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in
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FOREWORD

One of the major problems of today's society--that of narcotics addiction and drug abuse--was the subject of a recent CENTO Seminar on Public Health and Medical Problems Involved in Narcotics Drug Addiction. The topic was first proposed by the CENTO Subcommittee on Health at their Eighteenth Session, and later approved by the Economic Committee. Iran offered to act as host, and the Office of the United States Economic Coordinator for CENTO Affairs agreed to provide organizational and financial support. The seminar was held in Tehran, Iran, from April 8 to 12, 1972.

Briefly stated, the objectives of the seminar were:

- To explore the epidemiology of drug abuse in each of the CENTO countries
- To exchange information about various techniques of the drug abuser
- To evaluate the advantages and disadvantages of drug abuse education programs, particularly in the school system
- To exchange the latest research information available in the CENTO countries and to determine the advisability of initiating certain research projects.

Professional men and women, each well versed in the national and international problems of narcotics drug addiction and drug abuse, presented papers which were later discussed by all the delegates attending the seminar. All the papers presented at the seminar are included in this publication, at least in part, although some of them have been edited to meet printing requirements.

Also included is the CENTO report on the seminar, which contains a summary of the discussions, and the recommendations agreed upon by the delegates.

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WELCOME ADDRESS

by

*H.E. Dr. Hasan Morshed,
Undersecretary for Parliamentary Affairs
of the Ministry of Health, Tehran*

On behalf of the Government and the Ministry of Health of Iran, I welcome the honourable guests to our country. We now have real spring and I hope you will enjoy your stay here.

The subject you are going to discuss is the most dangerous epidemic or even pandemic of the present time.

In the history of public health and medicine we have had many dreadful epidemics and pandemics like cholera and plague. Still today we may have small or large epidemics in some parts of the world. But due to the fact that the etiology and epidemiology of these infectious and epidemic diseases are clear, the control of the epidemic is to some extent easy. But we must confess that there are still many question marks about the etiology, epidemiology and treatment of drug dependence.

Of course we must not be disheartened. In the same way that the new civilization has brought many infectious and epidemic diseases under control, by close cooperation of all members of the U.N. and especially by the cooperation of nations being directly under threat of this scourge, sooner or later this problem will be solved. This seminar, which is going to cover some aspects of the treatment of addicts, is very important to us, in view of the fact that the Government of Iran has always looked on addicts as real patients. I am sure that the discussions and decisions of this seminar will shed light on some of the dark points about drug abuse.

In conclusion I must especially thank the Central Treaty Organization for sponsoring this seminar.

Once more I wish all success for you, a pleasant stay here and a safe journey back home.

CENTO REPORT ON THE SEMINAR ON PUBLIC HEALTH AND MEDICAL PROBLEMS INVOLVED IN NARCOTICS DRUG ADDICTION

INTRODUCTION

The Seminar on Public Health and Medical Problems Involved in Narcotics Drug Addiction was held in Tehran, Iran from April 8 to 12, 1972, at the Family Planning Building, Ministry of Health, under the chairmanship of Dr. Mohammad Hadi Adham, Director General, Medical Services, Ministry of Health, and leader of the Iranian Delegation.

The Assistant Economic Secretary of the Central Treaty Organization, Mr. Brian J. Baxter, formally opened the seminar on behalf of the Secretary General. His Excellency Dr. H. Morshed, Undersecretary for Parliamentary Affairs of the Ministry of Health, delivered an address of welcome. The leaders of delegations replied to the welcoming address. The agenda for the seminar was then formally approved by the delegates.

PRESENTATION OF PAPERS

The Nature and Extent of Drug Abuse in Iran, presented by Dr. Hasan-Ali Azarakhsh, Director General, Ministry of Health

These points emerged from the discussion following the presentation of this paper:

On the question of the social acceptance or rejection of the excessive drug user the fact that dervishes use cannabis gives no reason to believe that the practice is held in high regard; indeed, those dervishes who use cannabis are considered the equivalent of hippies.

There was some doubt expressed as to the authenticity of the story of the Old Man of the Mountain and as to any evidence that cannabis was used as an aid to assassination.

There was some discussion on the role of mass media in increasing popular interest and experimentation in drugs generally.

The capital punishment measures introduced in Iran for smuggling or transporting opiates have resulted in a decrease in these activities.

The Social Aspects of Drug Addiction in Turkey, presented by Dr. Özcan Köknel, Clinic of Psychiatry, University of Istanbul

These points emerged from the discussion following the presentation of this paper:

There is a need in Turkey for a careful study of the prolonged psychological effects of chronic cannabis use.

The question of why Turkey, which was a major opium producer, has a low incidence of opiate addiction, raised the points that this might be due to indoctrination at an early age to the dangers of opium, or religious training, or the social stigma of being an opium addict.

A need was identified for an intensive study of people living in opium-growing areas and there was a suggestion that collaborative research might be conducted into the various cross-cultural values as related to drugs throughout the CENTO region.

The Problem of Cannabis in Pakistan, presented by Colonel M. Shuaib, Instructor in Psychiatry, Armed Forces Medical College

and in charge of Psychiatric Center, Military Hospital, Rawalpindi

These points emerged from the discussion following the presentation of this paper:

There is a need for projected studies to be conducted into various populations such as schools, gaols and factories to determine the reasons for starting charas (cannabis) use, for continuing or discontinuing the habit, and to identify a possible relationship with tobacco smoking.

It was agreed that a worthwhile study could be conducted into the composition and THC content of various kinds of charas.

The opinion that cannabis abuse leads to opium abuse may require re-evaluation since it is not borne out by the situation in Turkey, which experiences cannabis abuse, but practically no opium abuse, or in Iran, which has a relatively higher opium than cannabis abuse.

In three cases of acute cannabis psychosis it was found that a single electroshock treatment provided a remission.

The Nature and Extent of Drug Abuse in the United States, by Dr. William E. Bunney, Director, Division of Narcotic Addiction and Drug Abuse, National Institute of Mental Health, read by Mr. Besteman

These points emerged from the discussion following the presentation of this paper:

It has been found that amphetamine psychosis can occur in people with prior normal personality structure.

The point was made that the comparatively liberal attitude by many American authorities towards marihuana did not extend to charas, which was a product ten times stronger. The fact, however, that alcohol was a dangerous drug for some 9 million Americans did not provide the authorities with a basis for marihuana legalization.

On the question of heroin use in the United States, it was stated that this was attractive to antisocial individuals and that it required criminal activities by most addicts, e.g., for financial purposes.

It has been found that high doses of THC cause an abstinence syndrome.

The Drug Abuse Situation in the United Kingdom, presented by Dr. P.H. Connell, Physician, The Bethlem Royal Hospital and The Maudsley Hospital, Director, Drug Dependence Clinical Research and Treatment Unit

The following points emerged from the discussion on this topic:

There is evidence to prove that methadone addiction is now occurring in people who have never taken heroin.

The point was made that maintenance therapies are based on a medical model. In other words, a patient who is sick requires an opiate to alleviate his psychological or physical illness.

In an uncontrolled market situation, heroin maintenance could merely add to the supply. This situation would be undesirable in a city like New York, as opposed to London, where illicit supplies are limited.

It appears that in effect the United States uses methadone maintenance, the United Kingdom heroin and methadone maintenance, and Iran opium maintenance.

Following a question on hard and soft drugs, it was established that the difference between these two was not as great as the difference between injectors and noninjectors.

Management of Opium and Heroin Addiction by Detoxification in Iran, presented by Dr. M. Saba, Medical Director, Addicts' Hospital, Tehran

These points emerged from the discussion following the presentation of this paper:

It has been found that more than 90 percent of opiate addicts have relapsed if treated by detoxification alone.

It was thought that while the elimination of the opium poppy might stop the use of opiates without more extensive control and health measures, it could lead to even more serious addictions, for example barbiturates.

Many of the withdrawal symptoms were caused by apprehension and a need for attention rather than by physiological events.

Amphetamine and Barbiturate Dependence, presented by Dr. Sidney Cohen, Director, Council on Alcohol and Drug Abuse, University of California

These points emerged from the discussion following the presentation of this paper:

Hypertension following amphetamine abuse could cause cerebral hemorrhages in the young abuser and it has been found that tolerance to the hypertensive effect is partial.

Japanese autopsy material showing brain damage in amphetamine abusers is open to doubt, since, apart from petechial hemorrhages, no definite changes are known.

It was established that sleep deprivation contributed to the amphetamine psychosis, as did REM deprivation. In addition, the loss of REM sleep in people using sedatives and stimulants could cause nightmares after discontinuance.

Rehabilitation of Addicts, presented by Dr. A. Zarrabi, Director, Razi Medical Center, Tehran

These points emerged from the discussion following the presentation of this paper:

Group therapy in Iran must be designed for the Iranian patient, taking into account his cultural characteristics.

It was suggested that, as in the United States, the use of ex-addicts as members of therapeutic teams might be advisable since they provide a successful role model for the addict, but in Iran this needs further consideration.

The new narcotics scheme in Iran will require an extensive training program for psychiatric professionals and paraprofessionals. This new treatment scheme would be so designed as to give the addict the various services which he would require to establish a new existence after completing the treatment.

Treatment of Sedative and Stimulant Addiction, presented by Dr. H. A. Panahloo, Consultant Psychiatrist, Department of Mental Health, Tehran

These points emerged from the discussion following the presentation of this paper:

The goal of all treatment for addictions is similar. It is the re-education of the individual so that new ways of coping with life stress can be developed.

There is still a certain dispute as to the proper place where addicts should be treated since it has been found that real problems have been created by housing them with psychiatric or medical patients. It might be necessary to set up special units to deal with the psychopathic traits of many addicts.

Relapse of addicts should not necessarily be regarded as a completely negative result of treatment. It was agreed that if a patient had been helped for a period of time, this should be considered a partial success.

- 1) *Some Pharmacologic Properties of Synthetic Delta-9-Tetrahydrocannabinol (THC)*
- 2) *Tolerance and Dependence to Synthetic Delta-9-Tetrahydrocannabinol (THC) in Laboratory Animals*, presented by Dr. S. Kaymakçalan, Head of Pharmacology Department, Faculty of Medicine, University of Ankara

These points emerged from the discussion following the presentation of these papers:

There was evidence to indicate that high doses of THC produce both tolerance and a definite withdrawal effect in animals. The common impression that tolerance to cannabis does not occur is merely a low dose phenomenon.

At high doses physical dependence to THC seems to occur in animals and it is possible that a similar condition might on occasion occur in humans.

It was agreed that not all animal studies could be extrapolated to humans since, for example, it has been found that THC produces bradycardia and anorexia in animals while in man it produces tachycardia and hunger.

Testing for Drug Use: Why, When and What For, presented by Dr. G.G. DeAngelis, Acting Director, Manpower Development, Executive Office of the President, Special Action Office for Drug Abuse Prevention, Washington, D.C.

These points emerged from the discussion following the presentation of this paper:

The use of testing for employment purposes has been found to have both advantages and disadvantages. At times a person might be unjustly denied employment and, therefore, a positive test should be rechecked by another method.

It was agreed that no test is infallible and that false results might occur which must be carefully evaluated.

The high cost of testing procedures is a problem, but these costs are becoming less with improved technology and the situation will be improved still further with automation.

Insufficient information about the patient may be obtained by simply testing urines for opiates, and therefore it is necessary to check for other drugs of abuse.

Certain antidepressants and major tranquilizers, for example, the phenothiazines and the tricyclic antidepressants are not popular with drug-taking people, and therefore they can be used in treating them in anxiety without fear of their becoming dependent.

Attitudes in the United States about the employment of ex-addicts are improving, while in Iran addicts have traditionally been employed.

The question of the confidentiality of the patient was discussed and it was agreed that this must be maintained and protected.

Measures for the Prevention of Drug Addiction, presented by Dr. M. Sarraf, Chief of Medical and Rehabilitation Institutions, Narcotics Control Administration, Ministry of Health, Tehran

The Role of Education in the Prevention of Drug Abuse, presented by Dr. M. Ali Shamie, Psychiatric Consultant, General Department of Mental Health, Tehran

These points emerged from the discussion following the presentation of these papers:

Drug abuse education was discussed, and it was concluded that the fear that such education might seduce young people into experimentation was probably groundless. It was felt that since young people wanted information, they would obtain it from inferior sources if it were not provided by skilled and informed persons.

It is important that drug abuse education should be incorporated into a continuing general health program and not presented as a special problem in health education.

Updated information is generally required about drugs since the rapid changes in drugs available have made most textbooks obsolete.

Life in present day society requires new information which must be accurately provided by parents and teachers who themselves must be well informed.

A Controlled Comparative Study and Follow-up of the Treatment of Dependence on Opiates, presented by Dr. A. Hussain Tuma, National Institute of Mental Health, U.S. Department of Health, Education and Welfare, Washington, D.C.

These points emerged from the discussion following the presentation of this paper:

Cooperation in the study of drug abuse, its treatment and rehabilitation transcends national boundaries and is well conducted on an International level. It was noted, however, that transcultural and international studies were required to be carefully tailored to conform to the indigenous differences that exist from country to country.

Drug Abuse: U.S. Public Information and Education Efforts, by Mr. Gerald N. Kurtz, Associate Administrator, U.S. Health Services and Mental Health Administration, Washington, D.C.

These points emerged from the discussion following the presentation of this paper:

It has been found that the young person can achieve freedom from drugs by becoming involved in anti-drug abuse activities.

It is necessary that educational efforts in this area should incorporate community assistance and feedback in order to be locally effective.

Constant feed-in and feedback of educational information between producer and consumer is a necessary feature in order to keep the material up-to-date and relevant.

The Federal Effort in the Prevention and Rehabilitation of Narcotic Addiction, presented by Mr. Karst Besteman, Deputy Director, Division of Narcotic Addiction and Drug Abuse, National Institute of Mental Health, Washington, D.C.

These points emerged from the discussion following the presentation of this paper:

It has been found that ex-addicts working as a part of a treatment team are more successful in maintaining abstinence than those who go into other jobs.

The longer the narcotic addict stays under treatment--whatever the type--the better he will progress.

The importance was stressed of the greater desirability of the use of pilot units in the initial stages of treatment programs before embarking on large-scale programs.

It was established that training, treatment and educational policies in the United States could not be transposed to a country like Iran since the problems and the available manpower and funds are quite different.

It was generally agreed that voluntary treatment was preferable to compulsory treatment for most narcotic addicts.

One important error was identified in preparing to combat the current addiction upsurge. This was the attempt to treat large numbers of addicts before having properly trained people to undertake treatment jobs. The point was made that even after financial provision had been made for treatment programs, this did not mean that they could be undertaken immediately since the collection and training of staff would take considerable time.

Using the epidemiologic model of contagious disease, the more desirable strategy of treating narcotic addicts becomes apparent.

This would involve:

- 1) Controlling the infection, i.e., eliminating supplies of the drug
- 2) Treating those who seek treatment, i.e., giving care to those motivated to be cured
- 3) Treating the remaining patients in order to prevent a new epidemic, i.e., instituting compulsory treatment for the recalcitrant patient.

The Effect of 6-Hydroxydopamine on Morphine Abstinence Syndrome in Rats

Interaction Between Morphine and Lithium

The Effect of Lithium on Morphine Abstinence Syndrome in Rats, presented by Dr. Burhan Kıran, Associate Professor, Department of Pharmacology, Faculty of Medicine, University of Ankara

There was no discussion on these research papers.

The Possible Role of Mast Cells in the Action of Morphine, presented by Dr. Alaeddin Akçasu, Professor of Pharmacology, Cerrahpaşa Faculty of Medicine, University of Istanbul

These points emerged from the discussion following the presentation of this paper:

This paper presented a theory of the action of morphine and its withdrawal effects. Apparently the mast cells store morphine and release histamine. This histamine release resembles the peripheral effects of the withdrawal syndrome. Antihistamines and steroids could, however, alter these symptoms.

The flushing and itching seen in humans after morphine injections are also a histamine effect.

A Study on Morphine Demonstrating the Phenomena of Pharmacologic Tolerance, Behavioral Tolerance and Behavioral Habituation in Rats

Behavioral Tolerance to Morphine in Rats and Its Effect on Determining the Time-Response Curve, presented by Dr. Sabih Kayan, Assistant Professor, Faculty of Medicine, Department of Pharmacology, University of Ankara

There was no discussion on these research papers.

Charas Abuse and Psychosis, by Dr. S. Haroon Ahmed, Psychiatrist, Jinnah Postgraduate Medical Center, Karachi

These points emerged from the discussion following the presentation of this paper:

The difficult question of charas psychosis and personality type might be resolved by a prospective study of various personality types among chronic charas users.

It has been found that the charas psychosis appears to be a briefer event than the usual course of schizophrenia.

SUMMARY

The delegations agreed that this seminar had helped to identify many specific problems of drug abuse in member countries. The fact that these problems are not universal, but, on the contrary, highly diverse and unique for each country made the discussion stimulating and valuable.

The question of compulsory, as opposed to voluntary, treatment of narcotics addicts occurred frequently throughout the seminar and there was general agreement that voluntary care is preferable.

Participants agreed that they had found the interchange of views at the seminar very worthwhile and were impressed by the amount of work being done in regional countries at laboratory level and by projected efforts in educational fields on drug abuse. They were concerned, however, that these efforts are being made in isolation and were keen that further cooperative work should be carried out between different countries of the region, in particular to provide cross-cultural studies, which are so badly needed in this field.

Discussions revealed the importance of the rehabilitation process for addicts and the need throughout the region for further research and study of this matter as well as the effective education of people responsible for the care of addicts. In response to a request in this connection for a specialized training center on a regional basis, the Secretariat suggested that the Jinnah Postgraduate Medical School in Karachi might be able to provide the training required. The delegates suggested that Jinnah and other alternatives be considered.

A review of the seminar left no question of its value. It was suggested that future seminars, for which the necessity was felt, should be more specific as to subject matter and should explore drug addiction in particular areas which could not be dealt with in depth at this meeting. It was also felt that further seminars might report on progress and developments in drug abuse following this meeting.

RECOMMENDATIONS

The delegates, having agreed on the great value of the seminar and on the need for and potential value to the CENTO region of future meetings in the field of drug dependence, made the following recommendations for future meetings under CENTO sponsorship:

- 1) Seminar on treatment and rehabilitation efforts in drug dependence
- 2) Seminar on prevention and educational efforts in drug abuse
- 3) Seminar on the epidemiology of drug abuse in the CENTO region
- 4) Seminar on research developments in the field of drug dependence in the CENTO region.

The delegates also identified specific areas for possible research projects, which might be undertaken individually or on a collaborative basis. CENTO sponsorship might be required; specific requests would be made to the CENTO Secretariat by the regional governments. The following studies were recommended:

- 1) An intensive study of people living in opium-growing areas in order to determine the mechanisms which keep them from becoming addicted individuals
- 2) A study of the difference in pattern of drug abuse in the CENTO countries in an attempt to understand why these differences occur
- 3) A study of how individual groups of people become involved in charas smoking in order to determine whether educational or preventive measures could reduce this and its relationship, if any, with tobacco smoking
- 4) An examination for THC content of cannabis products in the regional countries
- 5) A study of the problems of confidentiality in each regional country
- 6) A study of the association of chronic cannabis use with mental health, physical health and social functions.

Approval of Report

The report of the seminar was approved as amended.

Acknowledgements and Closing Remarks

The heads of delegations expressed their appreciation to the Imperial Government of Iran and to the Ministry of Health for the excellent arrangements and facilities provided and for their very kind hospitality; to the Government of the United States, and in particular to Dr. Sidney Cohen, the U.S. Coordinator, whose support made the seminar possible; and to the CENTO Secretariat for their assistance at the seminar. They also thanked the Chairman for his admirable leadership throughout the proceedings.

COUNTRY SITUATIONS

THE NATURE AND EXTENT OF DRUG ABUSE IN IRAN

by

Dr. Hasan-Ali Azarakhsh,

Director General,

Ministry of Health

and Representative of the Government of Iran

in the United Nation's

Commission on Narcotic Drugs

The problem of drug dependence in Iran today centres around the widespread use of opium, which has a long traditional background, and the abuse of heroin, which made its first appearance in this country in 1960.

In order to understand better the nature and extent of drug abuse in Iran it is necessary that we know something of the historical background to the cultivation of the opium poppy in this part of the world. The use of opium can be traced back several centuries and the earliest known reference to the poppy was made by the Sumerians in about 3000 B.C. It is also recorded that Razi (850 to 923 A.D.) and Avicenna (980 to 1037 A.D.), two noted Iranian physicians, made separate clinical studies on opium and introduced it with precise care into therapeutics.

In the same way that some pharmaceutical preparations, such as vitamins and hormones, are used freely today without prior consultation with a doctor, opium was used by many rich people in the hope it would give them imaginary results.

It is possible for us to follow the process of opium use in Iran from early in the 16th century. It is recorded that the poppy, which had not had the opium juice extracted from it, was boiled in water and the liquid drunk like tea. This beverage was known as "kooknar" and was served in rooms much like tea rooms of the present day. There were many such kooknar rooms in Isfahan, the capital of Iran at that time.

The smoking of opium was unknown in Iran until the second half of the 19th century and this habit was an import from abroad. The production of opium at that time as a commercial proposition was a profitable business and Iran began to produce it for export. This inevitably led to a spread of addiction which eventually became a social disaster for the country. The Government of Iran, realizing the extent of the problem, made efforts to deal with it. One of the earliest laws under the Constitution of Iran, introduced some 65 years ago, campaigned against the use of opium. This law provided for a period of 8 years during which the problem of addiction was to be ended, and also banned the use of opium, except for medical and scientific purposes. In 1928 another law was enacted to cover a 10-year programme for the ending of addiction. Unfortunately these programmes were never carried out and the result was that the number of addicts gradually increased instead of decreasing.

Finally, in 1955, after a period of some 50 years, Iran took the decision to ban the cultivation of the opium poppy and to limit the use of all drugs under international control to medical and scientific purposes. The government was content to forego its revenue from the export of opium in the hope of creating a new, healthy and self-respecting society.

But the government's efforts were thwarted by the appearance of opium which was smuggled into the country from beyond its frontiers. What began as a trickle became a torrent which created many socio-economic problems for the country. This situation continued to deteriorate, and in 1969 the Government of Iran was obliged to decide on a new policy in an attempt to solve this problem. In that year a law on the limited cultivation of the opium poppy was enacted by Parliament, which provides for the limited cultivation of the opium poppy in the country for internal use and for the registration of opium addicts over 60 years of age and those medically certified as being in too weak a state safely to be withdrawn. Since that time about 100,000 opium addicts have been registered and permitted

to purchase opium for their own consumption from authorized pharmacies, the amounts being between 2 and 5 grammes daily.

Like other countries, we have in Iran no realistic information or statistics on the number of addicts there are in our country today. Only those registered, arrested for some offence and those volunteering for treatment are known to us. For this reason we are obliged to make an estimate, based on some information we have. In 1955 it was our estimate that there were a million and a half, out of a total population of 20 million, i.e., 7.5 percent. Today, out of a total population of some 30 million, we estimate there are between 200,000 and 300,000 opium users in the country, i.e., about one percent. Opium is abused in three ways--by smoking it, by eating it and by smoking "shireh," which is made from the residue of smoked opium. Two types of pipes are used, the Indian type for opium and the Chinese type for shireh.

Addiction to heroin is a new problem to Iran, one which first appeared in 1960. Heroin abuse in Iran differs from the problem of opium in the country, and also from the heroin problem in some other countries. For example, in some countries heroin abuse is found mainly among the poorer class of people and is considered a symptom of poverty and malaise. In Iran, however, much of the heroin addiction is to be found among the youth from the well-to-do class of family. I believe that modern methods of communication, such as films, radio, television, magazines and books, have all helped to hasten this process. These media bring to Iran news of what is happening in other countries, and much is being written and spoken about drug abuse in the world today. There is a wealth of craving by our youth today for new things, and an urge to copy what others are doing elsewhere, whether it is good or bad. Many will be influenced by the good things they hear and read about, while others will take an opposite course; they will be influenced to try the modern drugs about which they read. This is very much the situation today in Iran with regard to our youth. I think we can say that in Iran opium is for the older people and heroin is for the youth.

Our estimate of the number of heroin addicts in this country today is about 10,000. Again we have no reliable information on this; there is no registration of heroin addicts nor is this drug made legally available to those who use it. The maximum annual seizure of heroin in Iran was 91 kilos in 1968. If we accept the hypothesis of Interpol that only 10 percent of the total drugs are seized then we can say that 910 kilos of heroin are used annually by addicts in Iran. If an addict uses 25 centigrammes a day the total number of addicts to heroin would be about 10,000. Addicts use this drug by sniffing the powder, and by inhaling its fumes, a method which is known as "chasing the dragon." The amount needed for this process of inhalation is

higher than that required for intravenous use, which is a method not often used in Iran.

In some countries heroin has replaced opium as the main drug of addiction. This, fortunately, has not so far been the pattern in Iran. While opium users are to be found over most of the country the use of heroin is confined to the big cities, especially Tehran. The majority of addicts to heroin are to be found in the capital. In contrast to the typical opium addict, the average heroin abuser is to be found in the age group 20 to 30 years, with an educational standard of primary or secondary grade.

In the drug addiction treatment centre in Tehran, 3,184 addicts were hospitalized in 1970. Among these the age groups for opium and shireh were 20 to 30 years--22.7 percent, 30 to 40 years--43.5 percent and between 20 and 40 years--66.2 percent. For heroin they were 20 to 30 years--47.1 percent, 30 to 40 years--37.6 percent and from 20 to 40 years--84.7 percent.

The abuse of cannabis under the name of "bhang," and the use of cannabis under the name of charas, also has a long traditional background in Iran, as in other parts of the Near and Middle East. But its use has never become widespread in Iran. Its abuse is confined to some dervishes and people from the lower strata of society and is usually mixed with tobacco and smoked. Cannabis is not a drug which is attractive to the modern generation in Iran today, although it is known that some youths do use it in the name of marijuana cigarettes, merely because it is the modern thing to do in Western countries. Its abuse is on a very small scale and does not present us with any problem. I should mention that severe penalties exist under the law for anyone convicted of possessing cannabis.

The nonmedical use of psychotropic substances is unknown in Iran, but there is a small-scale abuse of barbiturates which are sometimes used with heroin. There is no problem in Iran over the use of such drugs.

A main deficiency which I believe we all admit exists today, and is common to most countries where there is a drug abuse problem, is the lack of sufficient and reliable information on all aspects of drug addiction. We need to study the causes of addiction within the social, cultural and economic framework of our country and indeed of this region. Information must be exchanged between all those who are in any way concerned with this problem.

As you are all aware, the narcotics problem is not the same in every country. In each there is a particular situation of both tradition and culture. For this reason I do not believe

that it is possible to apply the pattern of addiction in one country to that of another. Many different factors are involved.

