24 months (mean of 26.8 weeks). Followup data show that with increasing time on naltrexone the incidence of readdiction within 6 months after discontinuing naltrexone decreases. Note that the overwhelming majority of patients in Group I (82 percent) became readdicted within 1 month after their last naltrexone dose. It can also be seen that there is a direct relationship between time on naltrexone and the numbers of patients who have been opiate-free for at least 6 months since their last naltrexone dose: only 2 percent of Groups I and II fall into this category, as contrasted with 29 percent of Group III. Fifty-two of the original 265 patients fall into the category of "Other." These fifty-two include: (a) patients who left New York City opiate-free from 1 to 5 months after their last naltrexone dose; and (b) patients who terminated naltrexone treatment and were lost to followup.

Not included in the preceeding analysis are 20 patients who have been receiving naltrexone, without interuption, from 1-20 months.

Consistent with our earlier results (5), the present findings suggest that naltrexone's clinical efficacy is a function of treatment

duration. The longer patients stay on naltrexone, the better their prognosis for remaining opiate-free. It would appear, therefore, that a critical efficacy issue is to identify factors that help retain patients in treatment for at least some minimum period of time. Present findings suggest 6 months as a possible minimum: most patients who became readdicted did so within the first 6 months of treatment; Group III, who stayed on naltrexone for an average of 6 months, showed the most favorable treatment outcome.

What are some of the factors that affect patient retention in treatment? From the outset, our clinical experience has strongly suggested that individual counseling/therapy plays an important, if not essential, role in patient retention and rehabilitation in antagonist treatment (7).

Treatment Approaches

Narcotic antagonists do not pharmacologically alter the substrates of opiate-seeking behavior nor do they offer symptomatic relief. Their clinical efficacy derives indirectly from blocking the effects of potentially self-administered opiates. As long as patients stay on the antagonist, opiate-seeking behavior is thwarted and readdiction is virtually impossible. It would appear, therefore, that models for evaluating the clinical efficacy of antagonists cannot be the same as those used for pharmacologic therapies of other illnesses, that directly influence underlying malfunctions and alleviate symptoms. The efficacy of such therapies is readily discernable, as when imiprimine is found to have an antidepressant effect. By contrast, narcotic antagonists do not directly alter underlying psychopathology or its behavioral manifestations. Unless otherwise treated, intrapsychic and environmental factors which contribute to opiate-seeking behavior will remain unaltered by antagonist medication alone and predispose the individual to terminate treatment and become readdicted. It is our contention that psychotherapeutic intervention contributes positively to retaining patients in treatment and fosters overall rehabilitation. Accordingly, the efficacy of antagonist treatment is inseparable from the overall therapeutic context within which it is provided. If the efficacy of naltrexone depends upon other variables in an overall treatment approach, it is unreasonable to evaluate it without identification and control of these other variables.

Some of the clinical techniques we employ and consider most important will be discussed below. First, we must emphasize the obvious: Good clinical judgment is never fully explainable from a description of specific techniques.

When working with narcotic antagonists, it is important to emphasize to patients that the medication alone is not the whole treatment. Obviously, to do this, the staff themselves must know it, understand it, and believe it!

The medication can, however, be used as a tool for engaging the patient in therapy: It can be a way of enabling the patient to begin to trust the therapist and to establish a therapeutic alliance. Whatever therapeutic techniques are employed, the importance of good rapport and positive transference between the patient and a therapist cannot be overemphasized. This relationship can be beneficial in many ways, ranging from providing support the patient needs during the postwithdrawal period to substituting for emotional resources that are lacking in the patient's life, In early work with antagonists, when we did not provide such therapy, our results were poor; they improved subsequently when patients were seen by trained and empathetic therapists for regularly-scheduled counseling sessions.

With continued treatment, the patient can learn to look to the therapist rather than to opiates for gratification of dependency needs, relief of anxieties, and solutions to problems. Through this relationship the patient is reinforced for decisions that foster a more stable and socially acceptable lifestyle, which excludes opiates.

One aspect of treatment that should be considered is the benefit a patient may derive from having conditioning theory explained to him, so that he may begin to look for signs of conditioned responses within himself. The value for the patients who have this understanding has been remarkable in some of our followup interviews. When conditioning is explained to patients, it has the additional benefit of alerting them to the possibility that they could become readdicted at some time in the future, even after a long period of successful antagonist treatment.