An important factor in the widespread use of a drug within a nation is that of acceptability, in the same way that alcohol is accepted in most countries. If we look at the background to opium addiction in Iran we will find that in the 19th century the health situation, particularly in the villages and small towns, was poor. Modern medicine had not yet found its way to those places and there was also a scarcity of physicians. Under such conditions, opium was the best and only form of medicine for treating ailments of all kinds and was cheap to buy and readily available. In those days, of course, the people were not aware of the dangers from its use. Gradually the use of opium spread and became a common thing like smoking cigarettes. In many families, the wife, sons and daughters were all users because the husband had the habit.

The addict in this category can be described as accidental or social, whose use of opium is for a negative pleasure, and differs from the addict who may be said to be a mental addict with a personality disorder who seeks a drug for a positive pleasure. After the prohibition which was placed on the production and use of opium in 1955, I found that among a group of 1,167 hospitalized addicts, 41 percent had become addicted because of some physical ailment, 17 percent because of fatigue from their daily work and 23 percent took a drug for enjoyment. The remainder, 19 percent, had become addicted through association with other addicts. It could be seen, therefore, that only 23 percent took opium for a positive pleasure. Of this total group of addicts 54.5 percent followed a strenuous occupation.

This study suggested that in countries where a drug is readily available the majority of addicts would most likely fall into the first of these categories, namely accidental or social, while the second group, whom I have described as mental addicts, would fall in the unknown minority. A lengthy campaign against drug abuse would result in the first group of addicts gradually decreasing, with those in the second group becoming the majority of the total addict population. The majority and minority groups change places with each other as a result of such a campaign.

In Iran the ban on opium production was quickly successful. Between the years 1955 and 1960 there was a rapid decline in the number of opium users. By special measures some 150,000 of these received treatment in the 4 years following the 1955 ban, while many abandoned the habit by themselves. This rapid decline was also influenced by the steady improvement in health and educational services. But from 1960 the number of addicts to opium has remained fairly constant.

I mentioned earlier that opium is being smuggled into the country, and an important contributory factor, in the amount of addiction which exists, is the ready availability of a drug. The extent of addiction in Iran may, to some degree, be measured by the amounts of narcotics which are being seized by the enforcement authorities, and I should like to give you, in round figures, seizure totals for the past 4 years:

	<u>1971</u>	<u>1970</u>	<u>1969</u>	<u>1968</u>
Opium (all kinds)	13 tons	13½ tons	18½ tons	13 tons
Morphine	53 kilos	39 kilos	13 kilos	28 kilos
Heroin	35 kilos	39 kilos	35 kilos	91 kilos
Cannabis	2 tons	637 kilos	92 kilos	45 kilos

You will note that there have been large increases in seizures of cannabis and will remember that I said that little of this drug is used in Iran. I should explain that the bulk of the cannabis entering Iran is in transit to the West.

THE SOCIAL ASPECTS OF DRUG ADDICTION IN TURKEY

by

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Turkey has an area of 740,000 km², and the population is 35,000,000.

The percentage of hospital beds to the general population of our country is 0.2 percent, and the percentage of mental patient beds to the general number of hospital beds is 10.8 percent. There are no institutions or boards established for alcoholics or drug addicts in Turkey.

This brief study is concerned particularly with the growing problem of drug dependency, including drug addiction and drug habituation by reason of repeated consumption of natural or synthetic drugs and with a desire to continue taking the drug to secure a sense of improved well-being.

In such conditions we shall discuss the misuse or non-medical use of drugs and in some instances the social and illegal aspects of these problems.

According to the general conception, we are going to present our subject under four main headings, namely:

- 1) The types of drugs which are potentially dependence-producing
- 2) Psychosocial consequences and the origin of drug dependence
- 3) Control, traffic and legislative problems
- 4) Prevention, treatment and education problems.

TYPES OF DRUGS

The types of drugs which are potentially misused and dependence-producing in our country are the following:

- 1) Sedatives and hypnotics

Barbiturates (luminal)
Pentobarbital (nembutal)

Minor tranquilizers

Chlordiazepoxide (librium)
Meprobamate (miltown, franklin, pertranquil)
Diazepam (diazem)
Oxazepam (serepax)

- 2) Stimulants

Amphetamines

Amphetamine (benzedrine)
Dextroamphetamine (dexedrine)
Methamphetamine (methedrine)

Others

Methylphenidate (rifolin)
Pipradol (meratron)
Phenmetrazine (preludin)

3) Psychedelics and hallucinogens

LSD-25 (LSD)
Cannabis (hashish)

4) Opiate narcotics

Opium
Heroin
Morphine
Codeine

5) Non-Narcotic Analgesics

Acetylsalicylic acid (aspirin)
Acetophenetidin (phenacetin)

6) Antidepressants

Monoamine - oxidase (MAO)
Inhibitor (marplan)

Sedatives and Hypnotics

Barbiturate derivatives, phenobarbital (luminal) and pentobarbital (nembutal), are used medically to reduce anxiety and tension, to produce general sedation and, at higher doses, to assure sleep, for anticonvulsive purposes and in narcotherapy. These two drugs are among the most widely used hypnotics with 250 kg nembutal and 6,500 kg luminal consumed annually.

For medical and nonmedical use, barbiturates are often taken orally, in the form of powders, elixirs, capsules or oral tablets, but under medical supervision. These drugs are sometimes administered intravenously or rectally.

For therapeutic purposes, minimal and maximal daily doses of the barbiturates are 30 to 300 mg a day, depending on individual variations, severity and chronicity of the symptoms.

It appears that a number of nonmedical users were initiated into barbiturate use for medical reasons; medical users develop dependence and often continue to use these drugs later. On the other hand, some users of the other drugs such as cannabis, morphine, heroin and opium take barbiturate derivatives for want of these drugs or mix the drug with them. Minimum and maximum nonmedical doses of these drugs are 200 to 2,000 mg a day.

The tendency for tolerance is much lower with barbiturates. In chronic users, physical dependence may develop along with tolerance.

Barbiturate dependence is in some respects similar to opiate narcotic dependence, and withdrawal symptoms are frequently more severe.

Minor Tranquilizers

Chlordiazepoxide, meprobamate, diazepam and oxazepam are the minor tranquilizers widely used medically and nonmedically in our country. Of these 6,000 kg meprobamate, 250 kg chlordiazepoxide, 375 kg diazepam and 1,500 kg oxazepam are consumed annually. In medical practice these are used in the treatment of a wide variety of symptoms falling into the category of anxiety. But, in my opinion and according to many observers, the quantity used yearly greatly exceeds medical needs and a considerable percentage may be diverted for nonmedical use.

Minor tranquilizers are administered orally as elixirs, tablets and capsules or given as injections. But for nonmedical purposes these drugs are used only as elixirs, tablets or capsules.

Minimum and maximum doses for medical use of these drugs are:

Meprobamate	1,200 - 2,400 mgr
Chlordiazepoxide	15 - 50 mgr
Diazepam	5 - 30 mgr
Oxazepam	10 - 50 mgr

Normal doses usually provide relaxation, a feeling of well-being and decreased inhibition.

Excessive use of these drugs causes disorientation, confusion, memory impairment, double vision and personality alterations.

Side effects observed with these include drowsiness, ataxia, lethargy, skin rashes, nausea, diminished sex interest, menstrual irregularities, blood abnormalities and increased sensitivity to alcohol.

Medical users develop dependence and continue to use these drugs even after treatment has come to an end.

Tolerance usually develops to most of the effects of minor tranquilizers on repeated use and the dose must often be increased in order to obtain the desired effects.

Minimum and maximum doses for nonmedical use of these drugs are:

Chlordiazepoxide	30 - 100 mgr
Meprobamate	1,200 - 6,000 mgr
Diazepam	15 - 150 mgr
Oxazepam	10 - 160 mgr

These drugs produce both psychological and physiological dependence resembling that produced by alcohol and the barbiturates. The observed withdrawal syndrome is similar to that of alcohol and barbiturates.

We do not have sufficient information to establish exactly the number of medical and nonmedical users of hypnotics and minor tranquilizers.

During recent years, an increase in the abuse of hypnotics and minor tranquilizers has been observed, particularly in large cities such as Ankara, Istanbul and Izmir. Among users there are young people aged about 20 to 25 belonging to the upper and lower socio-economic classes. They use these drugs alone or mixed with other drugs such as opium, heroin and hashish, or in place of these drugs.

Scientific investigations, observations and publications based upon the nonmedical use of tranquilizers or hypnotics have been neglected.

Some apparent suicides were attributed to hypnotic and minor tranquilizers (45 percent of apparent and attempted suicides).

Minor tranquilizers and hypnotics are widely prescribed without any control mechanism in general practice and they are also obtained without any prescription.

Stimulants

Amphetamines

Amphetamine (benzedrine), methamphetamine (dexayn) and other drugs with similar pharmacological properties are phenmetrazine (preludine), methylphenidate (nitralin) and pipradol (mezetren) and psychostimulant drugs of limited use in medical

practice for the treatment of obesity, fatigue, narcolepsy and overactive children who show disorders of attention and impairment of learning capacity. These drugs are usually taken orally and occasionally in the form of both intramuscular and intravenous injections.

The therapeutic dosage of each of the amphetamines differs slightly, but generally daily therapeutic doses are 5 to 40 mg.

Without medical authorization and prescription these drugs have been widely used by vehicle drivers on long trips, night shift workers, students studying for exams and athletes for increasing performance.

Tolerance and Dependence with Moderate Doses

Many individuals who use amphetamines to control narcolepsy may stabilize the doses, but those using the drug to control appetite generally increase their doses. Certain people using amphetamines for other purposes, generally show a marked tendency to increase the doses with time. Psychological dependence on even low doses is frequently observed, but physiological dependence is obscure.

Widespread use of these drugs has spread rapidly among youngsters of high school age and university students. Approximately 5 percent of these students use amphetamines during examination periods.

The psychological response to amphetamines varies considerably among individuals, but might typically include increased wakefulness, alertness and vigilance, improvement in concentration and a feeling of clearer thinking, greater responsiveness to environmental stimuli, decreased fatigue and boredom, elevation of mood, mild euphoria, a feeling of sociability, increased initiative and energy and increased verbal and other behavioural activity.

A moderate dose of amphetamine in different individuals might produce irritation, restlessness, insomnia, blurred vision, tremors, nausea, headache, inability to concentrate, dizziness, heart palpitation, confusion, anxiety, chest pains, chilliness, diarrhea or constipation.

In cases of a higher dose, hypersensitivity, delirium, panic aggression, psychosis, hallucinations and cardiovascular abnormalities may occur at some time.

In chronic users this drug produces tolerance and dependence which have often been associated with irritability, hyperemotivity and anxiety.

In predisposed cases amphetamine psychosis, which closely resembles paranoid psychosis or paranoid schizophrenic types, may develop.

Up to the present time we have observed and published eight cases of amphetamine psychosis, one of which developed into chronic paranoid schizophrenic type.

Pyschedelics and Hallucinogens

LSD - 25

LSD-25 users do not exist in Turkey. But certain young people belonging to the upper socio-economic classes, particularly in large cities, organize drug parties and use some drugs resembling LSD-25, such as mellow-yellow (banana), lettuce, or morning glory seeds.

Cannabis (hashish)

Cannabis is an herbaceous plant which grows untended in temperate climates. There are several varieties of cannabis such as indica, americana and africana. The scientific name of this plant is Cannabis sativa or Cannabis indica. Indian hemp has separate male and female forms and may grow to 3 to 4 metres under favourable conditions.

Marijuana is a mixture of the flowers, twigs and stems of the Cannabis indica.

Similar preparations are known as bhang and the more potent ganja in India, as kif in Morocco, as dagga in Africa.

Relatively pure resin obtained from the flowers of Cannabis indica is called hashish (hash) in the West and a great part of the Middle East.

Hashish (esrar) is usually prepared by pressing or scraping the sticky amber resin from the plant. It is as potent on a weight basis as high quality marijuana.

The various forms of the drug are frequently listed under the general term cannabis since they differ primarily in the degree of potency.

Under optimal conditions, almost all parts of both male and female plants may be potentially psychoactive. But the female has generally been considered as the more efficient producer of the resin responsible for the pharmacological effects. Female flowers contain a high concentration of resin.

Actually, numerous cannabinols were considered active principles of cannabis, and as a result certain forms of tetrahydrocannabinol (THC) have the most potent psychoactive property. Many of these have been isolated and synthesized in recent years.

Tetrahydrocannabinol is the active ingredient of the hemp plant *Cannabis sativa*. All preparations contain tetrahydrocannabinol.

Although "hash" may be many times more potent than marijuana, these two forms of cannabis are generally used in Turkey and are often indistinguishable from each other.

The precise determination of the doses of hash or marijuana is generally not possible among oral users.

In our country different socio-economic levels have used both forms of cannabis of relatively pure or mixed quality.

In Turkey medical use of cannabis is not accepted in the pharmacological code. Medically it is used only in experimental pharmacology for animal research.

Nonmedically cannabis (hashish) has been widely used during recent years, particularly by hippy tourists and among young people from 20 to 35 years of age, belonging to both lower and upper socio-economic and cultural classes. Among the users it is commonly called yellow girl, pot, weed, of this, jook or snift.

It is generally smoked in a cigarette, mixed with tobacco, or burned in a pot, in ordinary pipes, water pipes (nargile) and a special cup. All these are employed for inhalation of the smoke.

Some cannabis users take it orally, with food containing sugar and honey. The effects of oral ingestion are often noticeably different from those of smoke inhalation and increase the psychic effects. The onset of psychological effects occurs in a quarter of an hour following smoking or inhalation and an hour following oral ingestion.

Effects of Cannabis

Publications on the effects of cannabis are of limited number, are based on few scientific standards, show disagreement regarding doses and clinical manifestation as well as the dependence problem of cannabis.

Cannabis has little acute physiological toxicity. On the other hand, we have no reliable information available regarding the lethal dose in human beings. To date we have encountered only one publication reporting a death caused by cannabis in Turkish literature. This was the case of an American boy, aged 16, who took orally an uncertain dose of cannabis--its active principle was confirmed by toxicological analysis performed in specimens of viscera and urine.

Post mortem examination showed a congested pia mater, a brain which had in its sections some haemorrhagic points and an acdematous appearance.

The anatomopathologic findings were not characteristic. The above mentioned laboratory results in this case are sufficiently convincing to relate the death to poisoning by a cannabis product.

Psychological Effects

The psychological effects of cannabis vary greatly, depending on many factors such as type of preparation, mode of administration, doses, the personality of the user and the chronicity of cannabis addiction. Ingestion with alcohol also increases the psychic effects.

Interviews with young addicts suggest the following psychosocial situations: poor communication within the family unit, breakdown of the family, desire to be in the peer group, a search for identity, means of rejecting certain values of the adult world, and finally social pressures caused by a change in the cultural environment.

There is little tendency for intermittent users to increase doses, but certain cannabis effects may be modified by repeated experiences with the drug. Smaller doses may produce the desired effects after the individual becomes familiar with the drug. In some users a reverse tolerance appears. Certain chronic users in our country consume amounts of cannabis that would seem to be rather large by Western standards.

Generally, the initial effects of cannabis are psychic stimulation, mild tension and anxiety. After this phase, the users experience happiness, heightened sensitivity to humour,

free play of ideational association, a sense of extraordinary reality, enhanced visual imagination and perception, feeling of enhanced interpersonal communication, enrichment of sensory experience, a feeling of play of the imagination, particularly with sexual pleasure and little sex stimulating effect, mild excitement and energy, increased or decreased activity depending on the personality, feelings of enhanced spontaneity and creativity and so on. This manifestation is called "have" by the users.

In certain users, at the beginning of cannabis addiction, some adverse reactions may be observed, such as fear and anxiety, depression, irritability, nausea, headache, backache, dizziness, a dulling of attention, confusion, lethargy, a sensation of heaviness, weakness and drowsiness, disorientation, delusions, suspiciousness, panic, loss of control, and sometimes acute psychotic states. The possibility of psychiatric disorders associated with the use of cannabis has attracted considerable attention.

Some Turkish authors have reported a short psychic reaction in cannabis users similar to schizophreniform psychoses. These prolonged psychoses have usually been attributed to an earlier personal predisposition; sometimes this schizophreniform reaction develops into a schizophrenic process.

Many observations made by Turkish authors have suggested that chronic high-dose use of the purer form of cannabis may have harmful psychic and psychological effects on the users. Apathy, inactivity, inaffectibility and loss of social contact are important manifestations of this type which also develop into a schizophrenic process.

The same authors have also reported neuronal disturbance similar to chronic schizophrenic neuronal findings, such as progressive disintegration and disappearance of tigroid substance, increase in fat content and decrease in volume. The cells lose the Nissl substance and undergo vacuolization of the cytoplasm.

Tolerance and Dependence

Tolerance of cannabis does not seem to occur in humans, but there is little tendency for intermittent users to increase the dose. Small doses may produce the desired effects and cause an increase in doses. On the other hand, the increase in dosage depends on the purity of the cannabis. Determining exactly the doses of hash or marijuana is generally impossible among oral users, and it is impossible to establish the exact quantity of pure cannabis taken by them.

According to the general conception, cannabis produces only habituation and psychic dependence. Physical dependence with cannabis has not been demonstrated unanimously.

In this way, theoretically and normally, withdrawal symptoms do not appear after interruption of cannabis. But, on the other hand, there have been several observations from Turkish psychiatrists that reported irritability, mild discomfort and certain behavioural symptoms occurring after interruption of cannabis in chronic users taking large doses. But these observations are not clearly documented and the purity of the substances involved is not certain. Perhaps the mixture of cannabis with other narcotics could be responsible for the withdrawal symptoms causing these manifestations.

Habituation problems of cannabis users are accepted in all the world. But addiction to cannabis and physical dependence problems are disputable. On the other hand, some cannabis users show certain manifestations, as mentioned above, similar to a withdrawal syndrome. This obscure and disputable question is very important from the legal viewpoint (Code number 403-304-405), because the legal attitude toward the users depends on the discrimination of habituation and addiction. If cannabis causes addiction, the police and legal agency must send the users to a mental hospital or to a medical jurisprudence organization. If no addiction is established the users will be punished by the law.

Opiate Narcotics

Opium gum is obtained from a poppy plant called pavot after fall out of flowers and stetching of the green fruit. This green and fresh fruit is called "head," "cone" or "helmet" in our country. The fresh opium gum is a white viscous substance like chewing gum. But after it comes into contact with air, it becomes dark and takes on a brown colour.

As of 1971, according to the law (Number 3491 regarding the Office of Soil, which is a department within the Ministry of Agriculture), the production, manufacture, importation and exportation of alcaloids of opium and their derivatives have been under the monopoly of the State. But in May 1971, the Turkish Government prohibited production of pavot and fixed a date limit up to 1972 for the producers to substitute another plant for pavot, and it began to pay a credit for this change.

Opium is divided into three groups:

- 1) Opium gum
- 2) Substances including opium alcaloids
- 3) Some substances obtained from opium alcaloids.

Opium is used in three forms:

- 1) Smoking with cigarette or pipe mixed with tobacco
- 2) Drinking with tea or wine
- 3) Taking orally in the form of tablets or elixir or capsules.

There is another form of using opium orally in Turkey, particularly among prisoners. The prisoners' linen is washed and dipped into opium juice. This linen is introduced in the prison where the opium users take this substance orally by sucking their linen.

In some regions of Turkey where pavot is sown, certain families use opium gum as a sedative for their babies and for the purpose of inducing sleep.

Medical Use

In Turkish code the most important drugs, including opium, are primarily used in individuals suffering particularly from pain and in the treatment of diarrhea and dysentery.

In the legal market opiate narcotics are produced in a variety of tablets and capsules, elixirs, injections and rectal suppositories. Legitimate prescription of morphine is under strict control. There is a special prescription form issued by the medical association that all physicians must use whenever prescribing morphine.

Tolerance and Dependence

Some users have become addicted to morphine after medical prescription. They generally use it parenterally. Intravenous injections of this drug are not used in our country. Persons who are motivated by the chronic avoidance of pain or other unpleasant conditions or for euphoric effects become addicted and are likely to increase the doses.

Generally, the doses of chronic users would be lethal to a normal person. The degree of physical dependence is strictly related to tolerance.

At the beginning of morphine addiction the user feels euphoria, depending on the dose and on his personality. But after some time, varying from user to user, these feelings disappear and a tendency appears to increase the daily doses.

In the chronic user physical dependence develops very early and very severe withdrawal symptoms occur. Usually after a

period shorter than 4 hours following the last administration, the user begins to feel irritable and anxious. He shivers and his eyes and nose become moist. A few hours after this onset phase the skin becomes clammy, the pupils dilate, chills, nausea, vomiting and severe abdominal cramps occur with uncontrollable defecation. Tremors and, rarely, convulsions may develop.

Tolerance is eliminated or greatly reduced with withdrawal. This physical dependence and withdrawal symptoms are generally seen in opium users and other opium alkaloid users and also in users of codeine.

Considerable cross-tolerance and cross-dependence exist among the opiate narcotics. We believe that the fear of withdrawal is often the primary motivating factor in continued usage of the drug. Many users return to the drug a very short time after withdrawal.

We have no statistical data showing the relationship between crime and opiate narcotics in Turkey. But the high cost of opiate narcotics and their illegal traffic lead the chronic users to some criminal acts such as stealing, beating, hitting, killing and robbing.

We could observe the users of opium derivatives, such as pure codeine, hydrochloride of ethylmorphine, particularly among people belonging to upper socio-economic classes, living in large cities. Unfortunately, we cannot give statistical data about the users.

Heroin is used only as a sniff tobacco, but actually it is not a problem for Turkey.

For these drugs, drug dependence is characterized by a strong psychic dependence, manifested as an overpowering drive to continue taking the drug. Tolerance and physical dependence develop early and increase in intensity with increasing dosage.

In chronic use, a considerable degree of tolerance to the sedatives and analgesics occurs, and respiratory depressing effects appear. An abstinence syndrome usually occurs a few hours after the last dose.

Cocaine

After the First World War, cocaine addicts were observed among Russian refugees in the larger cities of Turkey. This substance was then called "snow." But in recent years this is no longer a problem.

There are other types of drug addicts called "mixed" who use any drug they can get.

CONTROL, TRAFFIC AND LEGISLATIVE PROBLEMS

In Turkey the General Security Head Office, the Second Section of the General Security Office, the Financial Police and the Smuggling Bureau deal with the illegitimate traffic of narcotic drugs.

Individuals arrested by the above mentioned offices are sent to a court of justice for their preliminary inquiries. Later they are sent either to the Office of Legal Medicine, to a tribunal or to a mental hospital, depending on their condition.

Statistical Data

In 1969 the total area sown with opium gum was 16,686 hectares. This area has yielded 125 tons of opium gum (10 kg opium per hectare).

In the same year the total exportation of the alcaloids of opium and their derivatives was as follows:

Pure codeine	2,000 kg
Phosphate of codeine	2,000 kg
Hydrochloride of ethylmorphine	1,200 kg
Hydrochloride of morphine	10 kg
Hydrochloride of cocaine	5 kg

These are used in medical practice.

The total number of addicts from 1953 to 1969 was 16,774.

Events concerned with narcotic drugs:

<u>Year</u>	<u>Number</u>	<u>Number of arrested</u>
1966	1,217	1,994
1967	1,316	2,148
1968	1,503	2,470

Nature of addicts:

<u>Year</u>	<u>Hashish</u>	<u>Opium</u>	<u>Morphine</u>	<u>Heroin</u>	<u>Cocaine</u>	<u>Total</u>
1966	1,103	110	3	-	1	1,217
1967	1,207	98	11	-	-	1,316
1968	1,412	80	11	-	-	1,503

Number of events according to the nature of narcotic drugs in 1968:

<u>Nature of Narcotic drug</u>	<u>Addict</u>	<u>Salesman</u>	<u>Production</u>	<u>Total</u>
Hashish	1,227	185	-	1,412
Opium	29	51	-	80
Morphine	-	11	-	11
Heroin	-	-	-	-
Cocaine	-	-	-	-
Total	1,256	247	-	1,503

Distribution of total number of addicts and arrested according to their age in 1968:

<u>Age</u>	<u>Hashish</u>	<u>Opium</u>	<u>Morphine</u>	<u>Total</u>
Under 15	29	1	-	30
16-20	295	13	1	309
21-25	393	16	7	416
26-30	516	12	7	535
31-35	418	23	9	450
36-40	315	29	9	353
41-45	194	19	2	215
46-50	51	4	1	56
51-65	78	16	3	97
Over 65	9	-	-	9
Total	2,298	133	39	2,470

It has been observed that the majority of drug addicts using such drugs as opium and cannabis belong to the age group ranging from 20 to 40.

There is no statistical data concerning profession, educational degree, family status and social situation of the users or about any other punishment for other crimes.

Articles 403 to 408 of the Turkish penal code are related to the traffic of narcotic drugs. The general conception of these articles is as follows:

Any attempted or actual production without authorized licence, import, or export of narcotic drugs is prohibited and the penalty cannot be less than 10 years of imprisonment.

If the drug in question is heroin, cocaine, morphine or cannabis, the penalty is life imprisonment, and for every gram of the drug the individual is fined 10 TL.

To sell, buy, possess, keep, transport, or help in the process of its being bought or transported are offences. The penalty cannot be less than 5 years of imprisonment, and for every gram of the drug the individual is fined 10 TL.

If the offences in the above mentioned article are concerned with heroin, cocaine, morphine and cannabis, the penalty cannot be less than 10 years of imprisonment.

If the individuals committing these offences are organized, the penalty is doubled.

To use, or carry such a drug with the intention of using it, is an offence and the penalty is 3 to 5 years of imprisonment.

PREVENTION, TREATMENT AND EDUCATION

A drug user is sent to a hospital and is not given any penalty, but must stay there until his condition is improved.

There are no special hospitals for the treatment of drug addicts, but there are special services particularly dealing with drug dependence in Istanbul, Manisa, Elazig.

The number of addicts hospitalized in 1969 was: Istanbul 245, Manisa 14, Elazig 11.

The goal is treatment of symptoms of abstinence with neuroleptics, antidepressants and minor tranquilizers, and other analeptic drugs. Psychological and social treatment are also applied.

The educational and preventive problems are very important, difficult and dependent on many factors.

The direct education of parents and teachers is very important. But in our conditions the number of knowledgeable persons is insufficient, and for this reason it is questionable if much information is transmitted effectively to those who need it.

For this purpose there are the People's Health Committee of the Ministry of Health and Social Welfare, the Turkish Society for Mental Hygiene, and 10 societies for the prevention of harmful conditions.

These organizations prepare the radio broadcasts, press publications, conferences and seminars that are generally on mental health subjects and particularly on drug misuse, and adapt or translate the brochures on this subject.

Turkey has accepted all international conventions on narcotic drugs.