Discontinuing antagonist medication and resuming opiate use are insufficient criteria for labeling the treatment a failure. Would you say that digitalis is not clinically efficacious if a patient with congestive heart failure stops taking it?

The model we use should be similar to the one we use in treating chronic medical illnesses. Patients must be told that whenever medication is discontinued, they can and should ask to be put back

on the antagonist whenever they feel tempted, or have begun, to use opiate drugs again. Imagine the positive effect it has on patients and their families when they can view addiction as no worse than other recurrent medical problems for which treatment is available. The emotional impact on the patient is usually profound, since he has previously experienced negative attitudes and rejection whenever he has become readdicted.

The primary focus of treatment should be for patients to change their lifestyle rather than never to use drugs again. For some individuals, a meaningful commitment to rehabilitation can be made only after relapsing and becoming readdicted one or more times. Others have to know their therapist long enough to trust that the therapist cares and will help in times of need.

We have found that the most successfully rehabilitated patients are those who learn to rely more and more on the therapist for help, especially during the early phase of treatment. As this relationship begins to become a trusted and consistent source of satisfaction, these patients dwell less and less on the instant gratification afforded by opiates.

Clinic attendance is a crucial issue. Methadone patients come because they fear getting sick; antagonist patients don't have that worry. Their attendance must be based on a strong desire to remain drug free, fear of family or other external pressure, or a good relationship with their therapist. Few patients can be expected to come to the clinic because of a commitment to their therapist, initially. It becomes a very strong message to the patient, however, if he skips one day of medication and is called by his therapist to find out where he is. Our patients often express surprise and state that they have never been "cared about in this way" by other treatment programs. A few such calls, and soon many patients begin to respond to that caring with a commitment to their therapist that includes coming to pick up their medication.

Requiring daily medication is usually a good idea with antagonist patients, at least in the initial months of treatment. It not only provides some structure to their lives and puts them in frequent contact with the staff, but also can serve to alert the staff to the potential for readdiction whenever a patient skips a day of medication. Many patients feel they can skip medication and use opiates "once in a while." We have found that antagonists become useful in respect to this issue for two reasons. Since the patient must make a conscious decision to skip medication, he cannot deny responsibility for his impulsive drug use. Many good antagonist

candidates–those we believe have the best prognosis–are also those whose drug use is impulsive.

By helping the patient understand these dynamics, the therapist forces the patient to become aware of his choices, instead of believing that he used drugs because he was "weak-minded" and implying it was beyond his control. We often tell patients and their families that refusal to take medication is analogous to stating an intention to get "high." A patient who is ambivalent about taking medication on a particular day is less likely to act on his impulse to skip it, if he knows that doing so is equivalent to announcing to his family and staff: "Today I plan to shoot heroin." We have found that involving the family in this way places the patient in a situation where he can rely on external pressures to help him through times of ambivalence, until he can integrate his desire to remain drug free on a new emotional level, under more conscious control.

METHODS FOR RAPID INDUCTION ONTO NALTREXONE

Irrespective of overall treatment approach, there is the initial problem of induction onto the antagonist (in this case, naltrexone). Opiate-dependent patients scheduled for antagonist treatment must first be detoxified from opiates. Detoxification is usually accomplished by gradually decreasing doses of methadone. This must be followed by an opiate-free period of 5-10 days duration before naltrexone can be administered without precipitating severe abstinence symptoms (3). The final stages of detoxification (from 20 to 0 mg methadone) and the subsequently required opiate-free period are the most difficult for patients to handle, as evidenced by high dropout rates. Unless incarcerated, many patients return to illicit opiate use before receiving an initial dose of naltrexone. It is desirable, therefore, to have these high-risk periods be as short as possible.

Recently, we explored naloxone-precipitated withdrawal as a means for rapid opiate detoxification and induction onto naltrexone (4). The rationale was that by precipitating withdrawal directly we might reduce the total duration of the withdrawal syndrome without increasing its severity to unacceptable levels. Moreover, since naloxone is a short-acting antagonist, if precipitated withdrawal became unacceptably severe it would subside within a short period of time (i.e., within 1 hour). In patients dependent upon 5 to 25 mg methadone, successive injections of naloxone (1.2 mg IM) were administered over a three-day period. On the first day,

the initial naloxone injection precipitated acute withdrawal which was at times severe, but subsided within 1 hour after the injection. With subsequent injections, the severity of precipitation diminished, so that by the end of the first day naloxone was precipitating little or no acute withdrawal. On the second and third days, with continued naloxone administration, withdrawal signs did not emerge and all patients felt reasonably comfortable.

Patients found the procedure acceptable, and, as word spread among the clinic's population, it became increasingly common for patients to request this procedure in lieu of the more gradual detoxification procedures routinely employed. This high degree of acceptance was somewhat surprising, and was thought to be due to preference for a brief, albeit more concentrated, episode of abstinence over the milder but more prolonged experience with routine procedures. Moreover, naloxone-precipitated withdrawal was found to be safe in that vital signs (heart rate, blood pressure, and respiration rate) were only minimally altered, even at the peak of withdrawal severity. This procedure did not, however, significantly reduce the number of opiate-free days prerequisite to receiving an initial dose of naltrexone. We found that at least 5 opiate-free days were still required before naltrexone could be administered without producing additional manifestations of withdrawal.

In a more recent study (6), we explored the possibility of modifying the precipitated withdrawal procedure to see whether the prerequisite opiate-free period might be shortened. The most rapid procedure allowed induction onto naltrexone within 48 hours after a final opiate dose (5 to 20 mg methadone). This procedure consisted of 1.2 mg naloxone IM every 30 minutes for 3 to 6 hours, followed by hourly increasing doses (from 5 to 50 mg, in 10 mg increments) of oral naltrexone. Additional findings were: (a) that peak severity ratings of naloxone-precipitated withdrawal (signs and symptoms) were directly related to the patient's level of opiate dependence just prior to the start of the procedure; and, (b) that premeditation with diazepam and atropine helped mitigate the nervousness and gastrointestinal upset often experienced during precipitated withdrawal. Moreover, the procedure was found to be safe, and acceptable to patients.

FUTURE DIRECTIONS

Overall, our clinical experience indicates that naltrexone alone is not a highly efficacious treatment for opiate dependence, except,

perhaps, in selected individuals highly motivated to become opiate free, For the typical "hard-core" street addict, opiate dependence is part of a lifestyle and thus deeply ingrained in the individual's behavioral and intrapsychic repertoire. It is difficult to imagine that a medication which offers no immediate gratification or symptomatic relief would itself cure the "ill." One might ask at this point what is the "ill"? Although we would all agree that being opiate dependent is itself a serious problem with numerous ramifications for the opiate-dependent individual, the analysis must not end here. Opiate-seeking behavior is merely symptomatic of a host of underlying problems. We suggest, therefore, that treatment be directed toward the individual, as by the use of psychotherapeutic techniques. From this vantage point, antagonist medication is seen as adjunctive to psychotherapy rather than vice versa.

It would appear that the relative contributions of psychotherapy and antagonist medication to overall treatment efficacy need to be assessed. Although our clinical impressions suggest that the combination of treatment modalities is more efficacious then either alone, these impressions have not been assessed systematically. Therefore, we are conducting a study of treatment outcome wherein psychotherapy is the variable manipulated. Briefly, one group of patients receives naltrexone in conjunction with individual psychotherapy, whereas another receives naltrexone and concrete services only. Information obtained from this study may help to formulate the most appropriate clinical setting for naltrexone's application.

A factor which limits naltrexone's efficacy is that it is easily discontinued. Too often, patients discontinue naltrexone impulsively and fail to return to the clinic, before a therapeutic relationship with the staff has had an opportunity to develop. Cyclazocine, however, is more difficult to discontinue than naltrexone. Unlike naltrexone, abrupt cessation of daily cyclazocine results in withdrawal symptoms that serve as a "reminder" to come in to the clinic. This makes it more difficult for patients to miss clinic visits impulsively. However, induction onto cyclazocine is often difficult because of dysphoric side effects (1). These differences in ease of induction and termination between cyclazocine and naltrexone suggest the possibility of a combined regimen wherein patients are first inducted onto naltrexone and then begin to receive cyclazocine. After a maintenance dosage of cyclazocine is reached, naltrexone would be discontinued while cyclazocine remains. We plan to assess the acceptability and efficacy of this combined regimen in an upcoming study.