THE PROBLEM OF CANNABIS IN PAKISTAN

by

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INTRODUCTION

Cannabis in various forms has been abused in Pakistan, very long before this new name was given to a very old civilization. The literature dealing with the problem in Pakistan is very scanty. There are some common beliefs on the subject which need to be examined in an unbiased manner. Views of certain workers in the West about the attitude of the East towards indulgence in this drug also need verification, because these are not shared by the people of Pakistan. Review of the available literature gives an impression that fact and fiction have been mixed in some statements, and that may at least partly explain the conflicting accounts about cannabis in the literature.

STUDIES IN PAKISTAN ON THE SUBJECT

In order to remove some of the confusion, some fact finding studies have been started in Pakistan on the subject including:

- 1) A first hand study of the process of making various preparations of cannabis which may be different from the techniques in other parts of the world. This may lead to differences in the composition of the products, which may be responsible for the difference in the effects of the drug as described in some of the reports.
- 2) Interviews about various details of the problem with persons who give a past or present history of indulgence in drugs.
- 3) Sample survey to determine the extent and the pattern of drug abuse.

Methods of Consumption of Cannabis

Cannabis is taken in Pakistan in the following forms:

By mouth:

- 1) As a beverage (bhang). This is in the form of a freshly prepared drink made from the fresh top leaves of the plant *Cannabis sativa*. The leaves are crushed into a paste along with other ingredients like poppy seeds, nuts, etc., to which cold water is added. It is a time consuming process and is usually practiced in picnic parties.
- 2) In freshly prepared cutlets of "pikoras" containing leaves of the plant (1).

By smoking:

- 1) Ganja. Top flowering parts of the plant are dried and smoked after mixing with tobacco.
- 2) Charas. This is the most common form and is the main subject of this paper. It is smoked by different techniques:
 - a) by a special types of "chilams" where the smoke passes through water

- b) pipes through which smoke is inhaled directly
- c) placing a piece of charas on burning charcoal and inhaling the smoke through fine tubes or straws
- d) cigarettes containing charas--these are not sold as such, but are prepared by the users themselves. A common way is to remove the tobacco from half of the cigarette, put a dose of charas in it and fill the tobacco back so it forms a sort of sandwich.

WHAT IS CHARAS ?

The medical dictionary describes charas as "resin extracted from cannabis" (2), and the word appears synonymous with hashish. In the Multilingual List of Narcotic Drugs under International Control, charas is shown as "Cannabis resin" (3), and in the Single Convention on Narcotic Drugs, it is elaborated that "Cannabis resin means the separated resin whether crude or purified obtained from the Cannabis plant" (4). It is submitted that these definitions and descriptions do not appear to be very accurate, as may become apparent after the actual process of its manufacture is described.

It is prepared near the northwest border of Pakistan and is smuggled into the country and also to other parts of the world. Possession or smoking of charas is illegal in Pakistan, but as it is available at a very cheap price, it creates a major problem of drug abuse. At the place of manufacture it costs the equivalent of \$3 to \$6 per kilogramme, according to its quality. Inside the country near the border a dose does not cost more than the price of a tablet of aspro; of course the price goes on increasing according to the number of check posts through which it is smuggled successfully. It was considered desirable that a first hand study of the process of preparing charas should be made. The areas where it is prepared are not easy to visit, and special arrangements were made to go to one of those places to witness the actual process.

Techniques of Preparing Charas

The plant of Cannabis sativa grows in wild form in many parts of Pakistan and the neighbouring countries, but the wild variety is not popular for making charas. For that purpose the

plant is cultivated as a summer crop in certain areas, and is harvested in the autumn. It is dried in the shade; the leaves become brittle and are removed from the stems along with the flowering and fruit-bearing parts of the plant. These are rubbed over three grades of cloth or gauze, one after the other, starting with the finest, then less fine and finally the coarse. In this way parts of leaves, etc. are converted into powder, which is sieved through the cloth and is called the "gul." The finest powder passes out of the finest cloth, and is called "first gul." This is richest in the resin contents, and forms a loose lump if pressed together. It makes first quality charas. The second and third guls are coarser, less sticky and make second and third quality charas respectively. These powders are stored in dark rooms in airtight, lightproof bags made out of goat-skins.

The powder is mixed with glue-like paste prepared from linseed oil. The second gul needs double the quantity of paste as compared to the first gul and the third gul needs three times more paste. The paste and the powder are hammered by a special device for about half an hour so that they mix thoroughly and assume a semi-solid consistency. That is charas. It is then made into slabs roughly one pound in weight and a trade mark put on it. In this place a golden seal was being put which read "Chitral Bazar." Chitral is a state in the north of Pakistan and is nowhere near the area where charas was actually being made. The manufacturers told me that charas sold better in the outside world with that seal.

There is no official standardization of charas in Pakistan. I am not aware if this type of charas has been analyzed for concentration of tetrahydrocannabinol or other active substances, and whether it differs from the so-called hashish smoked in other parts of the world.

Opiated Charas

There is a variety of charas in which opium is mixed, which can be seen as black streaks in the brownish-green charas. It is not very common.

I would like to know the views of the experts on the subject of whether the definition and description of charas in the Multilingual List of Narcotic Drugs and the Single Convention are accurate. In this case, resin is not extracted or separated from the plant as mentioned in the Single Convention, but the resin-bearing parts of the plant are processed.

VARIOUS FACTORS ASSOCIATED WITH CANNABIS

Another study has been started to determine various factors associated with abuse of drugs in general and cannabis in particular. All outdoor and indoor patients attending the psychiatric department of the Military Hospital in Rawalpindi are asked if they had taken any narcotic, stimulant or tranquilizer without medical need. Those who give a past or present history of such indulgence are interviewed to determine the correlation of the act with age, education, socio-economic factors, effects of use, withdrawal symptoms, correlation with physical disease, psychiatric disorders, crime, the attitude of the person, as well as his friends and relatives towards these habits, and some other factors. This study is being extended to other psychiatric centres also.

The sample has limitations, but also advantages, because the therapeutic rapport acts as a safeguard against intentional misinformation. Cannabis abuse is not only illegal, but is also socially not approved, and without the above mentioned rapport the information volunteered may not be very reliable.

So far only 44 persons have been interviewed. These include six Armed Forces personnel and 38 civilians of various socio-economic and age groups. Only a few observations are considered worth mentioning at this stage.

Attitude of the People of Pakistan Towards Cannabis

Review of the literature and meeting some Western workers during the past few years has given an impression that is believed by many people in the West, that the use of cannabis is socially acceptable in the East, just as alcohol is accepted in the West. It was mentioned in the Second Opium Conference, 1924-25, of the state members of the League of Nations and signatories to the International Opium Convention of 1912, that in India cannabis had a place in the social and religious customs (5). I shall quote from a more recent publication of the British Department of Health and Social Security on *Amphetamine Barbiturates, LSD and Cannabis*, published in 1970:

"According to most observers in India and particularly in Bengal, taking the drug (cannabis) is not regarded with disapproval. Sixty or seventy years ago, however, most of the population looked down on the drug takers, largely because of the degraded class they came from" (6).

Almost all cases in my study revealed that they were conscious that taking cannabis was socially not approved. Almost all had tried their best to hide the practice as much as possi-

ble. They stated that their family members and friends, other than the group of drug abusers, showed embarrassment when this practice became known to them, because it meant humiliation to them.

One who indulges in charas is called "charasi," which is regarded as a derogatory label, and even the charasies do not like to be called by that name. Social disapproval acts as one of the deterrents against the practice.

The attitude of some of the Middle Eastern and Far Eastern countries towards this drug and the habit is harsher than that of Pakistan, and even capital punishment is prescribed in some countries for offences connected with this drug. Many Asiatic countries are trying to eradicate it, and one of them, i.e. China, is believed to have been successful in that effort. It is amazing that in most of the international discussions on the subject, the representatives of the Western countries advocate a softening of the attitude towards this drug and the delegates of the Eastern countries regard it a vice and maintain their firm stand against it.

Therapeutic Use of Cannabis

Nobody among these cases had admitted that any preparation of cannabis had been prescribed for them by any qualified or unqualified medical practitioner.

A Masculine Vice

Unlike many other countries of the world, indulgence in cannabis is a purely masculine vice in Pakistan.

Mental and Physical Health

It is commonly believed in Pakistan that smoking charas leads to mental disorder and deterioration of physical health. Colonel Dhunjibhoy of Pakistan described cases of hemp insanity in 1930 (7). Even textbooks have described "moral and mental deterioration and insanity" as a feature of chronic poisoning with cannabis (8). Whether right or wrong this belief acts as a deterrent against the habit. Many persons who gave up the habit after indulging in it for some time stated that they did so because they developed the fear of insanity or sexual impotence or bad general health.

Definite conclusions cannot be drawn by our study at this stage. The exact incidence of cannabis consumption in the population is not known. So it is difficult to assess what per-

centage of such people show psychiatric disorders. Often it has appeared that indulgence in cannabis and other drugs was the manifestation of psychiatric abnormality and not the cause of it. Some cases which appeared initially as "charas psychosis" turned out to be schizophrenics on follow-up, the first attack either being precipitated by charas intoxication or associated with it just by coincidence. In one case, schizophrenia was attributed by relatives and friends to indulgence in charas, but family history revealed that the father of the patient also suffered from a similar mental disorder, although he was not known to have touched charas or any other narcotic. There are also examples where relatives wrongly blamed charas as the cause of the mental disorder, although the person had abstained from it for many years before the onset of the disease.

However, some cases of temporary psychosis associated with cannabis have been noticed.

- 1) A 28-year-old ex-policeman, after a bout of bhang drinking, went into a very violent excitement with paranoid delusions, struggling to get hold of his rifle to shoot his imaginary persecutors. Luckily this "running amok" was controlled. Three weeks after the onset of the condition he was brought for treatment and he was still complaining of headache and his sleep was disturbed. He was restless, agitated, and expressed his desire to kill all the criminals and drug addicts. His orientation in time was disturbed and he lacked insight completely. Response to the usual sedatives was not satisfactory but he recovered completely after one E.C.T. (electric convulsive therapy). He could recollect partially his past experience and behaviour. He had experimented previously with smoking charas as well as opium, taking alcohol, barbiturates and amphetamines, including injections of methedrine. The exact recipe of the bhang beverage in this case is not known as yet, and efforts are being made to find that out.
- 2) A middle aged businessman had been treated many years earlier for a psychotic episode associated with charas smoking. He took charas again and started complaining of headache, apprehensions and a mild degree of depersonalization. That persisted for about a month in spite of symptomatic therapy. He himself requested an E.C.T. which he thought had cured him earlier, and his symptoms disappeared after one application.

Future Programme

- 1) Pakistan can provide good opportunities for research projects connected with cannabis. It is intended that the fact finding studies about the techniques of preparation of other cannabis products and their methods of consumption should be continued.
- 2) It is desired that these finished products, as well as the ingredients used in their preparation, should be analyzed for assessing the content of cannabinoids and other active substances.
- 3) The interviews with persons who have used cannabis are to be continued before the data are analyzed and conclusions drawn regarding various factors associated with the drugs.

SUMMARY

- 1) Studies started in Pakistan regarding various aspects of cannabis have been mentioned.
- 2) Methods of consumption of cannabis in Pakistan have been described.
- 3) Techniques of the manufacture of charas, the most common preparation of cannabis causing the drug abuse problem, have been described. Doubt has been expressed about the accuracy of the definition of charas mentioned in the official publications.
- 4) Based on interviews of persons with a past or present history of taking cannabis the following conclusions have been drawn:
 - a) Contrary to the belief in the West, indulgence in cannabis is regarded as a vice in Pakistan and has no social or religious approval.
 - b) In Pakistan it is a purely masculine vice.
 - c) It has no therapeutic use in Pakistan.
 - d) Correlation of the consumption of cannabis with psychiatric disorders has been discussed.
- 5) A future programme has been mentioned briefly.

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THE NATURE AND EXTENT OF DRUG ABUSE IN THE UNITED STATES

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The task of describing the nature and extent of drug abuse in the United States is fraught with difficulties, due to a lack of nationwide data in many areas, and to the differing dates and diversity of sampling techniques, instruments, and survey methodologies used in the variety of one-time studies of individual drug problems that have been made. Such studies as exist usually have been limited in scope, most often investigating a specific college or high school population, and it is generally impossible to compare results from one survey to another. Because of the apparent expansion of illegal drug use in the United States, the National Institute of Mental Health is

now sponsoring a variety of studies in an effort to overcome the many deficiencies in existing data.

The one illegal drug about which we now are beginning to have meaningful information regarding the extent of use in the population is cannabis, or marihuana, which is used primarily as a "recreational" drug in the United States. The uniquely advanced status of data collection on marihuana is one result of the concern expressed in the past several years about its widespread use in the U.S., and the controversy about the degree of harmfulness resulting from its use. In order to assess scientifically the health issues of marihuana use in the U.S., the National Institute of Mental Health has undertaken an intensive program of studies of marihuana, including a number of epidemiologic surveys. The second annual report on *Marihuana and Health*, summarizing results and information to date, has recently been prepared by the NIMH and sent to the U.S. Congress by the Secretary of Health, Education, and Welfare (1). The data on the extent of marihuana use in the United States will be discussed later in this paper.

In addition, the National Commission on Marihuana and Drug Abuse has prepared a separate report concerning marihuana use in American society, including recommendations concerning revisions in Federal and State laws pertaining to the use and possession of this drug (2). This paper will not attempt to deal with the legal or social questions regarding marihuana which are now under intense discussion in the United States.

For clarity and organizational convenience, the discussion below treats the extent and nature of drug abuse in the United States by drug category. This does not mean that the phenomenon of multiple drug use has been overlooked. Multiple use is a serious complicating factor in analyses of drug-using behavior in the U.S. It is probable that most heavy abusers do not restrict their use of drugs to one category or another.

The drug used at a particular time by multiple drug abusers may depend in part on availability. For instance, the occasional social user of marihuana may switch to the more potent hashish to achieve an even higher "high" when his usual supply is not available. Similarly, the heroin user who cannot get his supply for a "fix" may use barbiturates temporarily. A study by the New York State Narcotics Addiction Control Commission provides data that heroin users are also frequently users of barbiturates, as well as other drugs. Among 32,000 regular heroin users studied, 53 percent also used marihuana, 34 percent used barbiturates, 19 percent used "pep pills," 19 percent used LSD, and 9 percent used cocaine (3).

THE USE OF OPIATES IN THE U. S.

Heroin has been the main drug abuse concern of the Government of the United States for decades, with other drug use becoming an issue only within the past few years.

Because of the illegal nature of possession and traffic of heroin, the index of the heroin addict population has been reports of arrest statistics gathered by law enforcement officials. The only recording of information on narcotics abusers at the national level is the listing of "Active Narcotic Addicts of the Bureau of Narcotics and Dangerous Drugs of the Department of Justice." This compilation relies on data supplied on a strictly voluntary basis by State and local jurisdictions. Without question it does not reflect the total addict population, due to an unknown, but no doubt major degree of underreporting. The word "addict" is not defined by the Bureau for the benefit of the local law enforcement agencies, which therefore use their own judgment as to who is an addict in submitting reports. On the basis of the BNDD "Active Narcotic Addicts" list, on December 31, 1971, the number of known addicts was 82,294, with 23,881 of those reported for the first time that year. Based on this reported total, BNDD makes a statistical projection of 560,000 actual addicts in the United States at that time.

Of the reported addicts, 55 percent were between the ages of 21 and 30. This age group has consistently represented the highest concentration of addicts in the U.S. Twenty-three percent were between 31 and 40, and 12 percent under 21. The ratio of men to women addicts was nearly six to one.

By a wide margin, New York City has consistently had the largest proportion of the United States' total reported addict population. In the mid-sixties, 50 percent of all addicts in the United States were concentrated in New York City, according to BNDD statistics. In 1970 the figure was 39 percent.

Altogether, 35 metropolitan areas spread through the United States have for the past several years reported more than 75 percent of the total number of addicts. Although it is too early to predict, the future may see this pattern change. On the basis of local surveys and the development of new treatment resources at the community level, many medium-sized cities generally assumed not to have a heroin problem are now known to have addict populations. For example, cities of the southeastern and midwestern sections of the United States thought to be heroin-free have produced reports of sharp increases in heroin addiction.

Further, affluent suburbs also thought to be free of the heroin problem traditionally associated with American ghettos

are suddenly aware of beginning heroin use among their youth. Although the extent of this abuse is unknown at this time, it is believed still to be small. Survey statistics for 1969 and 1970 for high school and college populations indicate that fewer than 4 percent of the sample reported any use of opiate drugs (4). The cumulative effect of these new trends has caused a substantial revision of previous thinking on the true scope of heroin problems.

Clearly any attempt to estimate accurately the number of addicts encounters many complications. Aside from the very basic question of what degree of use defines addiction, there are the usual problems of accurately estimating the number of individuals involved in an activity which is illegal and which they must take pains to hide. A variety of methods is being proposed and tested by the NIMH, as well as other organizations in the United States, in an attempt to produce statistics with increased validity and reliability. In 1967, the President's Commission on Law Enforcement and the Administration of Justice recommended the establishment of a national registry of drug abusers (opiates and nonopiates) to be protected by legal assurance of confidentiality. The Commission stated that "The availability of such data on a national basis over a period of years, would provide unique and valuable data on the incidence, prevalence, and epidemiology of various types of drug abuse and would identify the magnitudes of various aspects of the problem" (5). The Commission recommended that NIMH set up such a national register. Because of the inherent difficulty of the problem, and the lack of trained biostatisticians for such a unit, the NIMH decided instead to underwrite a Narcotics Register in New York City as a pilot program. New York State law guaranteed confidentiality for data collected. The register uses a number of different kinds of sources, not only the police and correctional agencies, but also all hospital, health, and social agencies, the school and judiciary systems, and private practitioners. The volume of reports issuing from these various agencies differs, since there is no requirement in the law that all agencies must contribute data to the register. In spite of difficulties, however, the register remains, to our knowledge, the only attempt to collect data on narcotics users from a variety of sources.

Evidence accumulated from the register and other sources indicates that at present the typical New York City addict is a young male ghetto dweller; he is a member of a racial minority group; and he and his family are poor. As mentioned above, however, experimentation with heroin has begun to appear among middle class young people who live in suburbs.

In Chicago, a team of NIMH-supported investigators (6) is in the final year of an epidemiological project designed to obtain detailed current and historical data on the incidence and

prevalence of drug abuse, primarily heroin addiction, through the study of the social organization of drug users and other relevant concomitant social factors in four major drug-using neighborhoods. A second major objective of the study is to measure the relative effectiveness of the various treatment programs offered to addicts in these areas. The investigators are studying four major "copping areas," fairly fixed geographical centers of drug distribution which serve relatively stable clientele. The study population includes not only addicts and selected members of their families, but also local enforcement officials, businessmen, educators, community leaders and nonaddict residents. Study methods combine participant observation and interviewing by members of the field staff with the use of standard survey techniques. The investigators are also looking into the quality of heroin available on the street to see in what ways changes in quality and quantity may affect incidence figures. They are also examining narcotic arrest data in the four areas to see if there has been any change in enforcement activity over time. Cross patterns of court decision making in recent years have been identified through interviews with judges, high level narcotic officials and informed narcotic addict patients.

This study represents a significant attempt to develop and test new methodologies for the study of the incidence and prevalence of heroin addiction, and in the future should help us produce estimates of greater validity and reliability.

THE USE OF MARIHUANA IN THE U.S.

As already mentioned, many new data have been reported in recent weeks and months with respect to the extent of American marihuana use. In both the annual report on *Marihuana and Health* prepared by the NIMH Division of Narcotic Addiction and Drug Abuse and in *Marihuana: A Signal of Misunderstanding*, the report of the National Commission on Marihuana and Drug Abuse, there is every indication that use of marihuana in the U.S. is very widespread and is increasing.

Fortunately, as use in the United States has increased, so has the sophistication of investigations assessing such use. Researchers now are going considerably beyond the oversimplified question, "Have you ever used marihuana?" to inquire into the frequency of use, the level of use, and the circumstances surrounding use. Some of the latest findings are summarized below.

Based on converging evidence from several surveys, the NIMH report (1) estimates the total number of persons who have ever used marihuana in the United States to be 15 to 20 million, or 9 percent of the population over 11 years old. The National Commission report (2) estimates that the total number at present

may well exceed 24 million. Exact figures, of course, depend heavily on the data of the survey, the methodology employed and the underlying statistical assumptions which are made.

While many experiment with marihuana but do not continue to use it, over half are estimated to use the drug one or more times per month. About one in four who use it that often do so three times a week or more. Users fall heavily into the teenage and young adult groups. There is considerable variation from school to school, however, with rates of "having ever used" ranging from as low as 5 percent to as high as 90 percent. There is also a lack of even distribution of marihuana use among young people from one area of the United States to another. For example, one national survey reveals that among persons 18 to 29 years old, there are three times as many who "have used" in the western section of the U.S. as compared with other regions sampled (7).

Among a still younger age group, the 12 to 17-year-olds, a nationwide study has indicated that nearly one in four in the western U.S. has used the drug, with a slightly lower percentage in the northeast, and slightly more than one in ten in other parts of the country (8). The use rate among 12 to 17-year-olds rises rapidly with age, according to this study. In the span from 12 to 14 years, the rate increases sharply, suggesting that introduction to marihuana often comes at the junior high school level in the United States. The rate rises steadily through age 17, to a rate as high as that for the older age group of 18 to 29.

Among college students, also, a large increase in the number of users has been found in nationwide surveys (9,10). Thirty-one percent of students who reported having ever used marihuana in 1970 had increased to 44 percent in 1971, and 13.6 percent who used marihuana at least every week or two in 1970 had increased to 21.6 percent in 1971.

Among all those who have ever used marihuana, the following levels of use have been estimated: 3 percent using daily, 11 percent using three to six times per week, 40 percent using one to eight times per month, and 46 percent no longer using or using a total of less than 10 times (11). This investigator estimates that a daily marihuana user consumes about three cigarettes per day, or about 15 mg of THC.

It is noteworthy in all studies that where the percentage of those who have ever used is high, so too is the percentage who make regular use of marihuana.

Among different occupational groups, there is wide variation in the percentage who use marihuana one or more times per

month. In a study conducted in New York State, marihuana use ranged from one in seven among sales workers to no reported use among the farmers sampled. Nearly half of the sales workers who had used did so on the job, as did a fifth of the users in professional and managerial occupations (12).

Several studies suggest, not unexpectedly, that persons who are more psychologically disturbed or socially unstable are more likely to make regular, heavy use of marihuana. School dropouts are more likely to be using marihuana, as are those from disturbed families (13, 14).

Heavier marihuana use in the U.S. is statistically associated with the use of other drugs as well. For example, in one study of the use of barbiturates, only one percent of nonusers of marihuana have ever tried this class of drugs, while 18 percent of marihuana experimenters and 71 percent of occasional or frequent marihuana users had tried them (8). There is no evidence, however, that marihuana itself is the "cause" of the use of other drugs.

It should be emphasized that in the United States the marihuana used is extremely variable, ranging from the psychoactively inert at one extreme to hallucinogenic in large doses at the other. The type of marihuana generally available in the United States tends to be considerably less potent than that found in many other parts of the world. This fact, plus the absence of any population in the U.S. which has used cannabis for extended periods of time, are basic reasons why some studies of the health consequences of marihuana use have been undertaken outside the United States. These studies are part of the major NIMH program of marihuana research to determine its effect on the psychological and physiological functioning of the user. Preliminary studies of long-term users in Greece and Jamaica are noteworthy on the basis of an absence of debilitating effects after years of use of potent forms of cannabis. For detailed information on results being reported on the wide variety of investigations underway in the NIMH marihuana research program, see *Marihuana and Health*.

LSD AND OTHER HALLUCINOGENS

Few drugs can claim to have had so profound an effect on American culture in so short a time as d-lysergic acid diethylamide. The use of LSD, although never great in terms of the population who have tried it, helped to create an entire subculture in the United States--the so-called "hippie" groups which now have spread around much of the world, and which have drug use as one defining factor.

Unlike other illegal drugs, LSD first became popular in the United States among middle class professionals and artists. Repetitive use of these drugs today, particularly LSD, is found only among a relatively small number of individuals, although experimentation by young drug abusers continues to flourish. In a national survey of drug use among college students, 9 percent of the students had tried psychedelics as of Spring 1970. By Spring 1971, 13 percent had tried LSD-type drugs (9). At one West Coast university, 15 percent of the freshman class of 1970-71 had tried LSD, while 30 percent of the senior class had tried it (15).

At the high school level, survey data from a northern California county which has had a relatively high rate of drug use indicate that 15.4 percent of students using LSD in 1971 represented an increase of only one percent over 1970 (16). Surveys in consecutive years in this county have indicated a stabilization or lessening in the use rates of LSD at this age level.

Few data are available on the extent of use of other hallucinogenic drugs, such as peyote, mescaline, psilocybin, DMT, and STP, yet it is known that each of these drugs is used to some extent in the U.S.

AMPHETAMINES AND BARBITURATES

It is especially difficult to arrive at any sort of estimate of the extent of abuse of amphetamines and barbiturates in the U.S. The difficulty lies in part in how "abuse" is defined, which may range from the obvious abusive practice of using illicitly obtained drugs to the more "acceptable" forms of abuse represented by inappropriate usage of medically prescribed compounds.

Very large quantities of amphetamines and barbiturates are manufactured in the U.S. In the case of amphetamines, it has been estimated that a vast proportion of the production finds its way into illegal channels. Accordingly, within recent weeks, manufacturing quotas for amphetamines have been issued by the Government of the U.S., which will reduce production by 85 percent to a level determined to meet the medical needs of the population of the United States.

It is generally estimated that approximately 5 million persons have intermittently used oral amphetamines without medical prescriptions, a cause for considerable concern in the U.S. The NIMH also has been particularly concerned about a recent upsurge in the intravenous, high dose abuse of methamphetamine. Increasing numbers of young people are using a hundred times the

average dose in a single injection, which may be repeated a number of times daily. These "speed freaks," believed to number roughly 100,000, are a serious problem, due to the acute toxic state which results from this abuse, as well as the psychological depression which sometimes occurs when the drug is abruptly withdrawn and the user "crashes." The NIMH has a special ward at its Clinical Research Center in Lexington, Kentucky, for studies of this condition, and several grants have been made for investigations of the problem.

Data from college surveys indicate that use of amphetamines is limited among this population, and is most commonly related to "cramming" for examinations. In a national college survey in 1970, 17 percent had tried amphetamines; in 1971 this figure increased to 23 percent (9). At a West Coast university, of the 1970-71 freshman class, 5 percent had tried methedrine and 14 percent had tried other amphetamines. Of the senior class, 14 percent had tried methedrine and 38 percent had tried other amphetamines (15).

In a northern California county high school population, there has been a 4 percent increase in amphetamine use in 1971 over that of 1970. By 1971, 23 percent had tried amphetamines, 9 percent had used them 10 or more times, and 4 percent had used amphetamines 50 or more times (16).