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CHAPTER 29

The Development of Sustained Action Preparations of Narcotic Antagonists

Robert E. Willette, Ph.D.

INTRODUCTION

The use of narcotic antagonists in the treatment of opiate addiction is based on the concept of a pharmaceutical agent capable of blocking the reinforcing properties of a dose of opiate taken during an addict's rehabilitation. The rationale for use is that the antagonist blocks the opiate "high," making it pleasureless, thus removing the addict's incentive for continued use. Earlier successful therapy with cyclazocine and naloxone prompted the full-scale development of new and superior antagonists. Presently naltrexone is the drug under the most intensive clinical evaluation and appears to be a promising antagonist candidate.

It was felt from the outset that a most desirable component of antagonist therapy would be a long-acting drug, so that the need for an addict to repeatedly decide to take his medication would be minimized. Naltrexone in oral doses of 70 mg. will provide adequate blocking protection for at least 48 hours, or perhaps as long as 72 hours in certain individuals. This is not felt to be a long enough interval between dosages to aid the addict in becoming dissociated from his drug-taking behavior.

It was recognized very early that in order to achieve the desired one week, one month or longer duration between dosages, it would be necessary to develop a long-acting drug delivery system or a sustained-release preparation of an acceptable, but short-acting antagonist. A "drug-delivery system" is the unwieldly but currently favored expression describing any pharmaceutical preparation

capable of providing a sustained or long-acting antagonistic effect. This effect may be achieved mechanically (e.g., by implanted discs with timed release capacity) or chemically (e.g., microcapsules, tubes, solid balls, gelatinous masses injected intramuscularly). Distinct from the problem of finding an optimum antagonist is that of inventing suitable carriers for the antagonist in order to release it uniformly bit by bit over a period of time.

Efforts to achieve satisfactory drug delivery systems were launched in the early 1970's by the City of New York Public Health Department and by the U.S. National Institute of Mental Health's Division of Narcotic Addiction and Drug Abuse, now the National Institute on Drug Abuse (NIDA).

During this early period, the pioneering efforts of Dr. Seymour Yolles, of the University of Delaware (U.S.), demonstrated for the first time that sustained release of an antagonist could be obtained from a biodegradable polymer, i.e., polylactic acid. This success generated expanded and intensified efforts, which are summarized in this article. At the present time, the program supported by NIDA includes two contracts concerned with the development of new delivery systems and three contracts with the responsibility of evaluating them for potential clinical trials. The program is now narrowing down on those candidates that appear to have the best combination of essential properties to assure a successful clinical trial.

SYSTEM DESIGN SPECIFICATIONS

There are several properties and features that are important characteristics in the design and development of a clinically acceptable and useful delivery system. Some of these are:

1. An adequate and smooth drug release rate
2. Ease of insertion or injection
3. Balancing the desirability of making removal by the patient difficult versus the desirability of ease of removal by the physician
4. Biocompatability or lack of adverse tissue reaction or pain upon injection
5. Ease and low cost of manufacture
6. Stability when subjected to sterilization
7. Stability and storage characteristics
8. Patient and physician acceptability

Each of these considerations has a different relative importance, and it is the task of the development team to select an optimal compromise of specifications in order to bring a candidate preparation into clinical trial. It is recognized that the first trial preparation may not be the ideal system and that additional refinement may be necessary before a system can be introduced into wide clinical usage.

DEVELOPMENT PLAN

In the Spring of 1973, a new program for the development of a long-acting narcotic antagonist was initiated. It consisted of two contracts and two grants to design and prepare candidate delivery systems. Each group was also responsible for carrying out the preliminary screening of the systems by *in vitro* and *in vivo* tests to select those with the most promising release properties. This program included work on polylactide microcapsules, polylactide-polyglycolide beads, polyglyceride pellets, and an insoluble salt complex, the latter three having been originated under an earlier program supported by New York City.

In addition to these projects, three contracts were let to carry out in centralized facilities the evaluation of all promising candidates emerging from the developers. This consisted of a multiple level pharmacological and pharmacokinetic testing schedule as well as a range of toxicological measures. The overall scheme was designed in a pyramidal fashion with more rigorous criteria required to pass from one level to the next.

At the heart of this plan was the recognition that an advisory group composed of scientists from several relevant areas was essential to assist in monitoring progress and in making the difficult decisions about which leads to pursue. Their dedication and loyalty to the program has played a critical role in its success. The group has consisted of: Drs. Sidney Archer, William L. Dewey, James T. Doluisio, Fred A. Kincl, Fred Leonard, and James L. Olsen. Others, including Drs. Joseph Borzelleca, Douglas R. Flanagan, Stanley Kurtz, Grant Wilkinson, and Ann Wolven, have also provided important input. Valuable advice and sharing of information has come from Drs. Gabrial Bialy and Henry Gablenick from the Center of Population Research, U.S. National Institute of Child Health and Human Development, where a similar program for long-acting antifertility agents is being supported.

At the present time the program is concentrating on four systems that have demonstrated the most promise. These will be described next.

CANDIDATE DELIVERY SYSTEMS

Polypeptide Tubes and Rods
Arthur D. Little, Inc.

In order to minimize the amount of animal testing required to receive the U.S. Food and Drug Administration's approval for an early clinical trial, it was desirable to select a system capable of being removed at the end of a month, but which could eventually be left permanently implanted. A preparation that meets these and the other criteria is a tiny hollow tube of a synthetic polypeptide composed of a 22/78 copolymer of glutamic acid and ethyl glutamate. Slowly biodegradable, these 2 mm by 10 to 20 mm tubes are filled with a solid core of naltrexone free base or hydrochloride which diffuses out through the tube wall. Rates of release may be adjusted by varying the thickness of the tube's walls.

The tubes are manufactured in a fashion similar to candles, with a fine glass mandrel being dipped at a controlled rate into a heated solution of the polymer. The tubes are removed, filled with a little saline, a solid rod of 90 percent naltrexone bound in polymer, and sealed with a cap. Sterilization may then be achieved by autoclaving.

Originally polymers composed of glutamic acid and leucine were prepared and evaluated. Early samples of these gave up to 60 days of sustained release, releasing up to 30 micrograms of naltrexone per hour. Unfortunately, improvements in the release rates and the lack of significant biodegradation have forced the shift to the newer glutamate/ethyl glutamate polymer. Early prototypes appear to give good release rates and nearly complete biodegradation within 90 days. Further tests are underway.

This work is under the general supervision of Mr. Kenneth Sidman.

Polylactic/glycolic Acid Beads
Dynatech Corporation

Potentially removable by a surgeon, these l/16 inch beads of 90/10 polylactic and glycolic acid copolymer offer flexibility in

dose administration. Implantable by means of a trocar, the 70 percent naltrexone free base loaded beads have shown continuous release for more than a month. Samples of beads have been periodically removed from injection sites and examined for biodegradation. They gradually soften, grow smaller or crumble, and eventually become undetectable.

On the basis of the series of tests described below, this candidate system is currently undergoing toxicological testing to enable its administration to humans. To date, the toxicity studies have shown no adverse effects and it is expected that a clinical trial will be possible by early in 1978.

This work has been directed by Dr. Donald Wise.

Earlier contracts that have provided potentially useful preparations are:

Polylactic Acid Microcapsules
Washington University

Two major advantages of a microcapsule approach to drug delivery is their potential for zero-order release rates and injectability. To date microcapsules of less than 180 microns of micronized particles of naltrexone pamoate coated with dl-polylactic acid have shown sustained release for more than forty days. They have been injected to date as a suspension in 2 percent aluminum monostearate gel in peanut oil. Other more acceptable vehicles are beihg tried.

Additional work on perfecting capsules of naltrexone free base, considered more desirable because higher payloads of drug may be achieved, have not been very encouraging. A suitable sterilization procedure is not yet possible.

Because of the apparent incomplete release of naltrexone and the difficulty in removing traces of the solvents used to prepare the microcapsules, work on this approach has been temporarily halted. If such a preparation is judged to be more acceptable under clinical conditions, it would then be pursued further.

These systems have been developed by Dr. Kurt Thies.

Naltrexone Aluminum Tannate
IITRI

Based on older formulation approaches, this insoluble aluminum tannate complex of naltrexone, when injected intramuscularly in a

suspension of 2 percent aluminum monostcarate peanut oil gel, gives a sustained release of over thirty days. The complex is both readily prepared and easy to sterilize.