Barbiturates also confound the American drug scene. An estimated 2 million people take this drug regularly without medical need. When barbiturates are obtained illicitly or used in a "street" setting, they are most often used to modify the effects of other drugs, or to tide an abuser over when his drug of choice is not available.

Available statistics on barbiturates use among youths are as follows: In the national college survey, 20 percent of the undergraduate college students had tried barbiturates or sedatives in 1971 as compared with 15 percent in 1970 (9). In the West Coast university study, 8 percent of the 1970-71 freshman class had tried them compared with 20 percent of the senior class (15). In the countywide high school study in California, in 1971, 18 percent had tried barbiturates, 6 percent had used them 10 or more times, and 2.5 percent had used them 50 or more times (16).

EXTENT OF MEDICAL USE OF PSYCHOTROPIC DRUGS

Through its Psychopharmacology Research Branch, NIMH is supporting a survey of patterns of psychotropic drug acquisition and use within the general population. While the focus of this

survey is not on drug abuse, it is providing insight into the actual extent to which the United States has become a drug-oriented society.

In a national survey the investigators found that only 4 percent of men and 6 percent of women had ever used antianxiety or sedative drugs on a regular daily basis for 2 months or more, and that several long periods of regular daily use of psychotherapeutic drugs over a lifetime is quite rare. The same study provides evidence that less than half of the individuals who have high levels of psychic distress used psychotherapeutic prescription drugs. Attitudes toward the use of tranquilizers among Americans were also found to be conservative. Finally, the number of prescriptions filled per unit of population in the United States was very similar to the rates found in several European countries, slightly more than five prescriptions per person per year (17). These findings would tend to indicate that the increases in illegal drug use that have been reported throughout this paper cannot be easily explained on the basis of a general social affinity toward the use of mind-altering compounds.

It is not within the scope of this paper, however, to offer theories of possible reasons for the escalating drug problems of the United States, which most certainly are of highly complex derivation. Rather, it would seem appropriate to conclude with a brief summary of the program of the National Institute of Mental Health to reduce and prevent drug abuse.

THE NIMH DRUG ABUSE PROGRAM

The Division of Narcotic Addiction and Drug Abuse of the National Institute of Mental Health administers a rapidly expanding effort in the areas of treatment and rehabilitation, training of professional and paraprofessional personnel, research on all fronts of the drug abuse problem, and public education directed at slowing down the rising rates of drug abuse through prevention.

The treatment and rehabilitation program is based on the philosophy that the community is the optimal focus for effective treatment and lasting rehabilitation. To date, 83 community-based treatment and rehabilitation service programs for narcotic addicts and drug abusers have been funded by NIMH, as well as 174 aftercare agencies which provide necessary follow-up services to and monitoring of addicts who have been released from the NIMH inpatient treatment program at Lexington, Kentucky. Addicts may be civilly committed to this NIMH facility by the Federal courts for treatment. More than 30,000 individuals with addiction or drug abuse problems have been served thus far in the

community service programs and more than 2,000 in the civil commitment program. Another paper is being presented at this CENTO seminar which provides further details on these treatment efforts of the United States Government.

The training program of the Institute is designed to prepare new personnel for virtually all levels of work in the drug abuse field. Included are drug abuse fellowships for staff members of medical schools to allow them to prepare themselves in this subject matter area in order to help improve the level of training on drug abuse for future medical students. Also offered are pre and postdoctoral research fellowships and clinical investigator awards.

Furthermore, the NIMH is sponsoring several training centers throughout the U.S. which give short courses in drug abuse subjects. To date, approximately 2,000 persons with health, education, law enforcement, social service, community, and drug abuse agency responsibilities have been trained in these centers. Additionally, the NIMH and the White House Special Action Office for Drug Abuse Prevention, which was formally established by legislation passed by the U.S. Congress 3 weeks ago, will soon open a National Training Center in Washington, D.C., to train 1,200 persons per year.

The marihuana research program has been mentioned earlier in this paper. Through grant and contract mechanisms, the NIMH has been searching intensively for definitive answers concerning the marihuana drug and the consequences of its use. This program has already paid off in terms of vast amounts of new, though still inconclusive, data. This research effort will continue, including the provision of controlled stocks of pure marihuana to investigators.

Research has also been underway in each of the other major drug abuse areas. In addition to the epidemiologic data reported above, much information has been accumulated on the patterns of use, the metabolic pathways, and the psychological, sociological and physiological concomitants of these drugs. These data do not yet elucidate the many major drug abuse issues, and research is continuing in a search for broader understanding.

Finally, the NIMH has undertaken comprehensive and innovative programs of public education. These involve production of films on many aspects of drug abuse for use by schools and community groups, mass media programs, literature distribution, and teacher training focusing not only on imparting knowledge of drug facts but also on sensitizing educators to the complexities of the drug scene in the contemporary American youth culture. The Institute also has established the National Clearinghouse

for Drug Abuse Information as a central focal point for collection and dissemination of information on drug abuse and drug abuse programs.

Through these approaches, the goal of the national drug abuse program of the United States is to understand drug abuse more fully, to counter it on whatever fronts are possible, and to halt its continued expansion in the U.S. through improved means of prevention.

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The presentation by Dr. P.H. Connell, Physician, The Bethlem Royal Hospital and The Maudsley Hospital, and Director, Drug Dependence Clinical Research and Treatment Unit, London, was based on two of his earlier papers. The one which follows was originally given at the Symposium on the Scientific Basis of Drug Dependence of the Biological Society on 9 April 1968, just prior to the full implementation of the Dangerous Drugs Act. It is reprinted from Scientific Basis of Drug Dependence, edited by Hannah Steinberg, London, 1969. His other paper is included in another section, Background Papers.

THE DRUG ABUSE SITUATION IN THE UNITED KINGDOM

In this, the last session of a symposium during which we have heard a number of stimulating, provocative and academic papers, I present this paper with considerable humility, for I have no research data or original clinical material to present.

It seemed to me that at this crucial time, when new methods of dealing with the problem of drug dependence in this country are about to be instigated, it might be profitable to

attempt to examine the thinking behind them and take a look at the problems which beset the physician who is to deal with drug-dependent patients. This attempt might be of some value as a short historical statement.

DEVELOPMENT OF THE PROBLEM

The numbers of nontherapeutic narcotic addicts known to the Home Office began to rise slowly in 1958, and by 1963 it was realized that if trends continued a major epidemic was likely. The Second Report of the Interdepartmental Committee on Drug Addiction was published late in 1965 following deliberations which had begun when the Committee was reconvened in July 1964. Evidence presented to the Committee made it clear that the heroin being used by addicts was available because of gross overprescribing by a small number of general practitioners. Efforts on an informal basis to stop such overprescribing were fruitless, and so action had to be taken. This led to the Dangerous Drugs Act of 1967, which requires any doctor who comes into a professional relationship with a person addicted to certain drugs to notify certain basic particulars to the Chief Medical Officer at the Home Office (regulation brought in on February 22, 1968). The Act also denies the right of doctors to prescribe heroin or cocaine to addicts unless they hold a special licence to do so (regulation operative from April 16, 1968). The latter requirement has been delayed until a time when new treatment centres will be operating, which, it has been calculated, should be able to deal with the number of addicts seeking help.

RATIONALE OF THE NEW APPROACH

The rationale of the new approach, which includes the concept of prescribing heroin to addicts who do not wish to be withdrawn from the drug, can be summarized as follows:

- 1) The prescribing of heroin to addicts must be under some tighter control than before.
- 2) There is no evidence of a criminally organized heroin supply in the country and this must be avoided at all costs.
- 3) If supplies of heroin to addicts are stopped abruptly there is a strong chance that a criminally organized black market will spring up, for the numbers of heroin addicts are approaching the level at which it would be financially worthwhile for criminal organizations to move in.

- 4) When heroin is solely available in a criminal black market it has to be purchased, and the need to obtain money to purchase it drives the addict into criminal activities in order to obtain the money to maintain his dependence and to avoid withdrawal symptoms.
- 5) Heroin provided free at special treatment centres will obviate the need for the addict to commit crimes to obtain money for the drug.
- 6) Hospital clinics staffed by experts are much less likely to overprescribe and licencing regulations will allow for a doctor's licence to be withdrawn where necessary, for the licences are to be renewable yearly.
- 7) The treatment centres will be oriented towards eventual withdrawal of the patient units. Regular contact between the addict and the doctor of the centre gives the opportunity for a relationship to be built up which may eventually lead to the addict requesting to be taken off the drug.
- 8) The pure, British-made heroin which the addict will receive is less likely to cause complications and death than the impure material which circulates in a criminally organized supply system. This hypothesis may well be untenable in the light of recent findings (1).
- 9) If the hospital clinics do prescribe more closely to the actual dose taken by the addict there will be much less "spare" heroin circulating to involve more uncommitted individuals.
- 10) The addict is a sick person and properly comes within the ambit of medical practice. His dependence on the drug and his craving are so strong that he is unable to behave rationally.
- 11) Punitive detention of the addict under a penal system has not been shown to be successful in curing addiction in other countries and should not be adopted hastily.
- 12) Although it may well be that a population of addicts exists who can only be helped by compulsory detention in hospital (under, let us say, a new provision of the Mental Health Act), it is wiser to delay asking for such powers until the size of the population requiring such an approach and the features

which distinguish this population from other addicts can be delimited. Too hasty provision of such compulsory powers might well lead to their widespread use where not necessary, and such widespread use has not been found effective in other countries--notably the U.S.A.

THE DIAGNOSTIC PROBLEM

Since the treatment of heroin dependence is now to be passed over to special centres, it may be as well to look at the diagnostic problem confronting the physicians working in the centres.

The physician wishes to establish a number of facts, including: 1) Is the patient taking heroin at all? 2) If he is taking it, what is the dose? 3) Is he taking other drugs? 4) Is he taking it continuously or sporadically?

Here the physician turns to his colleagues concerned with chemical pathology, biochemistry and pharmacology and finds, to his dismay, that quantitative assessments are not possible in an outpatient setting (and the addict usually does not want to be admitted for observation) and that qualitative methods, such as the use of thin layer chromatography, cannot be done quickly. A result in 24 hours is the most he can hope for when the chemical pathology services have been developed. There is the nalorphine test to demonstrate morphine and heroin use (7,8) which is used extensively in California, but this has its limitations and snags. The physician, therefore, who is supposed to be an expert, has no immediate expertise to help him. He must, therefore, try to play a waiting game in which he attempts to gain the cooperation of his probably hostile and suspicious patient, in an attempt to bring him back when urine test results are available (many of the patients are unable to pass urine in sufficient quantity). In the meantime he must try and keep the patient going by giving a drug, such as methadone, to prevent possible withdrawal symptoms, should the patient actually be taking heroin. This is an unenviable state of affairs. Test doses of heroin or barbiturates could be given to demonstrate the presence or absence of tolerance but this method is time consuming and requires standardization. Individual differences are likely to be wide.

The physician is therefore facing a patient who may be an addict. The addict nearly always asks for more than he needs, partly because of his fear of being without any drug, and partly because he may wish extra to give to friends or sell for money. He is a skilled manipulator who plays on the kindness and weakness of doctors. During a month's visit to the U.S.A. in Novem-

ber 1967, I asked several groups of addicts what a British doctor should do in this situation to prevent overprescribing, and I was told to divide the dose demanded by two or by three. Should this be taken as a guide in dealing with the British addict?

The physician, in the special centre, has to face the fact that if he puts too many requirements on the addict, such as daily attendance, spending an hour each time he attends and so on, the addict may become fed up and seek a black market even though the drug may be costly. Should enough addicts feel thus, a black market would be worthwhile for the criminal organizations.

Thus physicians, chiefly for medico-social reasons, have agreed to take part in a treatment setting which includes maintaining a heroin addict on heroin, which is a very bad drug for maintenance purposes because of its short lived action. If taken intravenously it can lead to a number of serious medical complications (5, 2) and to a high mortality rate (1). The diagnostic armamentarium available to the physician is minimal.

The Interim Period

The past few months, during which clinics have been opening and taking over patients from general practitioners who have been prescribing for addicts, have been difficult, since only from April 16, 1968, will these clinics be the only places at which addicts can receive their heroin or cocaine. In the interim it is likely that there has been a good deal of overprescribing. This might be due to case load pressures; to the physician obtaining experience in handling the addict; and because of the need to be thought of highly enough by the addict to encourage continued attendance when alternative sources of supply are still available.

The number of addicts who will come forward on or after April 16, 1968, may make necessary the geographical redistribution of addicts to more conveniently situated centres, if contact between the centre and rehabilitation and social services is to be established.

The Dangers Inherent in the New Approach

There are many dangers in the new approach which have to be faced and are better stated in order to avoid a drift into disaster and a breakdown of the new approach. I will draw attention to these by stating certain propositions.

- 1) It has already been shown that a very small number of overprescribing doctors can encourage an epidemic of drug-taking where a socio-cultural demand expresses itself.
- 2) The experts in the special centres are not infallible and have no accurate tools to assess dosage of the drug.
- 3) All professional classes contain weaker brethren.
- 4) The number of doctors in London who are actually going to prescribe heroin to addicts is several times more than the number of general practitioners who undertook this task.

If these propositions are accepted then it must be acknowledged that without careful evaluation and careful practice it would be possible for the situation to become much worse than when general practitioners were free to prescribe these drugs to addicts.

Safeguards to Prevent Untoward Developments

There are two main requirements for cutting down the pool of "free floating" or excess heroin which has been used to involve the as yet uncommitted.

First, it is necessary to recognize that there is a need to cut down the dose of drugs already being prescribed to addicts. This could best be effected by an agreement between those working in the treatment centres so that on an appointed day all clinics would reduce the amount of heroin prescribed over a period of, say, a month, to about half the dosage.

Second, it must be agreed that no heroin addict will ever receive a dose higher than that considered to be necessary during the first few attendances at the clinic. This measure, in particular, would provide protection to those who, with the best of motives, might be led to increase the dose by pressure from the addict. This agreement would recognize the fact that addicts have two needs: the physiological need to prevent withdrawal symptoms and the psychological need to increase the dose to obtain pleasant effects. This latter need is the need that gets doctors into dose escalation difficulties and requires combating.

Other measures which will be essential in order to keep a close watch on developments will include the careful keeping

of records of the quantities of drugs prescribed in each centre; the prevention of transfer of a patient from one centre to another without full details of doses taken; agreement that no addict will ever be prescribed heroin as an emergency; that only methadone is given to prevent emergency withdrawal symptoms; and agreement that after April 16, 1968 no addict will be prescribed heroin until it has been established that he is in fact taking heroin, and until attempts have been made to evaluate the smallest dose which will prevent withdrawal symptoms. This is particularly relevant to the situation of postaddicts who claim that they have been readdicted and are only too easily prescribed the same high dose that they used to get before they were taken off the drug.

The Future

If all goes well and the heroin problem is contained and then diminished in size, it has to be recognized that there is still a socio-cultural pressure to take drugs. These pressures are worldwide and not just specific to Great Britain.

It is likely, therefore, that this demand will lead to an increase in the taking of other drugs, notably the psychedelics. But the amphetamines which have been widely abused in Japan and more recently in Sweden will need to be watched, as will the barbiturates. In this context it is only realistic to point out that amphetamines are very widely prescribed by medical practitioners in large amounts, often where the real indications for their use are lacking (3), and that Schedule IV of the poisons rules does not provide adequate supervision of recording of prescriptions. Furthermore, the regulations relating to manufacture and distribution are such that it is very difficult to keep track of the drugs and relatively easy for the drugs to be stolen. Much tighter regulations with regard to manufacture, distribution and the recording of prescriptions might well be imperative if escalating misuse of these drugs is to be prevented.

THE CHALLENGE TO BRITISH MEDICINE

The title of this paper includes the phrase "A Challenge to the Practice of Medicine." What are the challenges? Some of these can be enumerated as follows:

- 1) The challenge to physicians in the treatment centres to work together and adopt a reasonably uniform approach. This might mean agreement to give up the com-

plete right to do exactly what the physician wishes in some circumstances.

- 2) The challenge to the biochemist, pharmacologist and chemical pathologist to produce as quickly as possible some method of assessment of drug dosage on a quantitative basis and to develop such test for clinical usage, and also to explore urgently the possibility of a quick qualitative test so that the clinician can be in a position to know the drugs taken during the consultation.
- 3) The challenge to physicians to produce hard data relating to treatment programmes in order that most effective methods can be delimited. This research should not be left to just one or two special research units, but should ideally be by joint participation of all the centres. Follow-up studies are important here.
- 4) The challenge to the epidemiologists and sociologists to produce by careful research, data relating to the causes of drug taking, methods of spread and suggestions relating to prevention.

This country is in a unique and exciting position in relation to drug dependence. An epidemic has developed but the numbers of narcotic users are still small. It would be a tragedy if the opportunities given to us were lost because of lack of interest, lack of coordination, lack of support or rivalries and jealousies. We in this country need answers to many questions relating to drug dependence if we are to be in a position to deal wisely with the problem, and if we are to advise the legislators. The U.S.A. and other countries are looking with interest at our new methods--though with some scepticism concerning prescribing heroin. Let us hope that we are all equal to our task.

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PAPERS PRESENTED BY THE DELEGATES

MANAGEMENT OF OPIUM
AND HEROIN ADDICTION
BY DETOXIFICATION IN IRAN

by

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Over 16 years have elapsed since the beginning of the fight against the abuse of narcotics in this country. Unfortunately, despite all the efforts that have been exerted in this area, an adequate measure of success has not yet been achieved. During the early years of this fight, the results seemed satisfactory. However, due to the schemes of the unscrupulous profiteers and merchants of death throughout the country and the eventual popular use of heroin, particularly among the youth, our great hopes turned to despair.

From the very beginning, the treatment of addicts has also been fully considered. This was first undertaken in Tehran in various centres.

Presently the Addicts' Hospital in Tehran provides 125 beds and admits only volunteers. Since the number of volunteers at any given time exceeds the hospital bed capacity, we are forced to establish a waiting list and hospitalize patients in turn according to the dates of their applications for admission. Upon admission, patients no longer have access to heroin or opium and their detoxification is undertaken by means of 1/1000 methadone solution given orally three times a day. The average dose consists of up to 15 mg. On rare occasions a patient may require higher doses or, because of vomiting, he may require parenteral administration of methadone. Subsequently, the dosage is gradually decreased in such a manner as to allow termination of methadone by the end of one week. Further treatment which may require several weeks consists of prescribing various tonics, vitamins and even sedatives at night, depending on the patient's general health and such problems as severe and bothersome insomnia.

During this period we attempt to treat disturbances, nervous systems, and problems of behavior and mood. As you know, withdrawal from narcotics without medical treatment entails various symptoms which range from mild to severe. These include anxiety, craving for narcotics, increase in speech volume, blinking of eyelids, runny nose, watery eyes, lacrimatic drowsiness and yawning, sweating, chills and gooseflesh, dilation of the pupils, argumentativeness, jerky movement of limbs, poor appetite, muscular pain and pain in bones and internal organs, insomnia, increase in blood pressure and temperature, increase in frequency and depth of breathing, increase in pulse rate, difficulty in maintaining balance, nausea and vomiting, diarrhea, general weakness, drop in blood pressure, rapid loss of weight, spontaneous emissions, disturbances in blood counts (leucocytes and eosinophils) high blood sugar level, pale appearance and other symptoms. During the in-hospital treatment of addicts and because of the use of methadone, severe symptoms are not and should not be seen often. However, severity of symptoms may indicate that the amount of methadone prescribed is not sufficient; and with an increase in dose, symptoms that cause discomfort should disappear.

Clinical experience shows that withdrawal from narcotics is not a difficult problem, and it can be achieved in a number of ways, provided that patients do not have access to narcotic drugs. The major problem, however, lies in the patient's return to the use of drugs. According to the available evidence, the number of persons who relapse after withdrawal and a period of abstinence is indeed very high. Several factors have been considered relevant to addiction in general. These include, for instance, search for the new and novel, imitation, emotional immaturity, curiosity, hedonism, sexual problems, chronic diseases, severe and unbearable pain, lack of wholesome entertainment,

availability of narcotics, particularly frequent contacts with addicts; and even family, economic, political, social and geographic factors. However, it is certain that as long as the fundamental factors in each case for addiction are still present, the addict will neither be willing nor able to function without narcotic drugs.

Likewise there may be a new factor or factors which motivate the addict to seek treatment. Important among these are such factors as poverty, inability to secure narcotics, threat of losing one's job, pressure from parents, spouse or others, embarrassment or shame before one's children, lack of opportunities and availability of the drug. Here again the addict will seek treatment as long as the original motive is there. When this motive is no longer present or effective, the addict will automatically relapse.

Social expectations and attitudes are also relevant. A glance at biographies of addicts and the available statistics shows that the return of the treated ex-addict to his own home and family does not take place very smoothly or easily. Justifiable and unjustifiable lack of trust in him continues to exist. Finding suitable work is a problem and employers and foremen turn their backs to him and do not have any confidence in him. Society does not welcome him. In other words, even when the addict escapes the prison of his addiction, he continues to face social isolation that is accorded to him by the community.

Several different methods for the prevention of relapse have been and are being studied. Some of these methods are obviously fruitless, others are very costly and giving methadone or any other narcotic on a continuous basis does not constitute true treatment. Moreover, combating illicit traffic and the black market entails large expenditures of funds and the allotment of time on the part of many authorities and a waste of human resources. Occasionally it is associated with serious injuries and loss of human life. A great problem in the treatment of narcotic addiction and the prevention of relapse is the availability of narcotic drugs. The best way to combat its illicit traffic and marketing is to prevent planting and cultivation of the opium poppy.

Iran's successful experience in this area in the recent past has proved an outstanding example. Certainly we can all agree that eradicating a single crop, eliminating a single farm or fumigating an infested house will not effectively prevent the growth of harmful insects and parasites or the spread of a dangerous disease. True prevention must be carried out on a larger scale or on a regional basis. Therefore, if the problem of cul-

tivation of the poppy will be solved in the region and if all countries cooperate and do their share in a global effort, we can be more hopeful that the production and distribution of opium and its derivatives will be eliminated eventually. Mankind may thus be saved from this disabling social disease. We must keep in mind that finding and eradicating poppy fields is many times easier than uncovering opium and heroin supplies from their secure hideouts.

AMPHETAMINE AND BARBITURATE DEPENDENCE

by

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The synthetic mood-altering drugs have become serious, worldwide abuse problems. They are not difficult to manufacture, therefore supplies are plentiful. Effects are more predictable than those of crude, natural products, and the price is much less than an expensive item like heroin.

The amphetamines and the barbiturates have been overused by a few people almost since their appearance in the market place, but during the past decade the nature and magnitude of stimulant and sedative abuse have changed markedly in the United States. We can now detect a number of abuse patterns that have emerged.

It is possible to observe a variety of motivational and personality characteristics that predispose to illicit drug use. A fair amount of nonmedical drug taking is an effort at self-treatment. The individual is in some sort of psychological discomfort, and he seeks relief. It is becoming almost socially acceptable to use a mood-modifying agent to avoid or reduce even mild distress. A spectrum of unpleasant emotional states is relieved by the stimulants and sedatives.

There is the demand for relief from tension and depression, and for the escape from intolerable feelings of frustration and unease. This is the dysphoric syndrome consisting of admixtures of anxiety and agitation, irritability and unhappiness, helplessness and turmoil. It is quite understandable that relief from these noxious effects should be sought. To learn how to deal with anxiety is difficult and prolonged. It is so much simpler to seek quick relief in the contents of some bottle.

A second feeling tone for which surcease is sought is the lack of feeling--the inability to feel--what might be called aphoria. This consists of an inability to feel anything deeply, or to believe in some cause. It is an incapacity to enter into deep, meaningful relationships with other humans. These people live separated from life and people by invisible partitions. It is a lonely, painful existence that demands release. Aphoria may be more difficult to bear than dysphoria. Many of these people use psychotropic drugs in the hope that the partition will dissolve, emotional involvement will return, and intimacy will somehow be achieved.

Finally, there is the eternal search for euphoria--the pursuit of happiness--unaware as we are that the happiness of pursuit is more enduring, although more difficult. The long quest for chemical euphoria has a history and a geography of its own as we are learning at this conference.

Oddly enough, both the stimulants and the sedatives can be used to achieve these ends. They can serve as tension reducers, mild antidepressants, disinhibiting agents, and euphoricants. For this very reason, they can induce considerable psychic dependence. Why should the person who cannot enjoy sober existence, and who has been made euphoric or hyperphoric relinquish his magic potion?

THE BARBITURATES

One can identify a number of forms of illicit sleeping pill abuse:

- 1) *Sporadic use of average amounts*--Occasional use is usually in response to pressures to conform to peer group drug taking, or to deal with specific frustrating events. Curiosity and boredom are other stated reasons given for intermittent indulgence. This is a frequent form of juvenile intoxication.
- 2) *Regular use of average amounts*--Taken as an antitension or antianxiety agent, the user attempts to cope with daytime nervousness in this manner. When he attempts to discontinue use of the drug, he experiences jitteriness and discomfort. The discomfort keeps the habit going.
- 3) *Regular use of large amounts*--As tolerance develops, greater quantities of barbiturates are used to procure a "high" or to reduce anxiety. At this point the person is physically addicted, in addition to being psychologically dependent. Sudden discontinuance of the barbiturates would precipitate serious withdrawal symptoms. Withdrawal from a large sedative habit is a medical emergency which requires hospitalization.
- 4) *Regular use of large amounts intravenously*--The person seeking intense euphoria or separation from reality learns that it can be obtained more rapidly and more intensely by dissolving the powder in the capsules and injecting it into a vein. At this point the diseases of the unsterile needle are added to the hazards of barbiturates. The intravenous user is often an emotionally disturbed person.
- 5) *Combined with amphetamines*--It might be assumed that taking amphetamines and barbiturates together would produce a neutralization of effects. This is not so. The combination is preferred by those who find amphetamines too stimulating or the barbiturates too depressing.
- 6) *Combined with or instead of heroin*--Heroin addicts may supplement the effect of the weak heroin available on the black market with "downers." When supplies of heroin are scarce, many heroin users turn to barbiturates to control the withdrawal effects and to provide a degree of sedation.
- 7) *Combined with alcohol*--School children have discovered the potentiating effects of barbiturates plus alcohol in the form of sweet wine. That this pattern of use can lead to overdose is obvious.

- 8) *With suicidal intent*--Barbiturates are the most popular chemical for committing suicide. Suicidologists believe that if these drugs were less available certain suicides could be avoided.

At a Senate Committee hearing investigating juvenile delinquency 4 months ago, I said (1) "If 1966 was the year of acid (LSD), 1968 the year of speed (methamphetamine), and 1970 the year of smack (heroin), then 1972 may well become the year of the downer (sedative)." Obviously, such a statement was a broad generalization. LSD, amphetamines and heroin remain serious adolescent health problems. The point I was trying to make was that barbiturate use is increasing among the very young at an accelerated rate.