In preliminary studies on tissue compatibility, relatively little reaction was seen. It is known, however, that peanut oil suspensions cause occasional reactions. This preparation would require an extensive amount of toxicological testing before undergoing human trials and will await trials with other systems.

This preparation was developed by Dr. Allan Gray.

EVALUATION PROCEDURES

Preliminary Screening

Each developer was responsible for carrying out the screening of trial preparations by *in vivo* and *in vitro* methods. The test used by all groups was the mouse tail-flick method of Dewey and Harris. Animals were injected or implanted with the preparation, and at various intervals different groups were injected with morphine and their analgetic response measured in order to determine whether continued antagonism occurs.

Some variations in *in vitro* tests were used, with the primary purpose being to establish a correlation with the animal tests. Eventually, only the *in vitro* methods became necessary for general screening. As a followup to the animal testing, injection sites were examined for gross pathological reactions. If nothing is visibly apparent, little is usually found upon histological examination.

Advanced Pharmacological Evaluation

At Ohio State University, under the direction of Dr. Richard Reuning, all candidate systems selected from preliminary screening were tested using the mouse tail-flick test under standard conditions. Those systems showing unusual promise were then tested in rats using radiolabeled drug, and the pharmacokinetics of release were studied.

In the course of developing suitable test procedures, considerable work was done on the metabolism and pharmacokinetics of naltrexone. This was essential for the calculation of actual release rates of the systems themselves.

Advanced Toxicological Evaluation

As candidate systems passed on through the pharmacological testing, they were evaluated in parallel at Industrial Bio-Test by Mr. Carmen Mastri. Depending on the dosage form being tested, the systems were implanted or injected into mice, rats, and intramuscularly in rabbits. The last is the classical U.S.P. irritation test. When possible, suitable positive and negative control materials were run concurrently.

Final Animal Evaluations

The most promising candidates eventually find their way into the most rigorous evaluation. The pharmacological test is carried out in monkeys trained to self-administer morphine. Developed at Parke, Davis and Company by Dr. Duncan McCarthy, the suppression of morphine administration is an indication of how long the system delivers an effective level of naltrexone. At the same time, samples of plasma are obtained at various intervals and analyzed by the Ohio State group to determine the exact amount of drug released. Correlation of this data with pharmacokinetic measures of naltrexone in the same animals has thoroughly characterized the candidate systems.

As indicated above, the Dynatech beads have also been started in a detailed toxicological evaluation at Parke-Davis. This involves three species at three dose levels. Periodic sacrifices are being made to obtain a detailed pathological evaluation. The protocol is designed so as to assure an early clinical trial based on the idea of removing the test system at the end of one month.

SUMMARY

After several years of tedious and often frustrating efforts, a few promising systems are now near final evaluation, with the intention of conducting human trials in the near future.

CHAPTER 30

The Future of Naltrexone

Pierre F. Renault, M.D.

The immediate future of naltrexone involves the initiation of the final phase of clinical testing. In the United States, drug manufacturing is regulated by the Food and Drug Administration (FDA). The regulations are quite specific and detailed when it comes to the development of new drugs. For a drug to be marketed in the United States, it must initially pass preclinical, animal toxicity tests, and then a series of clinical trials in humans. The clinical trials in humans are in three phases. The first phase usually involves the determination of dosage and side effects. Phase two involves the determination of safety and efficacy in a controlled environment on selected patients. The third and final phase of clinical testing involves using the drug as it is intended to be used clinically. Naltrexone has completed phase two of clinical testing and has been shown to be both safe and effective. This testing was conducted in males who were healthy aside from their heroin addiction. Phase three will involve both males and females and no one will be excluded on the basis of health if he or she is otherwise appropriate for naltrexone treatment. The purpose of phase three testing is to determine therapeutic efficacy of the medication in the general treatment population and to search for low incidence side effects which may not have been detected in the selected phase two treatment population.

An important issue in the determination of the clinical efficacy of naltrexone is that of treatment compliance. Will addicts take naltrexone? Clearly, it must be taken if it is to do any good. The problem of compliance is common to all medications administered to an asymptomatic group with a disease in a latent form. An excellent example is the compliance of individuals taking antihypertensive medication. The basic question is whether the simple efficacy of naltrexone in blocking the euphoria and the develop-

ment of physical dependence will be sufficient for the drug to be marketed or whether the FDA will insist on evidence of treatment compliance as a further measure of efficacy.