I went on to say "Why is this so? For the youngster barbiturates are a more reliable 'high' and less detectable than 'pot.' They are less strenuous than LSD, less 'freaky' than amphetamines, and less expensive than heroin. A school boy can 'drop a red' (seconal) and spend a day in a dreamy, floating state of awayness untroubled by reality. It is drunkenness without the odor of alcohol. It is escape for the price of one's lunch money."

Death following barbiturate misuse may be due to a variety of causes. Unintentional overdose, especially when the drug is taken in combination with alcohol, tranquilizers or other sedatives is well known. Accidental death may occur because of poor judgement and impaired motor functioning. Suicide has already been mentioned. Abrupt withdrawal in barbiturate addicts is accompanied with a definite mortality.

AMPHETAMINES

The following forms of amphetamine misuse are known. The transition from one form to another is common:

- 1) *The occasional use of average amounts*--Large numbers of people use an amphetamine tablet or two to temporarily evade fatigue and sleepiness. Students preparing for examinations, truck drivers attempting to exceed their physiological limits, athletes attempting to excel in their sport, and others may make use of a stimulant. Even at average doses certain hazards can occur. The combination of high body temperature in athletes who are maximally exerting plus amphetamines have been the cause of sudden, unexpected death. Sleep deprivation and amphetamines make judgement and behavior erratic, and the combination can call forth hallucinatory and paranoid episodes.

- 2) *The regular use of average amounts*--Some patients who have been on a course of amphetamines for weight control may have difficulty discontinuing their medication. They feel lethargic and without energy when they try to stop and may continue using the drug long after any thought of losing weight is present.
- 3) *The regular use of large amounts*--It is now quite evident that tolerance to many of the physiological and psychological symptoms is acquired. People who enjoy the lift that amphetamines produce find that larger and larger amounts are needed until hundreds of milligrams a day are consumed.
- 4) *The intermittent use of large amounts intravenously*--One of the more recent developments has been the intravenous injection of hundreds or thousands of milligrams daily for up to a week or more. This is the "speedfreak" phenomenon, and it will be discussed in detail below.
- 5) *Combined with heroin*--In earlier days the combination of intravenous heroin and cocaine was called a "speedball." The modern speedball is heroin and amphetamines. Although cocaine has become much more available in the past 2 years, the amphetamines are much less costly and can mimic the intense euphoria quite well.

Although the intravenous use of amphetamine had taken place earlier in Sweden, 5 years ago the drug subculture in the United States turned to methamphetamine and other amphetamines. I would like to describe the speedfreak phenomenon because it is so novel that the textbooks of pharmacology have hardly caught up with this development (2). Ordinarily, the oral route is used first. Later the crystalline methamphetamine may be "snorted" nasally, or absorbed across other mucous membranes. Eventually, the indescribable "rush" or "flash" which follows immediately upon injecting the material is sought after. The "speed run" continues with three to five reinjections daily for a number of days, perhaps a week. Doses are increased because tolerance develops, and eventually hundreds to a thousand or more milligrams are injected at one time. As much as 5 grams of methamphetamine a day have been used in this manner.

Amphetamine and methamphetamine are not difficult to manufacture, therefore illicit supplies are readily available. It is a two-step process from precursors which are purchasable at chemical manufacturing firms, and the profits are substantial.

The clinical picture of the speedfreak duplicates that of the cocaine "fiend" of 80 years ago except that cocaine is shorter acting and tolerance to cocaine does not occur. He is apt to be irritable, impulsive, overactive, and displays a flight of ideas which often has a paranoid, persecutory quality. Incessant talking, stereotyped movements and notions of great power or suspicion are regularly observed. No desire for food or sleep is felt. Considerable weight may be lost, and careless personal hygiene makes the individual susceptible to infections. Micro-sleeps or naps may occur, but compete wakefulness for days is alleged by many speedfreaks.

Tolerance to the hypertensive effects may be partial or complete. The pupils are dilated, and the reflexes quickened. Muscle tremors, spasms, itching, and a variety of aches and pains often intervene.

Focal paranoid ideas are by no means infrequent. They may neither be verbalized nor acted upon, but an interview will elicit them. They can become overt, and accidental injuries or homicides as the result of acting upon a delusional idea are well known. Panicky or assaultive behavior accounts for at least a few of the bizarre and unpredictable acts of violence reported in the speed subculture.

It is believed that tolerance after a prolonged speed run can become complete for the euphoriant effects. That is, no additional quantity of amphetamine provides a high. Death, directly due to overdose, is infrequent in the tolerant individual. When the refractory point is reached, when supplies run out, or when the individual becomes so disturbed and disturbing that his friends insist that he come down, he "crashes." This is the withdrawal phase which is associated with a prolonged sleep of a day or two, and then ravenous eating. Multiple aches and pains, fatigue and asthenia are present. A severe, apathetic depression develops which is so intense that it has produced a few suicides. This is the dominant and significant feature of the stimulant abstinence syndrome. Reinjection of amphetamines quickly relieves the anergia and depression. It can mark the beginning of a new amphetamine binge.

This high dose, episodic consumption of amphetamines has produced new pharmacological and psychopathological data. For example, the long-taught belief that tolerance to and withdrawal symptoms from amphetamines does not occur, is untenable when we study the person who consumes fantastically large amounts. An incomplete tolerance to the autonomic manifestations develops, although a few instances of circulatory collapse are being re-

ported. Admittedly the abstinence syndrome is unlike the classical narcotic or sedative withdrawal states. It may be called the "central stimulant abstinence syndrome" whose hallmark is an intense psychic and physical depression.

The results of using unsterile material and syringes are identical whether methamphetamine or heroin are injected. Viral hepatitis, for example, is endemic among speedfreaks. In addition, there is evidence of parenchymal liver damage when enormous doses of amphetamine are used. Brain damage in chronic, heavy users is fairly well proven. In animals receiving equivalent amounts, hemorrhagic and cellular neuronal alterations are reported. Japanese investigators during their amphetamine epidemic in the early 1950's reported that 10 percent of autopsied amphetamine abusers demonstrated histopathological brain lesions. A generalized angitis has been found in chronic amphetamine users (3).

Prolonged psychotic reactions are definitely documented from many hospitals serving this population. Whether these represent the precipitation of a prepsychotic individual into a schizophrenic break, or whether amphetamines can themselves induce chronic psychoses remains undetermined. These psychotic states are difficult to differentiate from acute paranoid schizophrenia.

MULTIHABITUATION

A relatively new phenomenon is multihabitation. We described it years ago (4), but it has recently expanded well beyond our earlier assumptions. Multihabitation is the use of a wide variety of drugs together or sequentially, according to the vaporous notions of the user, and the availability of the compound. In a single setting, alcohol, methyphenide, amphetamines, barbiturates, an array of psychedelics and opiates might be sampled. In addition, such oddities as airplane glue, asthmador, nutmeg and freon spray may be tried. In a survey of 30 unselected, heavy LSD consumers we found that they sought out a variety of drugs (see following table). This pharmacologic potpourri can be understood as a sort of chemical anarchy. It reflects the mindless drive for loss of control and distorted consciousness. These people are searching for new combinations with which to bemuse themselves. Anything that dissolves sanity is attractive. The most bizarre concoctions are being ingested or injected, and it is not easy to say when such practices will subside.

MEDIAN NUMBER OF DRUG EXPERIENCES IN LSD AND CONTROL GROUPS

Drug	LSD Group		Control Group	
	Number of Subjects	Number of Experiences	Number of Subjects	Number of Experiences
LSD	30	70	-	-
Marijuana	30	500	6	11
Amphetamines (oral)	18	100	-	-
Amphetamines (sniffed or injected)	15	40	-	-
Dimethyltryptamine (DMT)	9	10	-	-
Codeine cough syrup	8	4	-	-
Barbiturates	7	50	-	-
Psilocybin	6	5	-	-
Heroin	6	4	-	-
Cocaine	6	3	-	-

TREATMENT

I would like to close by saying something about the management of barbiturism, and chronic, high-dose amphetamine use. The detoxification of the barbiturate-dependent person should be done under medical supervision. Otherwise the dangers of delirium, convulsions and collapse are very real. Phenobarbital or a faster acting barbiturate can be used in gradually decreasing doses for gradual withdrawal.

Detoxification from heavy amphetamine use does not represent so urgent a medical emergency. Gradual withdrawal is not necessary. Some sedation may be required. Antidepressants like imipramine are sometimes needed for profound depression.

It is the long-term management of these people that is particularly difficult and frustrating. There is no single treatment applicable to all such patients, perhaps because they have a high degree of personality disturbance. The best results in the United States have been obtained with a closed environment and intensive group therapy. Except for the group leader, all group members are either recent addicts or ex-addicts. The ex-addicts are trained to act as co-counsellors. They are important since they serve as a model of success for the addict. They also know the manipulations and rationalizations that the addicts use to minimize or deny their problems.

We have observed a gradual deterioration in the drug scene during the past 10 years. From the idealistic taking of LSD for religious or personal insights, it has deteriorated into the mindless "shooting up" of enormous amounts of the stimulants and depressants. The situation is not only more widespread, it is more life endangering. Just what the future is of this latest pandemic of drug abuse is unclear at this time.

CONCLUSION

Social and vocational rehabilitation are very important factors in dealing with detoxified amphetamine and barbiturate addicts. If they can be placed in a more gratifying work and family situation, the situation is hopeful. Otherwise relapse is all too common.

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REHABILITATION OF ADDICTS

by

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I appreciate this opportunity to appear before you today to describe our current efforts and future plans in the area of rehabilitation of addicts.

The term "rehabilitation," having both a broad and narrow meaning, creates difficulty in definition; but in general one can say it is "a service which under special guidance provides a variety of measures to correct the patient's disabilities or deficiencies and to supply the needs for further development." The aim of rehabilitation must be to re-educate the individual to live without drugs and to have a normal social life. In fact, rehabilitation begins when a person who is abusing drugs contacts the clinic, and as soon as a doctor accepts an addict as a patient.

For many years we have been concerned with the detoxification period of addiction and have concentrated our efforts in this field. I believe there were many reasons why we neglected other periods of the treatment of addicts:

- 1) The number of addicts was so widespread that one could hardly provide more than detoxification.
- 2) When opium was not available, at least legally, many poor people had to give up smoking opium and there was such a demand that one could only look for short-term detoxification (usually 3 weeks). Still, our hospital for addicts could have the same possibility.
- 3) The popular concept of smoking opium was more or less like having a pint of beer, and one only considered as an addict one who always took the drug. Once a person was not a slave of the drug then he became an ordinary citizen who was entitled to have opium if he wanted to enjoy himself. His brothers could have their whisky and vodka in Western society.
- 4) When the use of alcohol became more acceptable in the middle class and intelligentsia, then smoking opium became less popular. It was considered that if you were Westernized and so-called open-minded, then you would drink alcohol. To drink was a symbol of protest against superstition and prejudice, even in the old days of Omar Khayam. With this background there is no wonder that, just recently, we made plans to have four centres in Yaftabad (Tehran), Rezaieh, Kerman-shah and Meshed, and two centres later in Kerman and Zahedan. The main purpose of these centres is to provide a shelter for a patient who has had some treatment in hospital. These centres are now under construction and I would like to make a suggestion for their function and would be pleased if I could have your advice in this matter.

The patients will stay in these centres for a period of 6 months or more. These centres will help the addict to start learning and working in a new way of life, and an education for self-development must be available. With such development as a goal, the media through which it is to be accomplished could be varied. The former addict may need job training, vocational counseling, correction of physical deficiencies, education and many other things. The evidence available shows the following characteristics of an addict:

- 1) Lack of motivation for alteration of his style of life.
- 2) Bad employment record and often temporary labour.
- 3) Premature termination of education and so a difference between intelligence, potentiality of addiction and the present position. Such a condition will lead to a negative attitude towards a job and society.
- 4) A poor self-concept and inability to cope with frustrations and problems.

These characteristics may well end in inadequate social life. Each of these four centres will be equipped for 500 patients. The Yaftabad centre is being built on a 25,000-square metre site in a village near Tehran. Half of this area, about 12,000 square metres, is for building different departments. The Rezaieh centre is being built on a 100,000-square metre site, and an 80-bed hospital is finished and needs personnel and equipment. The Meshed centre also has an 80-bed hospital, which is ready, and the rest are under construction. The Kermanshah centre is being built on a 50,000-square metre site. There are also 15 detoxification centres, each with 30 beds. I believe these centres will have the following departments:

- 1) *Assessment Unit*: There is an urgent need for assessment of abilities, skills and personality structure of the addict. Such evaluation could be helped partly by tests, but the more reliable way would be through periods of observation in actual educational or vocational settings, and personal relationships between staff and patient. This department should accommodate 50 persons and be staffed by a psychiatrist, a psychologist, a social worker and nurses. In most of the centres this unit is finished.
- 2) *Occupational and Industrial Therapy*: The purpose of this department would be to provide opportunities for employment and training of the addict. In this country there are 16 workshops and facilities for training in farming, weaving (carpets and rugs), sewing handicrafts, car services, electrical machinery, plumbing, iron work, carpentry and other training on the demand of the market should be available. This service would be staffed by occupational therapists or artisans with practical training. Each workshop should have enough nurses.
- 3) *Medical and Physiotherapy Department*: Addiction is a debilitating disease and, during rehabilitation, ad-

dicts may need admission to a medical ward. Electrotherapy, massage and exercises should be applied by physiotherapists. This service would be staffed by a physician with enough beds for medical emergencies, two physiotherapists and enough nursing staff.

- 4) *Department of Recreation and Education:* Addicts are not interested in occupational therapy. In my visits to Poland, Holland and England, I was astonished by poor quality and lack of interest. In my later training in addiction units in London, I was witness to persuasion and group pressure to move these people to work. For this reason it is essential to have enough recreational facilities. The department should be equipped with a gymnasium for summer and winter, and enough space for ping pong, tennis and gymnastics. The physiotherapy department also could provide facilities for hydrotherapy which is needed for addicts. Early morning sport should be participated in by all patients. As a number of artists and persons with artistic aptitude are involved in drug addiction, facilities for plays, music and similar activities should be provided. Special classes should have regular talks by religious authorities, psychiatrists, educationists and physicians. General knowledge and health education, and any subject which might interest the addict should be available. These special classes should include the following:

- a) courses for those interested in drama, art, music, literature and poetry
- b) courses for training in sport, both on an individual and a team basis
- c) outlet for leisure time activities: chess, playing cards, clubs of different interests with guests from outside
- d) classes for formal education to provide better possibilities for further training
- e) sessions dealing with general and mental health, discussion about interpersonal relationships, values in society, vocational guidance and, if possible, suitable group therapy.

In my country people are progressively introduced into the new customs and values and patterns of behaviour. This "socialization" in a country with 2,500 years of civilization is

not easy. There is in every social problem an oriental version well rooted in society for more than a thousand years.

Heroin addiction in this country belongs to a disadvantaged subculture, especially in the intelligentsia, who express frustration and nihilistic attitudes to life as they see it in a wider society.

If we keep our service too institutional minded there is a danger that we will never reach these young drug abusers who mistrust this kind of service, and will never come to the attention of recognized treatment facilities. Many of the addicts who are admitted to Vanak hospital are natives of areas far from Tehran. They could stay for 3 weeks but a 6-month period of rehabilitation is not possible for them. It is necessary to establish a system for some financial reward while they are under training.

I would be very pleased if any distinguished member of this conference would advise and criticize our programme. We can learn from your experience and adapt it to our particular social system and custom.

TREATMENT OF SEDATIVE AND STIMULANT ADDICTION

by

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Sedatives and barbiturates are anxiety-reducing agents, and their sedative and hypnotic action can play a great part in the relief of symptoms of anxiety, suffering, restlessness, excitement, sleeplessness and restoring social adaptation. These drugs are often used both for relieving grave emotional disturbances of the psychosis and the less serious ones of a neurotic state.

Barbiturates and sedatives are cortical depressants of the central nervous system (C.N.S.). The brain adjusts to them and when they are stopped the patient is left for a period more anxious and restless than before they were started. Barbiturates are anticonvulsants. The brain adjusts to them and when they are stopped the patient is left for a period with an increased liability to fits.

Stimulants with a strongly stimulating effect on the C.N.S. produce euphoria and increase alertness and wakefulness, give excitement, with a feeling of increased muscular and mental strength.

The question of addiction to sedatives and stimulants in Iran is not yet regarded by the health authorities as a problem. It is extremely difficult to estimate the extent of sedatives and stimulant dependence in the general population of Iran. Some experts have suggested that it might be on the order of 18 to 20 per million people. The abuse of these drugs is also inadequately documented. From the year 1955 a gradual rise in medical prescriptions of sedatives began, but even so, it remains mostly within very moderate levels. At the same time, consumption of sleeping pills has risen sharply around the world in recent years.

Barbiturate prescribing doubled in the U.K. between 1953 and 1959, and doubled in Czechoslovakia between 1958 and 1968; hypnotics of all kinds doubled in use in Australia from 1962 to 1966, while in the U.S.A. retail sales of sedatives and tranquilizers increased eight times as fast as other drug sales between 1952 and 1963.

There is some evidence that the total number of people who abuse sedatives has decreased. We have no stimulant addicts and abusers at all, because at the present stage stimulants are not available in this country even on medical grounds.

The number of sedative addicts requiring inpatient treatment is estimated to be 2 to 3 per million people. During recent years very few cases of sedative addicts have been reported from hospitals and outpatient clinics. During the last 2 years I personally saw two cases of barbiturate/alcohol mixture addicts. In our society sedatives are seldom used alone or taken continuously. The sedatives are generally combined with opium, cannabis and alcohol to mitigate either extreme stimulant or depressant effects.

Doctors, nurses and other medical professionals in Iran are in a vulnerable position in relation to the field of sedative dependence and abuse in this country.

The sedatives which have been abused in Iran are as follows:

- | | |
|-------------------------------|-------------------------------------|
| 1) Meprobamates | } equanil
miltown
pertranquil |
| 2) Diazepam (valium) | |
| 3) Chlordiazepoxide (librium) | |

- 4) Quinalbarbitone (seconal)
- 5) Nembutal
- 6) Glutethimide (doriden)
- 7) Sodium amythal
- 8) Luminal gardenal
- 9) Chloral
- 10) Paraldehyde

Before starting on another topic, it is better to give a very brief and short account of the features of chronic intoxication and withdrawal symptoms of addiction to sedatives and stimulants.

Chronic intoxication with sedatives shows the following features: ataxia, dysarthria, slurred speech, nystagmus, poor judgement, impairment of consciousness, difficulty in grasp and concentration, a tendency to be sluggish and drowsy, impairment of mental functions and sometimes toxic psychosis.

Chronic intoxication with stimulants shows the following features: nervousness, insomnia, tremor, irritability, anorexia and loss of weight.

In sufficiently high doses, schizophrenic-like psychosis with hallucinations occurs. Sudden suspension of drugs produces marked somnolence, apathy, inertia and depression.

The abstinence syndrome with sedatives includes anxiety, tremor of hands and fingers, involuntary twitching of muscles, progressive weakness, dizziness, insomnia, vomiting and delirium, hyperpyrexia and grand mal convulsions.

Treatment: More recently, both in the field of general psychiatry and drug dependence, it has been realized that it is impossible to separate concepts of treatment from concepts of prevention on one hand, and the concept of rehabilitation on the other hand.

The W.H.O. Expert Committee on Drug Dependence in their Eighteenth Report No. 460 states: "In relation to drug dependence, the major goals of both prevention and treatment, including rehabilitation, are, for the most part, the same and largely overlap."

Treatment of sedative and stimulant addiction includes the withdrawal stage, treatment of the early abstinence phase and an attempt at rehabilitation. During these three stages of treatment we have to deal with three main problems: 1) physical, 2) psychological and 3) social. Although a great deal has been written and said about the physical aspect of treatments, it is, in fact, a relatively minor matter.

Withdrawal of the drug must be carried out in some institutions and hospitals:

- 1) To allow strict observation
- 2) Because of the liability to severe collapse which so frequently occurs following reduction of the drug
- 3) Because the drug-dependent patients are not frank and honest and can never be relied upon.

Unless the physical condition has deteriorated, abrupt withdrawal is to be preferred, except withdrawal of barbiturates, which in addicts commonly causes epileptic fits, even status epilepticus.

Withdrawal should, therefore, be slow, gradual and covered by anticonvulsant drugs. It is better to approach the matter gently by asking questions about the general health and social situation. In reaching a correct diagnosis, an account of the patient's past and recent history from a member of the family is valuable and prevents the doctor from thinking solely in terms of epilepsy, or from attributing the attacks of altered behaviour to hyperinsulinism.

Any patient presenting episodes of altered behaviour must be suspected of taking drugs. It is difficult to be sure which sedatives or hypnotics are being taken to excess, indeed several drugs may be used together. The E.E.G., however, shows characteristic abnormalities following not only consumption of barbiturates, but of many other hypnotics and sedatives. In the E.E.G. there is visible drug-induced fast activity at about 18 cycles per second, most prominent over the front of the head (Oswald, August 1970).

Everything that has been said or written about the treatment of addiction shows that it is beset by difficulties on all sides. Whereas some doctors believe that nothing could be worse than to gather addicts for treatment in one place, others have stressed the difficulties which arose when addicts came into contact with patients suffering from other psychiatric disorders. In spite of these difficulties, most doctors in Iran agreed that with some patients, withdrawal, treatment and psychotherapy could only be successfully carried out in hospitals which have been organized for addicts.

Occasionally people of previously good personality, who have perhaps become depressed in recent months, are found to be taking large doses of hypnotics by day as well as by night, but the great majority of the gross abusers of hypnotic drugs in this country are people of neurotic or psychopathic personality.

One will often get a history of financial debts, unwise use of alcohol, a broken home, unstable personality and with poor and superficial social relationships. It is, therefore, only realistic that the doctor should adopt limited goals.

General treatment goals and techniques have been discussed in earlier reports of this seminar. I am not going to repeat them again in detail. Generally speaking, the goal is to correct as far as possible personality difficulties, to give the patient a sense of security, self-reliance and self-confidence and a sense of responsibility towards himself, his family, friends, and towards the community--to replace his sense of anxiety and insecurity with a sense of well being. At the same time, a constructive attempt to strengthen poor insight and weakness of personality must be made.

The ideal goal with total abstinence, gainful employment, satisfactory social and personal adjustment, and emotional stability is seldom achieved.

The presentation by Dr. Şükrü Kaymakçalan, Department of Pharmacology, Medical School of Ankara University, was based on two of his earlier papers describing work done in Dr. G. A. Denean's Laboratory in the Southern Research Institute, Birmingham, Alabama, supported by a grant from the United States Public Health Service. Summaries of both papers follow.

SOME PHARMACOLOGIC PROPERTIES OF SYNTHETIC

DELTA - 9 - TETRAHYDROCANNABINOL (THC)

- 1) Using hot-plate or phenylquinone or acetic acid-induced writhing tests, it has been shown that THC has an analgesic effect in mice, rats, cats, dogs and monkeys.
- 2) The ED₅₀ of analgesic effect of THC is almost twice that of morphine, but lasts much longer.
- 3) THC potentiates morphine actions both in rats and cats.
- 4) THC produces hypothermia in rats, cats, dogs and monkeys.
- 5) THC reduces the iodine uptake of thyroid glands in rats.
- 6) The acute toxicity of THC in laboratory animals is very low. In monkeys 0.05-0.1 mg/kg of THC produces some pharmacologic effects, but in one case 60 mg/kg THC did not kill the monkey.
- 7) Treatment with SKF 525-A does not increase, or pretreatment with phenobarbital does not decrease, the analgesic effect of THC in rats. On the other hand, hepatectomy strongly potentiates the action of THC. Therefore, it was concluded that, at least in rats, THC itself, but not its metabolites, is the active substance.

TOLERANCE AND DEPENDENCE TO SYNTHETIC DELTA-9-TETRAHYDROCANNABINOL (THC) IN LABORATORY ANIMALS

- 1) Daily administration of THC produces tolerance in less than one week to the following effects in different mammalian species:
 - a) Rats: Analgesia, hypothermia and anti-thyroid effects
 - b) Dogs: Ataxia and general depression
 - c) Monkeys: Ptosis and docility
- 2) Tolerance to the analgesic effect after a single injection of THC lasts more than one month in rats.
- 3) THC-tolerant rats present a cross-tolerance to morphine.
- 4) Six naive monkeys were prepared for i.v. self-administration of THC. Automatic injections were delivered every 6 hours for one month at doses increasing from 0.1 to 0.4 mg/kg. When injections were discontinued, all monkeys showed abstinence signs.
- 5) After discontinuation of automatic injections, two of the monkeys initiated and maintained self-administration of THC. In one monkey self-administration of cocaine was replaced by THC, and this animal also continued to self-administer THC. These three animals showed a more severe abstinence syndrome after prevention of self-administration of THC.
- 6) In all experiments abstinence signs appeared at 12 hours and lasted 5 days. They were: yawning, anorexia, piloerection, irritability, scratching, biting and licking fingers, pulling hair, tremors, twitches, shaking, masturbation and sometimes ejaculation, sitting in abnormal positions, photophobia and apparent hallucinations (staring in circles, slapping at the cage wall, grasping as if catching flies).

TESTING FOR DRUG USE:

WHY, WHEN, AND WHAT FOR ?

by

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INTRODUCTION

The use of diagnostic tests and procedures is not new or even exciting. Tests for physiological or psychological malfunction are performed routinely and results therefrom utilized in the diagnosis and subsequent treatment of various disease states. Tests for pregnancy, bacterial or fungal infection, blood pressure, cardiovascular function, neurological, liver and kidney function span the spectrum from simple to rather complex procedures.

In few, if any, of these areas do the results of tests have the sociological, behavioral, psychological and medical implications as tests performed to detect illicit use or misuse of drugs (except for pregnancy). Although the same urine and blood sample may be used to measure heroinism, diabetes or prothrombin time, the former has somehow gained a mystique not accompanying other pathological states.

Tests done for the sole purpose of detecting drug abuse, whether performed by the physician during examination or by an outside laboratory, are really no different in design, execution or value from any other test. However, as I shall discuss later, intelligent use of the data provided by tests for illicit drug use is of paramount importance prognostically as well as diagnostically.

Before discussing drug testing advantages and disadvantages, it should be noted that some drugs of abuse interfere with some routine diagnostic tests. This is especially important since it has recently been noted that these interferences can lead to diagnostic test results which are not valid (1, 2).

Table 1 shows some usual laboratory tests which are most subject to interference by commonly abused drugs.