There is also a series of more difficult questions surrounding the clinical use of naltrexone. How should patients be selected for naltrexone treatment? On what basis should the decision be made to use the drug as a crisis intervention technique or as a maintenance drug? Can it be used safely and effectively in adolescents? How ethical and acceptable would it be to use naltrexone in work release programs for addicts in prison?

The real future of naltrexone involves a series of unanswered questions. Central and perhaps the most fascinating of all the questions which are provoked by naltrexone is what effect it has on the endogenous opioid or endorphine system. We know from subhuman data that narcotic antagonists block the effects of endorphines, and we can infer that the endorphine system is important in the normal functioning of human mood, pain, awareness of bodily processes, etc. As it now stands, we have very little understanding of the effects that chronic opiate use has on this endorphine system, although it is clear that it must have some effect. In all likelihood, chronic opiate use will diminish endorphine production. It is not clear, however, if in some or all individuals, chronic opiate use causes an atrophy of the ability to produce endorphine analogous to the inability of individuals to recover from prolonged corticosteroid treatment. It also seems probable that endogenous opioids produce a hypertrophy or a hyperactivity in those physiologic systems which antagonize the effects of endorphine.

It is conceivable that antagonists could stimulate the production of endorphine by blocking the natural feedback which presumably regulates that production, and thereby have a healing effect on a clinically suppressed endorphine system. The fact that naltrexone diminished craving in the phase two double blind study argues for this possibility. On the other hand, if naltrexone is reacted to by the central nervous system as an opioid substance, it could cause a decrease in endorphine production similar to the presumed effect of agonistic opioid drugs. It seems unlikely antagonists would have any effect on those physiologic systems which are antagonistic to the effects of endogenous opioid substances, given the fact that they produce the abstinence syndrome when administered to physically dependent individuals.

Answering these questions is basic to naltrexone's future. If naltrexone does not heal the damage done to the endorphine

system by chronic opiate use, then perhaps another antagonist could be designed which would. This system is critical to human functioning and, in particular, to a sense of well-being. In this way, chronic heroin addiction conceivably could cause a degeneration of the endorphine system which could, in turn, lead to a loss of sense of well-being and thus to a vicious cycle of intensified craving for opiates.

The issue of the effect of naltrexone on the endogenous opioid system also has implications for the use of drugs by adolescent patients. Such young patients have had a relatively short experience with narcotic drugs. The use of methadone in such individuals has not been acceptable, because they have had so little time to develop physical dependency that the treatment itself might produce a greater physical dependency than the initial "disease." This situation has left adolescents without a suitable pharmacologic adjunct to their treatment. Given the well-known impulsiveness of adolescents and the consequent difficulty in treating them, they are especially vulnerable to progress from drug experimentation to full-fledged, chronic heroin dependency. Then, only after years of dependency, will they become eligible for pharmacologic supports which have been shown to be so valuable in making it possible for older individuals to participate in treatment. Naltrexone appears to be an ideal agent for such an adolescent drug-using population. It can be used to prevent the development of physical dependence, and thus it can prevent an aspect of the disease without producing that aspect, as would be the case with an agonistic drug. For example, an adolescent who has fallen in with a group of drug users, who feels social pressure to use drugs along with his friends, and yet is concerned about this use and its ultimate consequences, could come to a physician and be given naltrexone to protect him when his resolve weakens and he feels compelled to use heroin.

On the other hand, the use of naltrexone to protect such individuals depends on the absence of any bad effects of this drug. And foremost among potentially bad effects would be a destructive effect on the endorphine system. In order for naltrexone to be widely used in an adolescent population, it will have to be demonstrated that it does not damage the individual's capacity to produce endorphine.

This leads to the larger question of the acceptability of naltrexone. Who will take this drug? How many will take it and for how long? Drug abuse treatment is one of those rare instances where a medication must not only be effective but must also carry with it its own guarantee of compliance. We can clearly conclude

from the phase two studies with naltrexone that the drug does what it is supposed to do; viz., it blocks euphoria, blocks the development of physical dependence, and blocks "readdiction" for as long as the person takes it. If an individual at risk of becoming an addict takes heroin in the presence of naltrexone, the phase two studies have demonstrated that the probability that he will again take heroin is diminished. In other words, when individuals who are taking naltrexone were compared with individuals taking placebo, those who actually used heroin after having taken naltrexone were much less likely to take another injection of heroin during the course of the study than were those who were on placebo. This difference was statistically significant, and needless to say, it is clinically significant as well. This finding leads one to conclude not only that naltrexone is effective, but also that motivation on the part of the patient is in itself not sufficient for treatment success. Presumably, levels of motivation were equal between the naltrexone and placebo groups, since they were randomly assigned and the medication was administered under double blind conditions. Thus, if an individual can be protected when his motivation falters, the effect will be to preserve and amplify his motivation.

It can be argued, and should, that treatment compliance is another matter. Compliance depends not only on the pharmacologic properties of a drug, although certain medications that taste bad or have to be taken frequently or produce discomforting side effects are associated with lowered compliance. However, the factors which determine whether or not an individual will take a drug when these factors are not operating are much more complicated. It should be possible to create incentives within the clinic, the social strata from which the addicts are recruited, and even in the society as a whole, to encourage the use of an antagonist drug by those who are at high risk of becoming readdicted. An analogous situation would be smokers wishing to give up cigarette smoking. Very often, the temptation is to take "just one cigarette," with the smoker finding that "just one cigarette" leads to a pattern of readdiction. This is also the rationale behind the abstinence imposed by Alcoholics Anonymous. A similar rationale underlies antagonist treatment: that is, to protect the individual from that chain of events by blocking effects of that "one fix of heroin."

Compliance is a problem in all of medicine, but especially so with medications administered to asymptomatic individuals who have a latent form of a disease. Convenient analogies are to antihypertensive and antituberculous medications. It is humanly characteristic to forget the pain, the symptoms which led us to treatment in the first

place, as soon as those symptoms are eliminated by the treatment.

Another apparent advantage of naltrexone maintenance treatment is that it satisfies one of the great objections to maintenance treatment in general, which is that with methadone individuals are maintained in a continued state of physical dependency. Since naltrexone does not produce physical dependency, maintenance with it is likely to be more acceptable both to clinicians and to patients who object to maintenance with such agonist drugs as methadone. This acceptability would be enhanced by a further demonstration of a salutary effect on the endorphine system, a correction of the defect which either preexisted the chronic opiate use or has been caused by the chronic opiate use. In the United States, opioid dependence is based on intravenous heroin use. It was in this context that the concept of methadone maintenance developed, because methadone, since it can be given orally and since it lasts for an entire day, is safer and less disruptive than heroin. In many parts of the world, however, opioid dependence is based on smoked heroin and opium and orally ingested opium. In that context, methadone maintenance is inappropriate except to the extent that methadone produces less disruption to daily functioning than a drug which produces intoxication. Naltrexone should have value in individuals who are dependent on opioids taken by less hazardous routes of administration than intravenously. Because it is a drug which does not produce physical dependency, but simply blocks the effects of opiates, the validity of this prediction will have to await the verdict of clinicians treating those who are dependent on ingested or smoked opiates.

The future of naltrexone is also dependent on the future of other forms of drug abuse treatment. In the United States, heroin addicts often use other drugs when they are available. They smoke heavily and a high percentage drink alcohol heavily. Thus, the future of naltrexone is dependent on our ability to develop treatments that are effective against these other forms of dependence. This also emphasizes the fact that while we are often criticized for our preoccupation with pharmacologic adjuncts to the treatment of heroin-dependent individuals, those same adjuncts have made heroin dependence one of the more treatable forms of drug dependence, while our ability to treat other forms of drug dependence lags behind.

Needless to say, it is our hope that the phase three testing of naltrexone will further substantiate the safety and efficacy of this drug. We are confident that problems with compliance can be solved where the drug is used on a large scale. We also feel that the

evidence that naltrexone decreased craving argues for its salutary effect on those systems responsible for the sense of well-being, systems which are disrupted by chronic opioid use. The future of naltrexone is the future of an important new addition to the pharmacologic armamentarium of those of us who wish to help individuals afflicted with chronic opioid dependency. Its further development also entails fascinating new research into the factors underlying that dependency.

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