Table 1. DRUGS AFFECTING LABORATORY VALUES

	Increased	Decreased	Interference
Serum Amylase			
Morphine	•		
Codeine	•		
Serum Glutamic Oxalacetic Transaminase (SGOT)			
Opiates	•		
Salicylates	•		
17-Ketosteroids			
Meprobamate			•
Chlordiazepoxide			•
Hydroxazine			•
Chlorpromazine			•
Serum Uric Acid			
Aspirin (ASA)		•	
Blood Sugar			
Amphetamine (poisoning)		•	
Chloroform		•	
Carbon Tet.		•	
Cholesterol			
Salicylates		•	
Vitamin A	•		

As you can see, the opiates, barbiturates, aspirin and solvents are mostly responsible. Consistently abnormal serological test results in a patient who ostensibly appears healthy should raise the clinical index of suspicion. It may be that your patient with elevated SGOT and Serum Amalyase levels has a drug abuse problem.

FALSE POSITIVES AND NEGATIVES

The terms "false positive" and "false negative" are familiar ones. However, in a drug treatment and rehabilitation program or in some office practices, they are more important than they appear at first glance. The patient population of any treatment program realize that their continuation in a program often rests upon test results. The false negative is to some extent less important than the false positive. The former allows the patient to cheat, since if he has taken an illicit drug, the patient will remain undetected and will have beaten the system. Too many of these results can be damaging to a treatment program as the patients soon realize that they can often take drugs, go undetected and remain in a program. Since most programs offer some immunity from the law or the bill collector and afford a certain degree of respectability, the patient has the best of both worlds.

The false positive is damaging both to the program and to the patient. The morale of the particular patient in question, as well as other members of a program, is rapidly undermined if a false positive test is used as the basis of either confrontation, dismissal from a treatment center or as a basis to begin legal proceedings against a patient.

When false positives and negatives are most likely to occur will be discussed under each specific methodology.

TESTING METHODS

In the office or clinic, taking a good history is still one of the most important procedures. A history can be considered a series of tests done in an office rather than in a laboratory.

Table 2 represents a number of observations helpful in the initial examination (test). Each observation can be considered a qualitative test for a *class* of drugs. Although it is often difficult to pinpoint a specific drug using the criteria from this chart, information gleaned from the observations cited here are often helpful in the initial examination of a person suspected of abusing drugs.

**Table 2. COMMON SIGNS AND SYMPTOMS OF PATIENTS
WITH MIND/MOOD ALTERING DRUG TOXICITY**

Signs and Symptoms	Sedative Hypnotics	Narcotics	Halluci- nogens	Stimu- lants	Solvents	Tranquil- izers	Alcohol
<i>Coma in overdose</i>	○	○			○	○	○
<i>Convulsions</i>	*		○			○ *	○ *
<i>Depression</i>	○		○	*		○	
<i>Hallucinations</i>	○		○	○			○ *
<i>Agitation (restlessness)</i>	* ○	*	○	○	○	○ *	*
<i>Aggressive behavior</i>	○		○	○			○
<i>Paranoia/Panic</i>	*		○	○	○		○
<i>Psychosis</i>	*	○	○	○	○		○
<i>Disorientation</i>	○	○	○	○	○		○
<i>Ataxia</i>	○	○	○	○	○	○	○
<i>Pain masking</i>	○	○	○	○	○	○	○
<i>Parkinsonism</i>						○	
<i>Slurred speech</i>	○	○			○	○	○
<i>Lacrimation</i>		*			○		○
<i>Nystagmus, lateral</i>	○						
<i>Pupils</i>							
<i>Pinpoint</i>		○					
<i>Dilated</i>		*	○	○			
<i>Normal</i>	○				○	○	
<i>Running nose</i>		*			○		
<i>Jaundice</i>	○	○		○	○	○	○
<i>Skin rash</i>	<i>Bromides</i>			○			
<i>Needle tracks</i>	○	○		○			
<i>Gooseflesh</i>	*	*					*
<i>Respiratory depression</i>	○	○			○	○	○
<i>Tachycardia</i>		*	○	○			○ *
<i>Cramps</i>	*	*		*			*
<i>Fever</i>				○			*

Seen in acute phase

○

Seen in withdrawal phase

*

NOTE: This table is intended to list common signs. It does not preclude rare exceptions.

This chart is reproduced by permission of Dr. David Smith of the Haight-Ashbury Free Clinic, San Francisco, California. The column on alcohol was added by Dr. G.G. DeAngelis.

Drug history taking is one procedure which is subject to a great deal of abuse by the patient, the physician and in some cases the staff of a hospital or clinic. In one study, it has been demonstrated (3) that judgements of heroin use made on the basis of interview data were inaccurate 70.6 percent of the time when compared to urinalysis of the same patient. Likewise, 51.7 percent and 19.3 percent of judgements relating to barbiturate and amphetamine abuse were also wrong. These data are true regardless of the professional acumen of the interviewer. However, in a recent paper (3a) it was pointed out that in some cases self-reports of amphetamine and barbiturate use by patients enrolled in a methadone maintenance program demonstrated a higher incidence of use than urine results indicate. By contrast, heroin use was lower in self-reports than urinalysis. The meaning of this is unclear except for the fact that urinalysis may still be as much an art as a science. It is also possible that in some cases patients were overrepresenting their illicit drug use, although reasons for this are not obvious. Further studies are needed to clarify this problem since literature reports in this area are conflicting.

Physicians and house staff are also susceptible to over-interpretation of data provided by the patient during the interview. A safe rule to utilize is that physical signs and symptoms are probably as valid as usual for assessing body functions but that information given by the patient regarding use, incidence, side effects and legalities should be accompanied by a good deal of skepticism by the examining physician.

Observations which can be misleading include pupillary findings--constricted pupils can be caused by either narcotic analgesics or barbiturates, although fixed dilated pupils associated with coma are found at later stages of barbiturate intoxication and may be associated with severe overdose.

Alcoholic breath may be due to a quick rinse to mask barbiturate intoxication, sweet breath (acetaldehyde-like) may be found in a diabetic, but is also caused by chloral hydrate, while halitosis is often found among amphetamine abusers. I should like to point out, however, that not all patients presenting with bad breath are amphetamine abusers, but may be in need of either dental work or a bottle of mouth wash.

The nalorphine test for narcotic analgesics was described by Terry and Braumoeller (4) and developed into a test for addiction by Wikler, Isbell and Frazer (5).

There are two dose ranges over which this compound (nalorphine) can be utilized as a testing method. At 2 to 3 mg subcutaneously, the usual response is dilation of pupils in an individual actively using narcotics and constriction of an ab-

stinent person's pupils. There may also be changes in respiratory rates which parallel pupillary findings in some individuals at this dosage.

At higher doses nalorphine precipitates almost immediate withdrawal symptoms in a person dependent on narcotics. In some states, Illinois and California, for instance, this test has legal status, and a negative test is one of the bases for fulfillment of parole conditions.

If the nalorphine test is utilized, adherence to the following rules will enhance its validity:

- Do not perform this test without the verbal and written consent of the patient
- Do not try to diagnose addiction to meperidine (demerol) with this test.
- Do not expect a positive test if patient is *currently* abstinent (not addicted).

With recent advances in testing methodology, the use of the nalorphine test in all but a few cases is questionable. As with a number of bedside tests, it is qualitative at best and the results should be considered circumstantial evidence.

In addition, the nalorphine test is time consuming and requires constant lighting capabilities which may not be generally available.

The nalorphine therapeutic/diagnostic maneuver which is utilized when treating a suspected or true heroin or methadone overdose is a *bona fide* and very important procedure. When used as a primary therapeutic tool, the peripheral test capability discussed above is a useful and adjunctive way to obtain corroborative evidence of opiate abuse.

It is important to note that with methadone overdose it is necessary to administer nalorphine for the time span covered by the duration of action of methadone (24-36 hours). Nalorphine (or the newer drug nalcron) treatment in these cases is the method of choice for treatment of the overdose and should not be considered a test procedure. The observation of pupillary and respiration changes accompanying the patient's recovery are the same as when nalorphine is administered solely as a testing method, but the rationale for its use is entirely different. Reference 6 cites advantages and disadvantages of nalorphine when utilized during the overdose syndrome.

The reliability of the nalorphine test has been compared to chemical methods and has been found to give comparable results approximating 60 to 65 percent of the time (4).

Naloxone has recently been used in efforts to increase the reliability of the pupillary test method (5a). Naloxone when used alone gave somewhat more reliable results than nalorphine when administered to prisoners given known amounts of opiates. Naloxone (.4 mg) in combination with nalorphine (3.0 mg) gave substantially better results than either agent used alone. It should be noted that although the sensitivity of the method may be increased using this combination, the operational difficulties alluded to above still limit the utility of this test.

Phenothiazine abuse can be detected by a fast, reliable office test. The FPN Universal Test was described by Forrest, Forrest, and Mason (7) [sic] and can be performed in the office or clinic. The test consists of adding ferric chloride, perchloric acid and nitric acid to urine and waiting for rapid color development. The reliability has been cited as good with few if any interfering substances.

One test which is specific for the morphine abstinence syndrome and which can be used clinically or in a hospital is the Himmelsbach Test. This test was developed over 30 years ago and is still in use today at the Addiction Research Center in Lexington, Kentucky for predicting abuse potential of new drugs. Table 3 shows the Himmelsbach point system for scoring this syndrome.

Insomnia, diarrhea and drug-seeking behavior are not on the Himmelsbach list but may also be demonstrated by the patient in withdrawal.

The total points ascribed to any patient can be correlated with how such a patient feels.

0 - 20 points--mildly ill

20 - 30 points--moderately ill

30 - 35 points--severely ill

When patients are asked "How sick do you feel?" (9) they usually supply answers in concert with the above scale. In general, 25 points and above result in a patient who feels miserable.

Table 3. HIMMELSBACH POINTS

Signs and Symptoms	By day		By hour	
	Points	Limit	Points	Limit
Yawning	1	1	1	1
Lacrimation	1	1	1	1
Rhinorrhea	1	1	1	1
Perspiration	1	1	1	1
Mydriasis	3	3	3	3
Tremors (twitching)	3	3	3	3
Gooseflesh	3	3	3	3
Anorexia (40% decrease in caloric intake)	3	3		
Restlessness	5	5	5	5
Emesis (each spell)	5		5	5
Fever (for each 0.1°C rise over mean addiction level)	1		1	10
Hyperpnea (for each resp./min. rise over addiction level)	1		1	10
Rise in A.M. systolic BP (for each 2 mm Hg over mean addiction level)	1	15	1	10
Weight loss (A.M.) (for each lb from last day of addiction)	1			

There are various modifications of this test. Table 4 is a modification for clinical use developed by Sapira and MacDonald.

For the most part, test results for drugs of abuse will be obtained from laboratories especially equipped to analyze urine, blood or tissue.

Table 4. MODIFICATION OF THE HIMMELSBACH
 SYSTEM FOR CLINICAL USE

Yawning
Lacrimation
Rhinorrhea
Perspiration
Twitching
Gooseflesh
Anorexia
Restlessness and irritability
Diarrhea
Increase in resting respiratory rate
Mydriasis
Drug-seeking behavior

Not all drugs of abuse can be detected in urine. Table 5 lists a classification of common drugs of abuse.

Table 5. COMMON DRUGS OF ABUSE

- I. NARCOTIC ANALGESICS - heroin, morphine, codeine, meperidine (demerol), propoxyphene (darvon), metharone
- II. SYMPATHOMIMETICS - amphetamine, methamphetamine, dextroamphetamine, cocaine
- III. HYPNOTIC-SEDATIVES - barbiturates, glutethimide, phenothiazines
- IV. *HALLUCINOGENS - lysergic acid diethylamide (LSD), Cannabis sativa (marihuana), mescaline

* In general, members of Class IV cannot be detected in blood or urine at present, due mainly to the very small quantities taken.

The need for rapid, accurate, low cost tests capable of detecting opiates in the urine first became evident during the occupation of Japan after World War II. During this time large numbers of American servicemen began utilizing heroin and other opiates. Prior to that time opiate content of urine was measured by purifying various urine extracts and subjecting them to color

tests performed on a spot plate. When crystalline, pure alkaloids (opiates) were used, characteristic colors were obtained. However, the reagents used invariably contained sulfuric acid, and this resulted in much charred material when impure residues from urine were tested. Colors were different or impossible to see and the sensitivity of the method was poor. False positives and negatives were often obtained.

Paper chromatography was subsequently utilized, and proved to be an effective method for detecting small quantities of narcotics in urine. Using this method morphine was separated from codeine for the first time as well as from most interfering substances in urine.

Utilizing this methodology, codeine was found to be transformed into morphine *in vivo*. Consequently, any test to prove that morphine or heroin were administered must test for codeine to be medico-legally acceptable. In addition, heroin is converted very rapidly to morphine and one will not find heroin in the urine. This is true even after analyzing immediately after intravenous injection of pure heroin.

While the sensitivity and accuracy of urinalysis were improved utilizing paper chromatography, other criteria for its general use were absent. Mule (9) has discussed the requirements of a general applicable testing methodology. These are listed in Table 6.

Table 6. URINALYSIS TESTING METHODOLOGY

- SPECIFICITY - Drugs separated by groups (narcotic analgesics, barbiturates, psychotomimetics, "tranquilizers," amphetamines) and identified.
- RAPIDITY OF ANALYSIS - Entire procedure from acquisition of the biological sample to recording of the results should not exceed 24 hours.
- SENSITIVITY - Able to detect the presence of the administered drug or metabolites at least 24 to 48 hours following drug usage.
- SIMPLICITY - Methods require skills or training normally achieved by a laboratory technician.
- COST - The cost must be kept to a minimum. However, in the final analysis the cost should be evaluated in terms of the cost to society should the tests not be performed.

Specificity implies that drugs can be separated into groups or classes (narcotic, analgesic, amphetamines, barbiturates, hallucinogens). More than one analytical test is required for medico-legal purposes. The entire process, from acquisition of the sample to analysis, should not take more than 24 hours. Therefore, *rapidity* of analysis is important when monitoring patients. *Sensitivity* implies that the test utilized can detect the presence of administered drugs or metabolites 24 to 48 hours following usage. The *skills required* to perform the tests should require not more than the skills of a qualified laboratory technician and the *cost* should be kept to a minimum.

While no technique presently available meets all established criteria, thin layer chromatography (TLC) comes closest, although even it is subject to a number of limitations. *Specificity* (discussed above) is adversely influenced by a number of variables--the particular extraction technique applied, the solvents used, the number of extractions performed, the humidity of the chromatography chambers, the quality of the thin layer plates used and the visualization procedures used. *Specificity* may be enhanced by multiple extraction at different pH, spotting two plates from the same sample and performing two dimensional chromatography (9a) with different development solvents. All of these steps take additional time and add to the cost of analysis. *Sensitivity* is also adversely affected by experimental conditions, apparatus and methodology used (9a). In spite of these limitations and conditions, urinalysis has become an important tool in drug abuse programs.

The value of urinalysis as a testing method of monitoring drug abuse was first utilized on a large scale by Dole in New York City (10). His procedure utilized cation exchange resins to absorb the drugs from urine and then eluted with a series of buffer-solvent systems. Utilizing this method, small amounts of narcotics, amphetamines and some tranquilizers and barbiturates were detected. Jaffe (11), using ion-exchange resin impregnated paper, and more recently Montalvo, have reported increased sensitivity in some cases over that originally reported by Dole. However, Montalvo points out that in some cases, Dole's original data are difficult to duplicate. He suggests that the more realistic limits of detection are as listed in Table 7.

Mule (13) has recently presented data which cite improved sensitivity by using extraction rather than ion-exchange methods.

Table 8 lists a number of testing facilities in the eastern half of the United States. Included are data which may be helpful when deciding where to send samples.

Table 7. LIMITS OF DETECTION

Drug	Dole	Montalvo	Mule
Morphine	0.5 mg/ml	0.4 mg/ml	0.2 mg/ml
Methadone	1.0 mg/ml	6.0 mg/ml	1.0 mg/ml
Quinine	*	0.10 mg/ml	0.10 mg/ml
Cocaine	1.0 mg/ml	*	*
Secobarbital	5.0 mg/ml	*	1.0 mg/ml
Phenobarbital	5.0 mg/ml	4.0 mg/ml	1.0 mg/ml
Pentobarbital	8.0 mg/ml	*	1.0 mg/ml
Amphetamine	4.0 mg/ml	8.0 mg/ml	1.0 mg/ml

* No weight given.

In every class of compounds, there are considerations to be made prior to testing a sample and after the results are delivered.

- A negative test implies that a subject has taken less than 10 mg of heroin (or morphine) in the past 24 hours (14).

Davidow has shown that morphine can be detected for as long as 2 days after administration of 15 mg morphine sulphate.

Clinically, it is impossible to distinguish between a large amount of drugs taken occasionally or a small amount of drugs taken regularly. Thus, the urinalysis data, which may be accurate and precise, in no way help determine the nature of the patient's involvement with opiates.

In the U.S.A. quinine is often utilized to dilute heroin and is easily detected during urinalysis. It is detectable for a period of 3 to 5 days and may be present when morphine is absent. While the presence of quinine may be suspicious, a positive test for quinine alone is not conclusive proof that the patient is using heroin or morphine. Quinine may be ingested in tonic water and some over-the-counter medications (10).

Table 8. TESTING FACILITIES

Lab	Location	Cost		Hydrolysis of Urine	Time	Drugs Tested for
Cybertek	200 Express St. Plainview, N.Y.	\$3.25	> 50 samples/wk.	No. Board of Health does not require	2-3 days	Opiates Barbiturates Amphetamines
		\$3.50	< 50 samples/wk.			
Auto	294 Mass. Avenue Arlington, Mass.	\$3.50	> 50 samples/wk.	Yes	3-5 days	"
		\$3.75	< 50 samples/wk.			
		<u>One Drug</u>				
		\$2.00	> 50 samples/wk.			
		\$2.50	< 50 samples/wk.			
Beddinger & Schlissinger	3rd Avenue & 10th New York, N.Y.	\$3.50	> 70 samples/wk..	No	3-5 days	"
		\$3.75	< 50 samples/wk.			
		<u>One Drug</u>				
		\$3.00	> 50 samples/wk.			
Hines	San Francisco California	\$3.50	> 50 samples/wk.	No	3-5 days (in area)	"
		\$3.75	< 50 samples/wk.			
		<u>One Drug</u>				
		\$3.00	> 50 samples/wk.			

Bio-Metric Affiliated Research	42-05 27th St. L.I.C., N.Y.	\$4.00 \$4.75	> <	50 samples/wk. 50 samples/wk.	Yes		"
Biochemics	127 Hempstead Tpk. Elmont, N.Y.	\$4.50 \$5.00	> <	25 samples/wk. 25 samples/wk.	Yes	3-4 days	"
Kings County Research	705 Sixth Avenue Brooklyn, N.Y.	\$4.00 \$6.00	> <	50 samples/wk. 50 samples/wk.	No	5-7 days	"
Central Biological	63 Wantagh Ave. Levittown, N.Y.	\$5.00 \$10.00	> <	50 samples/wk. 50 samples/wk.	Yes	2-4 days	"
Lakeville	2035 Lakeville Rd. New Hyde Park, N.Y.	\$ 7.00 \$10.00	> <	50 samples/wk. 50 samples/wk.	Yes	3-5 days	"

When properly done, thin layer chromatography may be very suitable for detecting barbiturate use. Many requests for barbiturate analysis are made when patients are comatose. Historically, comatose patients were usually suspected of barbiturate overdose. However, since the introduction of meprobamate (equanil), glutethimide (doriden) and newer agents, this assumption is no longer valid.

Consequently, a negative barbiturate analysis does not exclude a chemical agent as the cause of coma (15).

Chromatographic tests for amphetamines are more difficult to do than the other classes of compounds. False negatives are often reported. When amphetamine use is suspected and confirmation is necessary, a second method of analysis, such as gas liquid chromatography, should be utilized.

GLC chromatography employs a totally different methodology than TLC. While the sensitivity of this method is as great or greater than thin layer, it has been until recently more time consuming.

GLC is, however, useful as a cross-checking tool and as such has been used to verify the presence of drugs of abuse in urine and blood samples. This is especially true when testing for amphetamines and meprobamates. The levels of detection for these drugs are 0.1 mg/ml and 0.005 mg/ml respectively (16, 17).

On a per sample basis, the rapidity of analysis--one hour--afforded by GLC is important, especially in overdose cases. This is pertinent, useful information in poisoning cases. For instance, 464 meprobamate poisonings occurred recently within a one-year period. This represents more poisonings than caused collectively by pentobarbital (nembutal), secobarbital (seconal) or the phenothiazines reported for that same year (17). GLC is one of the most sensitive techniques for detecting meprobamate and its utility in this type case is obvious.

The newest technique for analyzing urines of drug abusers is still in field trial status. The FRATTM (free radical assay technique) system is currently being test marketed by Synva Associates and has been field tested by Dr. Avram Goldstein in Palo Alto, California, by the U.S. Army in Vietnam, and is currently in use by a number of laboratories in the United States.

This testing method utilizes antibody-antigen in combination with stable free radical and electron spin resonance (ESR) techniques which allow development of very fast, very inexpensive, accurate sample testing. What the system offers is shown in Table 9.

Table 9. FRATTM SYSTEM

- AN EXCELLENT METHOD for drug abuse detection and screening--in addiction treatment programs, for employment applicants, etc.
- NO CHEMICAL PROCEDURES--can be done by unskilled personnel
- IMMEDIATE (less than one minute) feedback of results
- GREATER SENSITIVITY than TLC methods
- HIGHLY SPECIFIC (employs antibodies) minimizing false positives

At the present time, the system is limited to opiate detection. Reagents to detect barbiturates and amphetamines have been developed, but are not yet generally available. FRAT does not distinguish between drugs in a given class of compounds. It simply "reads" opiate, barbiturates or stimulants.

The sensitivity of the FRAT system has recently been demonstrated (9a). In a recently completed experiment single doses of 2.5 and 5.0 mg/70 kg of heroin were administered intravenously at weekly intervals in random order to 10 volunteer subjects. All urine samples were collected for a one-week period following drug administration and subsequently combined into approximately 8-hour aliquots for analysis. All samples were analyzed by organic solvent and ion-exchange resin impregnated paper extraction, with and without acid hydrolysis, followed by TLC with iodoplatinate spray. In brief summary, nearly 100 percent of the samples for the first 8 hours following both doses were positive by most tests. By 16 to 24 hours nearly all samples were negative by all tests with the exception of ion-exchange extraction with hydrolysis. With this test the low dose of heroin showed about 60 percent positive at 16 hours and 25 percent positive at 24 hours; subsequently most samples were negative.

Following the high dose of heroin, ion-exchange extraction with hydrolysis resulted in approximately 85 percent positive at 16 hours, about 50 percent positive at 24 and 32 hours and subsequently mostly negative. The same samples were also analyzed by the FRAT system and the results were very similar to

those obtained using ion-exchange extraction techniques with hydrolysis and TLC. A slightly higher percentage of positives was found from 32 to 64 hours with FRAT.

A summary of the specifications of this testing method is outlined in Table 10.

Table 10. SUMMARY OF TENTATIVE SPECIFICATIONS

TIME REQUIRED per separate test.....	Less than one minute
NUMBER OF SAMPLES/per 8-hour day.....	Over 500
REAGENT COST per test.....	\$1.00 - \$1.50
SYSTEM COST	
Semi-Automatic System	
Lease option.....	Straight lease or lease dependent on volume of tests
Outright purchase.....	Less than \$12,000
Fully Automatic System	
Lease option.....	Straight lease or lease dependent on volume of tests
Outright purchase.....	Cost to be announced later
AVAILABILITY	
Semi-Automatic System.....	Late 1971
Fully Automatic System.....	Soon thereafter
SENSITIVITY	
More sensitive than TLC methods. Preliminary studies demonstrate, for example, that FRAT can detect previous heroin use for at least one day longer than TLC methods.	

Once routine testing has been initiated, the question of how often urine samples should be taken becomes important.

Urinalyses are expensive (\$2 to \$10) and time consuming. If a testing schedule which statistically verifies the probability of detecting the self-administration of drugs of abuse can

be fashioned, a savings of time and money can be realized. Goldstein and Brown (18) have recently published a thorough analysis of testing schedules.

Criteria for arriving at a schedule include:

- All urine samples must be collected under supervision.
- Unless urine testing is to be done daily, sampling must be truly random.
- A sampling schedule must be worked out using some device utilizing random sampling action.

Utilizing these criteria and statistical methods, it can be shown that random sampling one day in five allows the calculation of results within 95 percent confidence limits. For example, a run of 20 consecutive negative tests taken over a 90-day period assures the physician that 95 times out of 100 he may be sure that the patient has used opiates less than 12 days out of 90 (13 percent of the time). This is shown graphically in Figure 1.

Utilizing a random sampling technique has the disadvantage of not being able to detect a relapse to heroin use within 95 percent confidence limits before approximately 14 days. This is shown in Figure 2.

It is possible, utilizing random sampling as described, to obtain all essential information pertinent to illicit drug use by a single individual over the course of a year.

ANALYTICAL ERRORS

Urinalyses are subject to the same analytical errors as other testing methods. False positives and negatives are reported and are the nemesis of most drug program directors.

An important point to consider when choosing a laboratory to analyze urine is whether or not the urines are hydrolyzed prior to analysis. Approximately 30 percent of the results will be false negatives if this is not done. This is due to the formation of glucinides which are inefficiently extracted from urine into organic solvents.

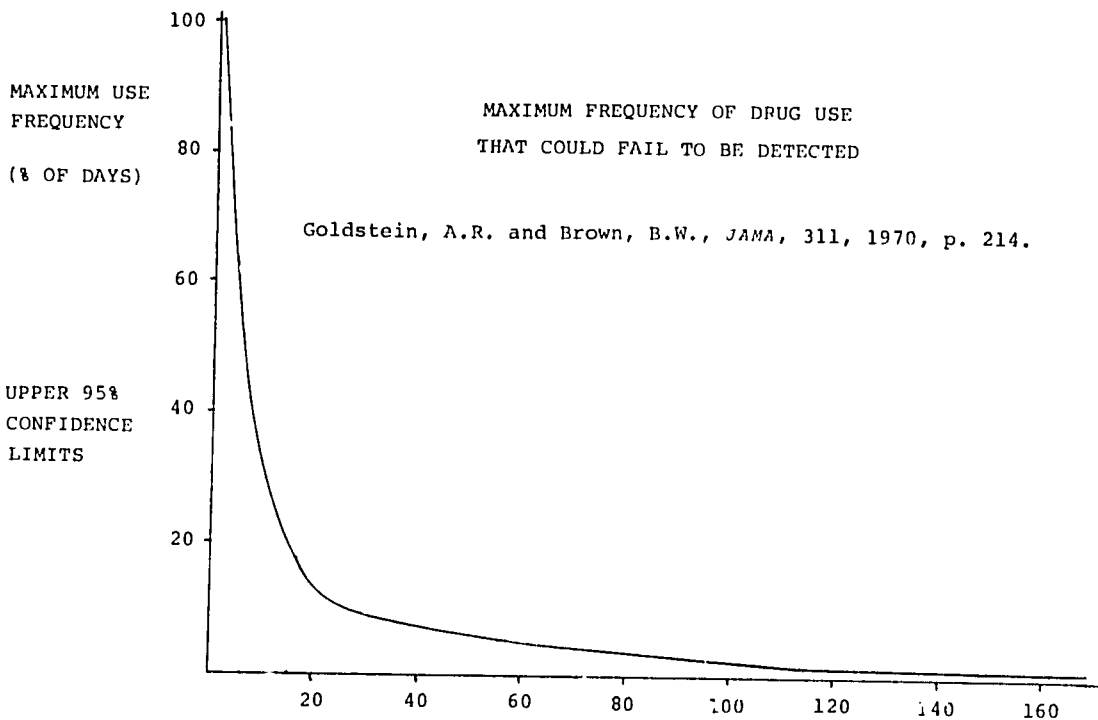


FIGURE 1. LENGTH OF NEGATIVE RUN

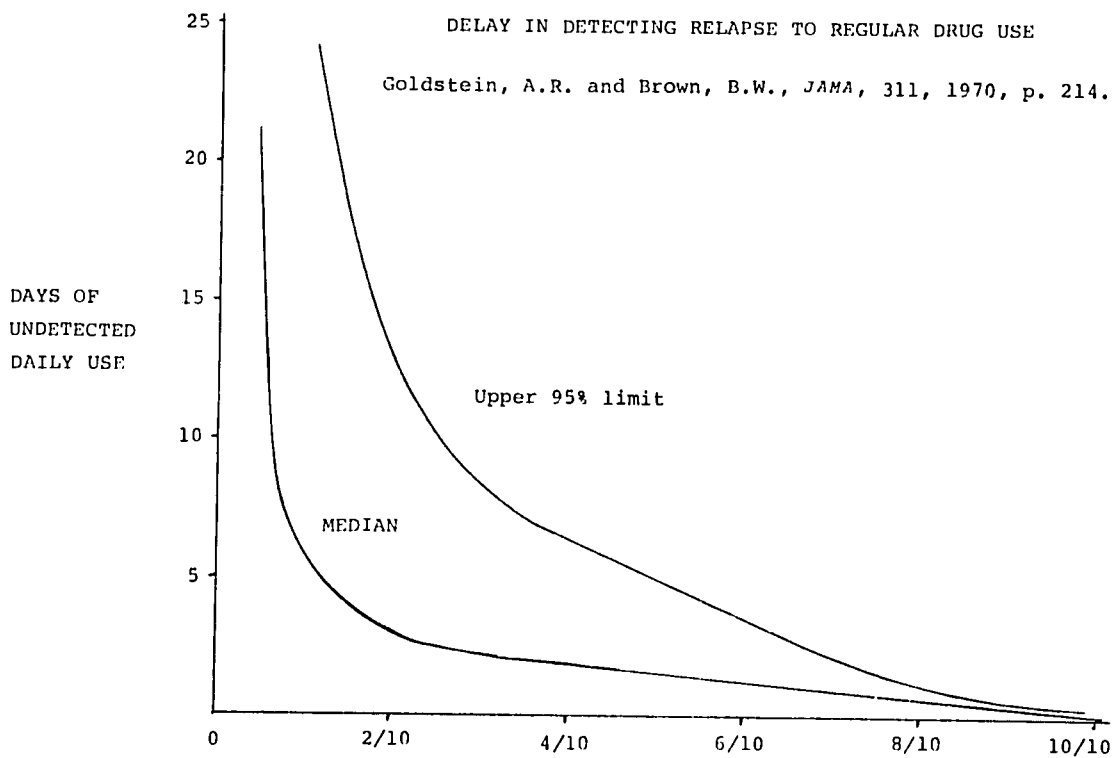


FIGURE 2. AVERAGE TESTING FREQUENCY (days)

In the TLC-extraction technique, one source of false negatives is pale urine. It can be shown that false negatives are reported as much as 50 percent of the time when tests are done on pale or diluted urine specimens. Barring severe kidney disfunction, the most common cause of pale urines is the intake of large amounts of fluids such as water and beer. This results in large volumes of urine with low mg/ml drug content. The "junkie" adage that he could "beat" the urinalysis by drinking a large quantity of beer prior to leaving a specimen is probably more true than we like to think.

Tests should not be performed on pale urines for the reason stated (false negative) but also because these urines, which are useless for program monitoring, result in expenditures which provide no benefit to either the program or the patient.

Too long a waiting period prior to taking a urine sample results in false negatives and the assumption that the presence of quinine connotes heroin or morphine use represents a false positive.

Another source of error lies in the analytical laboratories. Unfortunately, results obtained in efforts to determine limits of detection are not always duplicated in the routine urinalysis situation on a programmatic level. Primm *et al* (10a) [sic] have reported that results obtained from analyses of known (spiked) samples by different laboratories seldom correlate. In a series of experiments designed to check interlaboratory reliability, these authors found that the two laboratories tested agreed on the presence or absence of methadone only 61.4 percent of the time, and on the presence of barbiturates only 0.2 percent of the time. These results prompted the authors to ask, "How would results in clinical situations change if a treatment program required the laboratories to agree when a given specimen was positive?" In this case, samples were divided between two laboratories and analyzed. In laboratory A, 27 percent of the methadone samples were correctly identified. In 43 percent of the cases, methadone false positives were found. Results were very similar for laboratory B. However, it is important to note that the same mistakes were not made on the same samples.

Results on subsequent samples tested in the same laboratories were dramatically improved when each laboratory was advised of its errors. A close working relation between treatment program and analytical laboratories coupled with random spot checks of the laboratory's detection ability is warranted in light of these results.

In the FRAT system, the nasal spray afrin (oxymetazolinehydrochloride) as well as some tranquilizers and the analgesic darvon affords a false positive for morphine; and while hydrolysis of urine is unimportant, utilizing this free

radical technique, unhydrolyzed urines give rise to approximately 30 percent false negative results when using TLC methods.

The improper use of the pupillary test for opiate addiction also gives rise to erroneous results.

Some phenothiazines mask spots for opiates and occasionally methadone and quinine metabolites interfere with TLC tests.

Blood tests are not routinely used to monitor illicit use of drugs. These tests are difficult to do and discrepancies often exist between reported blood levels and clinical states. This is in large part a pharmacokinetic problem since blood levels at a given time point do not give information about dose or tissue concentration.

ADVANTAGES AND DISADVANTAGES OF DRUG TESTING

The advantages of testing for drugs include:

- The ability to monitor illicit drug taking in a treatment and rehabilitation program. This allows some measurement of the success of the program as well as patient progress.
- Ability to monitor whether or not the patient is taking medication (i.e. methadone). Testing data are very useful from a medico-legal point of view.
- Personal contact. The ritual of leaving a urine sample keeps the user in touch with a particular program. Positive urines then become a source for confrontation and group or individual therapy--negative ones a chance for verbal reward.
- More rapid and reliable tests which are a definite aid in diagnosis as well as treatment procedures.
- They provide basis for a bond between patient and counselors and patient and physician.

The disadvantages of testing for drugs are:

- Routine analyses are expensive and time consuming.
- Results can be incorrect thereby creating morale and/or behavioral problems.

Positive results tell only that the drug had been ingested or administered just prior to testing. The test tells nothing about whether or not the patient has either an acute or chronic problem.

Test results tell nothing about the clinical picture.

CONCLUSION

In the last analysis, what does all the testing, cross-checking and subsequent reaction to positive or negative tests mean?

When an adolescent is seated before you and you possess an accurate piece of test data to verify that the patient is using drugs, what courses of action are open to you?

Does the positive test for morphine signify a junkie? How many positive tests do you need to prove that this person is addicted to heroin? This is important since three positive tests are usually necessary as evidence of addiction and serve as a prerequisite for admittance into methadone treatment programs.

Since the underlying problems leading to drug use are often behavioral, psychological, social or a combination thereof, of what use is a test which tells you that the patient is taking drugs when the problem is not drugs but a lack of self-esteem, or interpersonal relations or a complete inability to solve his problems?

Urinalysis may be compared to a thermometer. Both indicate that something is wrong somewhere. Both say that treatment is needed. The comparison ends there, however. A fever can often be traced to an infecting organism or a malfunctioning organ. It is difficult to trace the causes of drug taking signaled by a positive urine or blood test.

Nonopiate abuse can also be detected by laboratory procedures. The same questions apply. Does a positive amphetamine test signify a "speed" freak, an experimenter, an occasional user or a housewife who believes amphetamines result in weight reduction? Each situation would be handled differently, although a casual glance at the test results from any one of the above would read "amphetamine--positive."

The data obtained in routine analysis are far more important than a positive or negative result may signify. Results can help you shape a course of treatment. Sporadic relapse may

mean that you are missing important behavior patterns in the patient, a change in attitude, personal problems or a treatment regimen not effective for this patient or group of patients.

In your office, positive data can be used by you to refer patients to treatment centers.

Regardless of how the data are used, one caution is needed. Too much reliability on test results can depersonalize a program to the point of negating other treatment aspects.

No number of accurate urine analyses gathered over any length of time ever convinced an addict or a person habituated to drugs to stop taking them. Precise data tell physicians and counselors nothing about the patient's real progress. Often when a patient stops taking heroin and begins methadone, he turns to alcohol, or becomes depressed and restless. Seldom is alcohol analyzed for routinely, and sociological and psychological problems cannot be detected in urine or blood.

We must look further than urine and blood tests. We cannot be satisfied that the chemist has the solutions to the problems.

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MEASURES FOR THE PREVENTION OF DRUG ADDICTION

by

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The problem of drug addiction has plagued humanity for hundreds, even thousands, of years, and is causing social, economic and cultural difficulties in many countries.

During recent years addicts and their use of psychotropics and narcotic drugs have created a phenomenon among peoples throughout the world. This problem has remained inexplicable even though great effort has been and is being made to solve it.

New and fast means of communication, general knowledge and the exchange of information have helped this.

The addicts hold no respect for social traditions and beliefs and do not care about the realities of life. We all know that our future lies in the hands of our youth, but addiction is their great enemy. For preventative measures it is still most essential to combat supply with cooperation and collaboration of the CENTO countries in the areas where there are narcotics problems.

Simultaneously, the sources of supply should be diminished, and at the same time, a system for the treatment and social reintegration of the addict must be established.

Drug addiction is not the perversity of an evil character; it is the consequence of psychic and personal crises with the myriad influences of the victim's social, economic, genetic and cultural background.

For this reason programs of prevention must give consideration not only to methods of dealing with the addict but also to instruction and making the person feel better and improve his ability to function.

The aim is to permit a person to support himself and regain his self respect. Generally speaking, facilities for the registration, diagnosis, treatment, aftercare, etc. of drug-dependent individuals and groups should be regarded as an indispensable and integrated part of the health and social services structure of any community in which drug abuse exists.

- 1) It is evident that any program of prevention must give attention to local circumstances, with particular reference to the drugs used in the country and the degree to which their use creates a problem, together with consideration of the local customs, attitudes, predominant mores and institutional patterns.
- 2) Primary prevention is aimed at reaching everyone in the community, especially the vulnerable individuals and groups, and providing them with information designed to protect them against the use of harmful drugs.
- 3) The strict use of legal controls in the distribution of narcotic drugs will ensure that they are used only for medical and scientific purposes.
- 4) Similarly, a preventive program may be required to counteract popular misconceptions about the value of drugs for dietetic and medical purposes.

- 5) The treatment and cure of drug addicts, including their rehabilitation and aftercare, constitutes an important part of preventive measures.
- 6) It is necessary to understand the character of the drug addict and not to look on him as a criminal, but as a patient who is in need of medical and social rehabilitation. Help must be given to the patient to re-establish himself as a productive member of society. Fortunately this is the approach which we take to the problem of the addict in Iran.
- 7) Studies of the effectiveness and cost of the various programs against addiction should be taken into consideration.
- 8) There should be public education regarding the health, social, psychological and economical aspects of drug addiction.
- 9) Cooperation of different supervisory committees involved in the problem of drug addiction is also an essential point in prevention.

THE ROLE OF EDUCATION IN THE PREVENTION OF DRUG ABUSE

by

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Education is a long-term measure of the prevention of the drug abuse problem. We ought to give proper attention to this aspect of prevention as we mostly give to the legal controls, illegal production of narcotics, treatment of drug-dependent individuals and, to a lesser degree, the social rehabilitation and reintegration of addicts.

It is the belief of our time that "The long-term solution to the drug problem does not rest with law and order techniques alone, but rather with education."

In every prevention program against drug abuse, we have to consider all aspects of the problem, whether they are medical, economical or psychological in nature.¹ It should also be

1. See Appendix.

clear that the execution of a concerned action against drug abuse does not lie in the hands of one single agency in a given country alone. If we are going to find a solution to this vast social and international dilemma, we have to have a coordinated effort of all governmental and social agencies dealing with this human problem in our societies.

One of the approaches to the prevention of drug abuse as considered by the W.H.O. Expert Committee on Drug Dependence (which met in Geneva in 1970) is "Education Measures Providing Information about Drugs and Influencing Attitudes to Drug Use."

The other approaches to prevention of drug-dependence are the legal controls and the community approaches. We are going to discuss the educational aspects of prevention in this paper, leaving the other aspects to other speakers in the seminar.

As the result of the lack of adequate studies and information in this area of prevention, there are, as you know, a great deal of controversy and many opposing opinions about education in combating drug abuse. Some would be opposed to the idea of drug education, rationalizing that any kind of education program would further spread the drug-dependence problem in certain populations. Some claim that the knowledge about drugs would not be protection by itself if the drug is readily available. This latter view has generally been accepted while there is a lack of evidence to support the former one.

But how to give an effective education and by whom this information is to be given remains a crucial question. This question has to be answered in each country and region of the world separately. We all have different ways and means to give effective education to our people which cannot be exactly duplicated by any other country. Nevertheless, we can learn from others' experiences, advancements as well as failures. Although we do not have much experience in this area in Iran, we believe that education would be greatly beneficial along with the application of other means of prevention of drug abuse. Thus education has been an integrated part of our prevention program against drug-dependence and drug abuse.

In our General Department of Mental Health, we are developing programs in areas of prevention of mental illness and the drug abuse problem which is going to be facing us in an increasing degree in the future. We are going to develop coordinated programs with the cooperation of the other involved government agencies on these lines.

Our educational program to combat drug abuse and to give drug information to the population in general and to the "at

risk" group in particular, would be executed along the following lines of order.

First of all it is crucial for the medical and pharmaceutical professionals, educators and the law enforcement officials who are handling drugs or dealing with the potential or actual drug abusers, to have adequate knowledge and information about drugs.

In Tehran we have recently started to give lectures on this topic upon the request of different professional groups. We believe that it is absolutely essential to provide the right information about drugs to different groups of people, but not to overemphasize the subject so that it is misleading to them.

What would also be needed in our present mental health activities is to have a coordinated program of drug education for educators who are in the first line of defense in combining the drug abuse problem.

It is also important to have a well integrated drug education program in school systems. This should not be dealt with as a separate entity from the general curriculum but rather it should be a part of the general teaching process, avoiding unnecessary attention to the subject and not causing any undue curiosity about drugs.

This continuous education on drug subjects at school would include information about the handling of drugs, use and misuse of drugs, as well as social and psychological implications of drug abuse.

Education programs on drug abuse would also be developed for adults and specifically for the population "at risk" along those lines mentioned above.

Granting that the framework of a drug training program has been established, there are not too many trained personnel in the field of mental health and drug education available at present in Iran to execute this vast educational program as mentioned. This same difficulty faces every developing country. To meet some of our national and international duties and obligations, we plan to have several training programs to train an adequate number of mental health professionals in the near future.

APPENDIX

We are living in a world where drugs are an integral part of the environment. In every household we have drugs which can be potentially dangerous if handled by children or misused by adults. They can also be life savers if used with adequate knowledge. The same idea is generally true with the majority of the dependence-producing drugs which are under international control laws.

Opium and its derivatives have long been used, and are still used, as the best pain killer of all in the world of medicine. In Iran, opium was traditionally and historically used by peasants and people living in rural areas, where medical treatments were scarce or not readily available. Of course, this traditional pattern of opium usage has changed, due to the new social reforms and new drugs control laws and regulations which will be touched upon later in this paper. For some other people opium was used as a social habit on occasions, without a great stigma attached to it, much as Europeans enjoyed social drinking habits for many years.

Since the enactment of the law prohibiting opium cultivation in Iran in 1955, and also the institution of the Health Corps in 1964, along with the expansion of medical services to rural areas, we expect to have less and less drug dependence of this type.

The pattern of drug dependence in Iran has greatly changed during the past decade. It appears from general studies that other etiological factors have played an important part during recent years in drug dependence, especially among youth, besides the self-medication factor mentioned already. Professor K. W. Bash, M.D., (W.H.O. Psychiatric Consultant) in a paper about drug addiction in Iran has stressed the fact that social and psychological factors are specially important etiological reasons among the drug-dependent population in urban areas.

The psychosocial phenomenon affecting our city population is likely to be fundamental for any society going through a rapid and constant change of traditional social structures and value systems.

The new group of drug-dependent individuals is made up of the victims of urbanization and industrialization which is characterized by an impersonal, materialistic and consumer-oriented society. This group of drug abusers is mostly from the middle or upper class families, who are mainly experiencing feelings of frustration, unhappiness and dissatisfaction originating from their personal and social conditions, in which drug dependence becomes a pathological way of readjustment or relief of their psychological problems. (This view has also been supported by the findings of Dr. Bash's Psychiatric Epidemiological Survey of Shiraz, done for W.H.O. in 1969-70.)

A CONTROLLED COMPARATIVE STUDY AND
FOLLOW -UP OF THE TREATMENT
OF DEPENDENCE ON OPIATES *

by

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INTRODUCTION AND BASIC AIMS

In the next few minutes I would like to present for your consideration and reaction a brief outline of a research project on the treatment of dependence on narcotics which we are planning to undertake here in Tehran. Our aim in making the presentation at this seminar is twofold: one, to inform you of the main features

* This project is in collaboration with the Ministry of Health, Iran and the International Committee Against Mental Illness, Nathan S. Kline, M.D., President. Dr. Kline is responsible for the initial phases of this research and is coprincipal investigator of the present project.

of this research activity, its major aims and our rationale for undertaking it; the other reason is to invite your thoughtful and expert advice either during the discussion period today or at some later opportunity during this seminar. I would like further to call upon this distinguished and knowledgeable group which represents countries that have in common this socially critical and scientifically puzzling problem, to consider developing multidisciplinary research programs on the etiology, epidemiology, treatment and prevention of drug abuse in general and the abuse of narcotics in particular. Such programs could very well have some common features and goals that would be of interest to all participating countries, as well as some features that are unique to the needs of one or another member country. Within such a broad program, it will be possible to pool many resources and skills and to carry out many needed studies in this very critical area.

I am pleased to inform you in this regard that the program we are about to launch here in Tehran is a product of such international cooperation. In addition, we have the promise of both technical and material help from the United Nations and the Drug Dependence Unit of the World Health Organization. In carrying out the earlier planning and feasibility stages of the project, we have had the full support of the Narcotic Drugs Control Administration of the Ministry of Health here in Iran, the staff of the Addicts' Hospital in Vanak, and the personal support of the United Nations advisor in this area in Iran. At present we are planning to collaborate with other research groups, including one in New York City, in replicating this study with a special interest in cross-cultural comparisons. Perhaps there will be a further opportunity during this seminar to discuss the feasibility of collaboration on concrete research projects among members of this organization.

In conceptualizing the aims of our program, we made certain working assumptions that are not only relevant but perhaps basic to an appreciation of the rationale that underlies our efforts. These assumptions are: *one*--although there are several quasihypotheses about the biological and psychological etiology of drug dependence, such as the notion that opiate addiction is a metabolic disease (3,4,5), or the widely endorsed assumption of learned, developmental, psychodynamic disorders of behavior as precursors to addiction (1,2,8,9,10,12,17,18,19,20), I think we can all agree that we have yet to develop rigorously testable hypotheses that would provide more adequate conceptualization of the problem and would be more amenable to experimental validation than the above notions. *Two*--our second major assumption is that we have not as yet developed effective and comprehensive methods for the treatment of drug dependence and the maintenance of a narcotic-free and socially functioning individual for a period of time that is sufficiently long to warrant the label of

recovery or cure. *Three*--we postulate that any large population of drug-dependent persons is not a homogeneous one in that the phenomenon of drug dependence is not etiologically speaking a unitary event in all cases. Consequently, any large population of persons who are dependent on drugs either psychologically alone or both physically and psychologically, will consist of subgroups of persons whose *needs* for and *pathways* to addiction, that is their treatment and rehabilitation, must also be different. This notion of both etiologial and treatment specificity, I am sure, is a very familiar one to those of you who are working in health and other sciences. Therefore, you may be interested to hear that in our study we assume that one substantial subgroup of opiate addicts consists of individuals who, due to a variety of psychological, social and biological factors, are suffering from some form of depressive illness and whose treatment must, therefore, include such psychological, social and pharmacological methods of intervention as are thought to be effective in the treatment of depressive illness. Consequently, one of the approaches to treatment that will be used in our project will be to treat one patient group as one does in the case of psychiatric patients with the diagnosis of depression. Hence, following the detoxification stage, we will utilize an antidepressant medication combined with a tranquilizer in this treatment group for a period of one year. Of course, this group, as all other comparison groups, will receive in addition supportive psychotherapy and social case work. As you note, we will attempt to deal with the three factors considered crucial in the treatment of drug dependence: the drug, the patient and his social milieu (21, 22).

Another hunch that has been advanced in recent years is that the heroin or morphine addict is an individual with a specific metabolic disorder who must be maintained on some narcotic such as methadone that will satisfy this metabolic deficiency or need and also block the craving for heroin. Patients on methadone maintenance, unlike those maintained on morphine or heroin, are reported to be free of apathy, sedation and preoccupation with narcotic drugs and are able to function and work normally and plan effectively for the future (3,4,5,16). This, as you well know, is the position taken by many researchers and clinicians with programs that provide prolonged methadone maintenance as a method of treatment (3,5,16). It can be argued that the assumption of a specific metabolic deficit is a highly speculative one that has yet to be carefully tested. Moreover, it is more likely that the phenomenon of craving in drug-dependent subjects is a psychologically motivated and cognitively triggered learned phenomenon representing an attempt on the part of the drug-dependent individual to achieve a state of psychological comfort, calm or relief from anxiety rather than to meet a specific tissue need. Careful clinical examination of the personality of a large proportion of the drug-dependent individuals and their so-

cial and familial lives almost always reveals the presence of serious psychological stress which may constitute at least a major factor in the patient's complex drug-craving behavior (11, 12, 15, 20). In any event, although we have a long way to go before an adequate formulation of the above stated notions could be properly articulated and tested, it is essential to provide a comparative evaluation of the relative efficacy of methadone maintenance, at least according to the criteria of social and occupational performance; the criterion of abstinence from narcotics will of course be irrelevant for this group.

Our study will focus, therefore, on the problem of treatment and will seek to evaluate the comparative outcome of two pharmacological approaches that are based on the assumptions mentioned above. We will also aim to identify certain characteristics of responders and nonresponders to each of the procedures utilized in an effort to arrive at some preliminary notions of patient subtypes. Despite the rather different conceptual formulations of the etiology of addiction that underlie these two approaches to treatment, they both share the aim of aiding patients to function socially and occupationally. In addition, we believe that regular and frequent contacts between patients and their therapists will provide a basis for extending a real and concrete opportunity for psychological help and social support in the management of their affairs and in their rehabilitation.

Our criteria of outcome will thus include social and occupational performance ratings of general and psychiatric status, particularly with regard to anxiety and depression, legal status and, of course, abstinence from narcotic drugs.

METHODS OF PROCEDURES

The study subject will be male patients between 18 and 45 years of age, with no serious physical illness, mental deficiency, serious criminal record other than for drug abuse or involvement in the illicit sale of narcotics. Patients should be able to read and write and be residents of Tehran or its immediate vicinity. Since these patients are selected from the general voluntary admissions to the regular detoxification program of the hospital, they must agree to stay in the hospital for additional treatment for a total of 4 to 6 weeks, to maintain their treatment for a full year, to cooperate in the required monitoring of their medication and to provide blood and urine specimens along with social and occupational data throughout the study period. While the number of patients in the study will remain a function of the resources that will be available to us, a

minimum of 168 subjects will be randomly assigned to the four treatment groups under investigation. Briefly these groups are:

- 1) A no-treatment control group consisting of patients who are given the routine detoxification program now available at the hospital. These patients will be followed up and evaluated for one year, as will all other patients in the study. They will serve to provide base rate information on social and occupational adjustments and abstinence or relapse for comparison with other groups.
- 2) A placebo control group which will receive inert substances and medication following the initial detoxification period and will be evaluated as will all other patients for one year.
- 3) The third group will be treated with an antidepressant in combination with a tranquilizer¹ on the assumption that has been stated earlier, that narcotic drug dependence in a substantial segment of addicts is symptomatic of an underlying disturbance. The hypothesis under test here is that once the patient is detoxified and physical dependence on the narcotic agent is presumably removed, the psychological (cognitive and emotional) need for it can be obviated when the psychic pain or discomfort that is conceptualized to be the primary motivating factor for drug-seeking behavior, has been reduced or removed.² It is further assumed that the patient will learn that he can cope with the stresses of his life without the narcotic drug (6, 7).
- 4) The fourth group will receive methadone maintenance treatment as typically outlined by Dole and Nyswander (3, 16).

Selection of patients is on the basis of consecutive admission to the hospital and assignment to treatment is double blind according to a predetermined, random schedule. All patients will be stratified into three age groups and two levels of depression on the basis of the patient's own self-ratings and the ratings of physicians. The four treatment groups will be

1. Matabon, also known as etrafon or triavil: 2 mg perphenazine plus 25 mg amitryptiline.

2. Drug dose will range from two to eight matabon tablets daily: 50 to 200 mg amitryptiline plus 4 to 16 mg of perphenazine.

equated by matching patients with regard to age and level of depression. The resulting design is thus a factorial one consisting of four treatment groups, three age levels and two levels of depression, allowing for control over two important patient variables (6, 14).

All assessments will begin after initial screening and prior to the initiation of experimental treatment and will continue during the period of hospitalization on a once-a-week basis. During the follow-up period in the community, patients will be interviewed and evaluated once a week for the first 6 weeks, every other week during the next 6 weeks and once monthly during the balance of the year.

Although elaborate detailed data, which may discourage both clinical staff and patients, will be avoided, minimum data essential for an adequate evaluation of outcome will be gathered. These will include factual demographic information about the patient and his family, medical and psychiatric history and examinations of the patient, type and history of the patient's drug dependence and that of other family members, prior efforts at abstinence and their dates, shifts in type and amounts of drugs used including alcohol, present status including ratings of depression and anxiety and prevailing target symptoms as well as laboratory blood and urine tests. Records will be kept of legal history including court actions, types of offense, arrest dates, etc. History and status of other medical and behavioral problems will be recorded. Areas of strength and resources of the patient and his family, such as education, occupational skills, special talents, financial status and general support of the family will be assessed.

All ratings and judgements of clinical status and improvement will be based on a personal interview lasting about 30 minutes. Two independent clinical ratings will be sought, one from the treating doctor and the other from an independent clinician who is not involved in the patient's treatment. Continuity of care will be maintained by planning for each participating staff member to continue working with the same patients throughout the study period. Quality control, particularly regarding completeness and validity of data will be given special attention. Background and historical data will not only serve as a basis for evaluating outcome, but will provide specific grounds for therapeutic and rehabilitative interventions.

RESOURCES AND FACILITIES

Aside from administrative and secretarial personnel, the project staff will consist of two to three physicians highly ex-

perienced in the treatment of narcotic dependence; a fully trained psychiatrist who will provide psychiatric services to the patients and also furnish ratings of clinical status; two social workers who will aid in the collection of background information in the follow-up of the patients in the community, in vocational rehabilitation and employment and in assuring continuous contact with patients; and finally, one nurse who will be responsible for dispensing medication and the collection of blood and urine specimens both during hospitalization and afterwards. Patients will be hospitalized at the Addicts' Hospital in Vanak and may also be interviewed there during the posthospital period or at the Outpatient Mental Health Clinic in downtown Tehran, at the patient's own residence or in a mobile unit that will be provided for this purpose. Statistical and computer facilities of the National Institute of Mental Health and the Rockland State Hospital Department of Research will be available for data analysis. The primary model of data analysis that follows from the experimental design is the analysis of variance. Additional models will be used, such as the multiple regression model in the prediction of outcome from antecedent personality and socio-economic variables.

CONCLUDING REMARKS

Thus far our efforts have been devoted to carrying out pilot and feasibility studies and making preliminary arrangements for this project (13). In planning our future efforts, we hope that our past experiences will aid us in an effective execution of project plans as outlined for you, and also help anticipate and prevent serious problems, particularly in the area of community follow-up that are unique to the study of drug-dependent individuals or characteristic of the particular circumstances under which we work. We are scheduled to begin data collection within the next 2 months as we complete tooling up and hope to report some preliminary data in about a year; optimistically the final report should be available in the Fall of 1973.

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DRUG ABUSE :

U. S. PUBLIC INFORMATION AND

EDUCATION EFFORTS

by

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I am very pleased to participate with you in this first CEN TO Seminar on the Public Health and Medical Aspects of Drug Addiction.

Within the last year, there was an opinion survey taken in the United States which indicated that drug abuse was the third major concern of the American people. This is only one indicator reflecting just how aware American citizens are regarding the crucial problem of drug abuse.

It wasn't too many years ago that this was not the case. When we at the Federal level began our drug abuse information/education campaign a few years back, we had great difficulty in convincing concerned citizens and organizations that the problem of drug abuse was of such a scope that it warranted their high priority involvement. There was great apathy.

However, as the problem grew, those who said it "couldn't happen here" saw that it was happening--in their communities, in their neighborhoods and even in their homes. Subsequently, this awareness and concern was transferred into action. There are now substantial numbers of Americans involved in programs which are trying to curb the spread of drug abuse. The problem, however, has not abated. It is a complex problem which defies simplistic solutions.

The solution of choice to the drug abuse problem would have to be prevention. This is also true with other illnesses. But the complexity of the drug problem makes unusual demands on the prevention process. In general terms, prevention of drug abuse has come to mean the healing of a tear in the social fabric--a tear around which this destructive phenomenon festers. In these terms, a communication program is the essence of the prevention process. As with any malady, we must begin with diagnosis. In this case it is a matter of searching out some understanding of who is using what and why. In this analysis, several interesting facts come to light. Drug abuse is not solely a phenomenon of the young. For example, in the United States we have at least 80 million adult citizens who use alcohol to alter their moods and to seek euphoria. Some 9 million of these can be classified as chronically ill and unable to function productively because of this use. According to the latest figures, 36 percent of the U.S. adult population smokes cigarettes despite an increasing awareness of their potential for harm and despite the absence of any describable benefit resulting from their use. We have, in the United States, virtually every adult ingesting, applying, inserting, spraying, smoothing on, or otherwise making use of a myriad of chemicals to make him smell better, look thinner, sleep more soundly, get started in the morning, appear less wrinkled. One fourth of the prescriptions written by physicians in the United States are for drugs which alter the mood or perception of the user in one way or another. These figures have a telling effect on any assessment of the nature of today's drug problem.

All of these substances have one thing in common: they are advertised and taken with the promise and expectation that they will make the user better in some respect, or happier. And, described as a whole or in selective groups, they constitute the much publicized "drug problem." This perspective of the drug problem has drastic implications for the preventive thrust. Sermonizing and exhortation by adults to the young seems totally ineffective, though this is obviously for many adults the easiest course to take.

One element in the recent upsurge in drug use is the alienation that exists between the adult world and that of the young. We like to feel comfortable as providers for our chil-

dren, yet ours is, despite these beliefs, an adult-centered society. When we talk with young people about their use of drugs, we must keep this in mind.

In the face of the complexity of the drug problem and the tragic suffering that calls both our attention and our emotions to it, how do we set out to begin the prevention process? Perhaps a brief description of the stages of development of our national program will provide useful insight.

In early 1969, though the drug scene was burgeoning across the country, many citizens, parents, teachers, even doctors, preferred to seek comfort in the view that the problem could never affect them or their families. They preferred to view the drug problem as remote--a phenomenon of the poor and the alienated, self-contained in urban ghettos. In many cases, even after the damage of drugs became apparent in a family, it was ignored. The first task of our communications program was to make people aware of the problem. An important objective of the campaign to stimulate awareness was to provide parents and concerned citizens with factual information that would make them better equipped to deal with the situation as it developed in their jobs, in their communities or in their own families. To accomplish this, we sought the cooperation of the nation's media--radio, television, newspapers and magazines. Advertising agencies worked without profit to assist us in the preparation of information materials for all media. To attract the attention of the audience, television and radio advertisements about drug abuse were created with the same fascinating quality that is usually associated with commercial products. In our country the print and broadcast media have a healthy tradition of donating time and space for public service messages. Some corporations also sponsor public service advertisements to express and enhance their public image of social concern.

Our program, with the cooperation of the media, succeeded in generating, over a period of 18 months, more than 20 million requests for information. When we began to put materials on the public airwaves, we made an important decision which remains, today, the underlying principle of our total effort: we affirmed that we would present only the facts--only information that is scientifically accurate. We avoided moral overtones. We did this because the messages would have little value if they misinformed--already young people knew more than most adults about the effects of different drugs. And our premise was that scientific accuracy--honesty--was the way to build credibility with today's sophisticated young people. Messages were designed to reach different audiences, both adult and young, yet they reinforced each other. Television spot messages warning adults of the potential dangers resulting from the abuse of diet and

sleeping pills helped to persuade young people that what we said about LSD was fact, not propaganda.

The results of the awareness campaign were greater public interest in, and indeed recognition of, the fact that there was a problem, thus pointing the way to the next phase of our program--the involvement of individuals and groups at the local level in mobilizing to deal constructively with drug abuse. We recognized that it was at the community roots level where there was an understanding of the unique characteristics of the local problem, that work towards solutions would have to take place. We therefore undertook on a national scale the job of stimulating, reinforcing, and supporting community action.

To deal with the growing number of inquiries that flowed into offices of Federal agencies, it was decided to establish a central point to which individuals could write or telephone for materials, information or assistance. On March 11, 1970, President Nixon announced an action plan. He established the National Clearinghouse for Drug Abuse Information, designed to respond to the nation's need for information about drugs. Clearinghouse computers maintain data banks on programs of treatment, rehabilitation and prevention around the U.S. so that groups working in the same geographical area could be informed of each other's existence and work together, or so that one city could find out about programs that have been successful in another city of similar size and demography. The Clearinghouse also distributes films, fact sheets, booklets and other materials to citizens who request them. The Clearinghouse also publishes collections of abstracts, or guides on available materials, and bibliographies, film evaluations, government programs and information from its files, which are constantly being updated. The President also established, at this time, a program with the immediate goal of training 150,000 teachers in drug abuse education.

With citizens around the country aware of the problem and beginning to organize local action programs in schools and communities, we set about the next task--providing a more comprehensive and detailed range of information and education materials for them to use. Materials were prepared, not to propagandize, but to inform; not to preach, but to educate; not to scare, but to stimulate. Exhaustive use is being made of all media, books, posters, films, even complete training courses to help teachers deal with the problem both preventively and pragmatically in the classroom.

Communications between parent and child, between teacher and student, are essential. Each side must be willing to listen as well as talk. Through creative use of mass media and through widespread dissemination of factual information, many of the anxieties which preclude such meaningful discussions can be al-

leviated. Perhaps most significant, we are beginning to make what I believe will be the most important contribution to prevention--the development of alternatives to drug use for young people. Several years ago this was a notion that was discussed with little enthusiasm. Then it meant, if I may paraphrase: Why can't these young people get involved in sports and other similar normal healthy pursuits? But, increasingly, we look to the opening up of attractive options for young people to join society in a way that can be meaningful for them. Many of our young people are bored with the kinds of activities schools and communities have provided for adolescents. They want to make and carry out decisions affecting their own lives, and have little chance to do so.

The development of alternatives, like the mobilization of local resources of which it is a part, demands innovative use of both material and human resources. Communications can spread the word of successful local efforts and provide some insights. It must be remembered, however, that each local situation is unique, and like good wine, good programs rarely travel well. But the principles do transfer. We are currently engaged in a project aimed at developing alternative pursuits that could serve as models for various communities across the nation. More than one thousand young people and adults are now being contacted and asked to forward programs that would attract youth and provide them with exciting alternatives to drug abuse. These projects--ranging from the aesthetic to the physical, from practical work-related activities to exploration of various forms of mysticism--will be developed in stages with our people in continual communication with project leaders. Those projects offering the most promise will be selected to serve as the agenda during a forthcoming conference. There they will undergo a final critique and then be implemented in the initiating communities. They will be subsequently evaluated and the histories of the successful projects will be given wide distribution.

The development of alternatives demands both great sensitivity and a willingness to accept change. Here, as elsewhere in the task of drug abuse prevention, there is great need for effective communications.

With this in mind we also launched what is to date our most ambitious and comprehensive program: The Social Seminar--Drugs, Education, and Society. Basically, this program was designed to train teachers with the focus on their attitudes and behavior toward students. As it evolved, however, it became clear that it would have other uses as well. The theme around which this series was developed is: "If you have knowledge about drugs, and an understanding of young people and their cultures, then you can effectively interact and communicate to prevent drug abuse."

The Social Seminar approaches the problem of drug abuse within the context of total society. Its purpose is to help create a healthier society by integrating current knowledge about the attitudes toward drugs and their abuse into American family, school and community life.

It is designed to give teachers, parents, and anyone who deals with young people an opportunity to examine the human, social and cultural issues surrounding the problem of drug abuse.

The core of The Social Seminar consists of an 18-part multimedia package, including 15 films made by young, enthusiastic film makers at the Extension Media Center at the University of California at Los Angeles. Included in the package is an overall descriptive film, general guidelines, and a discussion of each film designed to facilitate and encourage participant interaction. Discussion is an indispensable part of The Social Seminar: it is a chance to lay attitudes and feelings on the table to examine them, get feedback, and redefine behavior, if necessary.

Also included in the package is a programmed text covering the factual and pharmacological material relating to drugs. The Social Seminar is completed with a role-playing simulation program which includes a leader's guide, role cards, and a player's manual for each participant.

The perspective underlying The Social Seminar is that there are no simple solutions to complex problems. The Social Seminar does not pretend to answer all the questions related to drug abuse and drug abuse education. It is, however, a comprehensive orientation upon which school systems, universities, and individual communities may build drug education programs to fit their particular needs.

Because of its flexibility, The Social Seminar can be adapted to meet specialized local needs, and will continue to be useful even as the drug scene continues to change.

The Social Seminar, for instance, can be used as the basis for a full semester's course for would-be teachers and counselors who will be relating to students in teaching and counselling situations. Or, The Social Seminar can be used as an inservice teacher training program within a school system, or within one school.

In one school in the State of Maryland, where The Social Seminar was pretested, it has become a successful daily education course. A teacher and a counselor decided to use The Social Seminar with students who had drug or drug-related problems. They recruited the students and then asked adults to join a pro-

gram based on The Social Seminar, which has been held for an hour every morning for a full semester.

The counselor, who directs the program, has made use of all the films with students, teachers, parents, and other adults from the community. "The results," he says, "can be summed up in one word: successful."

"How can that be measured?" According to this counselor, "by the behavior and attitude changes of the students, which include less frequent use of drugs by some, complete nonuse of drugs by former users, and a complete change of perspective about drugs by all the students. One boy who had decided not to use drugs when he began school last fall said the only way he could successfully deter his use was through his experience with The Social Seminar."

An outgrowth of this program in Maryland is that the students who participated now want to go into the other neighboring high schools and junior high schools to help prevent drug abuse by bringing about attitudinal and behavioral change.

The Social Seminar is basically a program geared toward understanding some of the social and cultural phenomena which trouble many of today's youth. It is a program designed to sensitize adults to the pressures and anxieties of adolescence. It is a program intended to help create a school environment which is relevant to the students' needs and aspirations. To accomplish these goals The Social Seminar is aimed at understanding adult attitudes towards drugs and young people so that a meaningful contribution can be made to curb the abuse of drugs in our society.

The Social Seminar represents a Federal effort to add to the school community's resources to help prevent drug abuse. Hopefully, it will also enable the kind of spontaneity, dialogue and discussion needed to influence youth's attitudes and behavior.

While we are excited about the potential of The Social Seminar as a program we are under no illusions that we now have the perfect vehicle to prevent the spread of drug abuse. We are convinced that for many people--certainly not all--we have developed a vehicle through which mutual understanding can be reached, by which attitudes can be examined and evaluated, and from which alternatives to drug misuse can be spawned. We don't know how successful we will be, but the early indications are encouraging. Those of us involved in drug abuse information and education must base our efforts on what we know has failed and what we think may have some success. I say "think" because there has yet to be developed a barometer which can gauge the success of any educational approach that intends to dissuade individuals

from certain behavior. The factors which will bear on a young person's decision whether or not to use drugs are many, including parental relationships, attitudes towards living, environment, sense of values, etc. Perhaps in years to come our social scientists will develop a mechanism which will be able to determine what educational tool or approach is the most effective in any given situation. In the meantime, we will continue--because the problem does not afford the luxury of waiting--to develop programs that try to give more than information and knowledge; that try to create an atmosphere of understanding and mutual trust, between parent and child, teacher and student, and among peers. Without this atmosphere, we face an impossible task; with it, we have a chance...a chance to help people--both adults and youth--to direct or redirect their lives away from drugs and towards more involvement in self-achieving and self-satisfying pursuits. It is a tremendous challenge, yet one that must be met.

The presentation by Mr. Karst J. Besteman consisted of a summary of the two following papers. They are included in full because of the interest shown by the delegates in these closely related subjects.

THE FEDERAL EFFORT IN THE PREVENTION AND REHABILITATION OF NARCOTIC ADDICTION

by

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The efforts of the U.S. Government were limited until recent years exclusively to the support of two facilities for the treatment of narcotic addiction. From 1935 to 1967 there were no additional Federally-sponsored efforts at prevention and rehabilitation of narcotic addicts. From 1967 to 1970 there were three explicitly focused laws which extended the Federal authority to assist and support local and State efforts at rehabilitation. There was also in the fall of 1970 a law passed which authorized explicit program activities in drug abuse education. The most recent major legislative effort was the enactment of the Drug Abuse Office and Treatment Act of 1972, which was signed into law by our President in March of 1972.

In addition to legislative activities enacted to bear directly on the drug abuse population in our country, other authorities designed primarily to train for employment, rehabilitate the disabled, and impact on poverty populations were being focused in such a manner as to serve in the treatment of the heroin addict.

With this somewhat uncoordinated approach and the many organizational units of government involved, the administration and the Congress set forth the following proposal which is now implemented. The Congress makes the following findings:¹

- "1) Drug abuse is rapidly increasing in the United States and now afflicts urban, suburban and rural areas of the nation.
- 2) Drug abuse seriously impairs individual, as well as societal, health and well-being.
- 3) Drug abuse, especially heroin addiction, substantially contributes to crime.
- 4) The adverse impact of drug abuse inflicts increasing pain and hardship on individuals, families, and communities and undermines our institutions.
- 5) Too little is known about drug abuse, especially the causes, and ways to treat and prevent drug abuse.
- 6) The success of Federal drug abuse programs and activities requires a recognition that education, treatment, rehabilitation, research, training, and law enforcement efforts are interrelated.
- 7) The effectiveness of efforts by State and local governments and by the Federal Government to control and treat drug abuse in the United States has been hampered by a lack of coordination among the states, between states and localities, among the Federal Government, states, and localities, and throughout the Federal establishment.
- 8) Control of drug abuse requires the development of a comprehensive, coordinated long-term Federal strategy that encompasses both effective law enforcement against illegal drug traffic and effective health programs to rehabilitate victims of drug abuse.

1. Public Law 92-255.

- 9) The increasing rate of drug abuse constitutes a serious and continuing threat to national health and welfare, requiring in an immediate and effective response on the part of the Federal Government."

Declaration of National Policy

"The Congress declares that it is the policy of the United States and the purpose of this Act to focus the comprehensive resources of the Federal Government and bring them to bear on drug abuse with the immediate objective of significantly reducing the incidence of drug abuse in the United States within the shortest possible period of time, and to develop a comprehensive, coordinated long-term Federal strategy to combat drug abuse."

After setting forth so complete a policy the law then establishes a focal point for action and responsibility: the Director of a Special Action Office for Drug Abuse Prevention, which office is located immediately in the Executive Office of the White House.

Concentration of Federal Effort

- "1) The Director shall provide overall planning and policy and establish objectives and priorities for all Federal drug abuse prevention functions. In carrying out his functions under this subsection, the Director shall consult, from time to time, with the National Advisory Council for Drug Abuse Prevention.
- 2) For the purpose of assuring the effectuation of the planning and policy and the achievement of the objectives and priorities provided or established pursuant to subsection (a) the Director shall:
 - a) review the regulations, guidelines, requirements, criteria, and procedures of operating agencies in terms of their consistency with the policies, priorities and objectives he provides or establishes, and assist such agencies in making such additions thereto or changes therein as may be appropriate
 - b) recommend changes in organization, management, and personnel, which he deems advisable to implement the policies, priorities, and objectives he provides or establishes

- c) review related Federal legislation in the areas of health, education and welfare providing for medical treatment or assistance, vocational training, or other rehabilitative services, and consistent with the purposes of this Act, assure that the respective administering agencies construe drug abuse as a health problem
- d) conduct or provide for the conduct of evaluations and studies of the performance and results achieved by Federal drug abuse prevention functions, and of the prospective performance and results that might be achieved by alternative programs and activities supplementary to or in lieu of those currently being administered
- e) require departments and agencies engaged in Federal drug abuse prevention functions to submit such information and reports with respect thereto as the Director determines to be necessary to carry out the purposes of this Act, and such departments and agencies shall submit to the Director such information and reports as the Director may reasonably require
- f) except as provided in the second sentence of section 213:
 - i) coordinate the performance of drug abuse prevention functions by Federal departments and agencies; and
 - ii) coordinate the performance of such functions by Federal departments and agencies with the performance by Federal departments and agencies of other functions which the Director determines may have an important bearing on the success of the entire Federal effort against drug abuse
- g) develop improved methods for determining the extent of drug addiction and abuse in the United States."

Annual Report

"The Director shall submit to the President and the Congress, prior to March 1 of each year which begins after the enactment of this title, a written report on the activities of the office. The report shall specify the objectives, activities, and

accomplishments of the office, and shall contain an accounting of funds expended pursuant to this title."

Content of Strategy

"The strategy shall contain:

- 1) An analysis of the nature, character, and extent of the drug abuse problem in the United States, including examination of the interrelationships between various approaches to solving the drug abuse problem and their potential for interacting both positively and negatively with one another
- 2) A comprehensive Federal plan, with respect to both drug abuse prevention functions and drug traffic prevention functions, which shall specify the objectives of the Federal strategy and how all available resources, funds, programs, services, and facilities authorized under relevant Federal law should be used
- 3) An analysis and evaluation of the major programs conducted, expenditures made, results achieved, plans developed, and problems encountered in the operation and coordination of the various Federal drug abuse prevention functions and drug traffic prevention functions."

Preparation of Strategy

To facilitate the preparation of the strategy, the Council shall:

- "1) Engage in the planning necessary to achieve the objectives of a comprehensive, coordinated long-term Federal strategy, including examination of the overall Federal investment to combat drug abuse
- 2) At the request of any member, require departments and agencies engaged in Federal drug abuse prevention functions and drug traffic prevention functions to submit such information and reports and to conduct such studies and surveys as are necessary to carry out the purposes of this title, and the departments and agencies shall submit to the Council and to the requesting member the information, reports, studies, and surveys so required.

- 3) Evaluate the performance and results achieved by Federal drug abuse prevention functions and drug traffic prevention functions and the prospective performance and results that might be achieved by programs and activities in addition to or in lieu of those currently being administered."

The Federal effort in prevention and rehabilitation can be quantified in dollar volume per fiscal year. Simply for comparative purposes the trend is as follows:

FY 1969	\$ 45,000,000
FY 1971	\$ 132,200,000
FY 1972	\$ 310,100,000
FY 1973 (proposed)	\$ 365,200,000

The significance of the increase is best displayed in light of what are emerging as the early strategies on the Federal level.

(I must insert a disclaimer at this point. The Director, Special Action Office for Drug Abuse Prevention, has not announced his strategy. My opinions as to what form or direction these strategies will take result from my analysis of various public statements made by him and members of his staff.)

First I will review the treatment and rehabilitation area. The overwhelming concern nationally is with the heroin addict. The effect of heroin addiction on the quality of life in the city, the criminal justice system, and human misery is so severe as to demand immediate attention. The first major obstacle is the lack of an adequate service delivery system to respond to those heroin addicts desiring treatment. The development of expanded and new service delivery systems for heroin addicts will get priority efforts. It is my opinion that in an effort to place as many people in treatment in as brief a period as possible and maintain an adequate level of care, methadone maintenance will be a primary treatment modality.

At the time that sufficient treatment resources exist for heroin addicts efforts will be made to develop treatment resources for amphetamine and barbiturate abusers. Today in our country there are very few drug abusers who abuse only one substance; however we are referring basically to a "drug of choice" classification.

Research strategies are mandated in the law and direct extensive work to develop an ideal narcotic antagonist which will not have negative side effects while having an extended pe-

riod of action, preferably beyond 24 hours. Another research need is a highly sophisticated epidemiology to accurately define populations at risk and obtain a standard history of drug addiction to enable us to devise more focused intervention strategies.

The prevention priority appears to be the evaluation of existing efforts to define their actual impact and to eliminate efforts which are: 1) ineffective or 2) counter-productive. In this endeavor we are perplexed because personal values and beliefs appear critical to drug-taking decisions. In our social context many citizens are concerned if the Federal Government appears to be interfering with personal value or belief systems.

Much of the Federal activity in prevention is funding, thus allowing more homogenous local groups to determine much of the content for their specific programs.

In addition to these types of strategies and concerns there is now an additional program consideration. In many cities with significant drug problems, special enforcement teams are operating to reduce the effectiveness of the illicit supply and distribution system. In those cities there are special efforts to enable those addicts adversely affected by aggressive law enforcement to enter treatment resources especially established to accommodate this crises in the addict's life.

The several government agencies being coordinated include the Department of Labor, selected programs of the Law Enforcement Assistance Administration, Office of Economic Opportunity, the drug abuse treatment units of the Veterans Administration, the scientific and education activities of the Bureau of Narcotics and Dangerous Drugs, drug abuse activities of the Food and Drug Administration, the drug education and prevention activities of the Office of Education, the drug abuse rehabilitation efforts of Rehabilitation Services Administration, and the activities of the National Institute of Mental Health as administered through the Division of Narcotic Addiction and Drug Abuse.

The National Institute of Mental Health has the largest role of all the agencies mentioned, since it administers authorities in treatment, training, and research.

The remarkable aspect of this entire scope of the special Federal effort is that it has been conceived as a short term, high-impact effort. In the legislation the termination

date of the newly established office was set at June 30, 1975. This gives a 3-year period in which to impact the situation in our country.

On December 30, 1974 the legislation will establish a National Institute of Drug Abuse. Hopefully at that point its major responsibility will be to sustain a successfully implemented program strategy which will have begun to reduce the terrible toll which drug addiction extracts from our society.

THE TREATMENT OF HEROIN ADDICTION

by

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In this paper I will describe the most commonly used treatment techniques for heroin addiction in the United States. A review of treatment research efforts of particular concern will follow, and I will conclude by outlining issues that merit some discussion because of a lack of consensus among those concerned with heroin addiction in our country.

TRADITIONAL INSTITUTIONAL TREATMENT

The modality which has been used for the longest period of time involves the traditional institutional treatment. In this approach the addict is removed from his community to a closed institution where efforts are made to retrain and re-educate him. The cost for this service is usually higher than community-based approaches, and the treatment environment is frequently characterized by an atmosphere of isolation. Outcome studies of Federal, State and local efforts with this modality have been less than encouraging and were in large part responsible for the new Federal focus on community-based treatment of narcotic addiction beginning in 1966 with the passage of the Narcotic Addict Rehabilitation Act.

THERAPEUTIC COMMUNITIES

This term has come to mean live-in treatment environments staffed primarily by ex-addicts where "total personality restructuring and re-education" is the *stated* goal. Encounter therapy and confrontation in a somewhat authoritarian setting are characteristic. There are two substyles. First, the closed community where the expectation is that continued residence and employment for or by the therapeutic community itself is the desired goal. Treatment, therefore, is tantamount to lifelong participation. The second substyle involves a treatment period of from 18 to 36 months with the goal of completely reintegrating the addict into society at large without requiring repeated chemical support. The largest organization operating a relatively closed system in Synanon. Experience with this approach has demonstrated that addicts often experience difficulty when they make the transition to independent living in the community. Most therapeutic community ventures are operated as private nonprofit organizations.

PSYCHIATRIC OUTPATIENT MODEL (AFTERCARE)

The use of intensive counselling, group and individual, utilizing the full range of community resources for training, job placement, specialized medical care, etc., has become more widely used during the last few years. This service rarely stands alone, and usually has a programmatic affiliation with other treatment efforts such as institutional treatment. Its effectiveness in assisting the abusers in achieving personal and social productivity is slowly being documented through evaluation studies.

PROBATION - PAROLE

Both the states and the Federal Government continue to utilize small, selected populations to demonstrate the effectiveness of quality supervision in assisting drug abusers who enter the criminal justice system. Outcome data suggest that this is a worthwhile investment to reduce recidivism. Program implementation has in general been less than the evaluation data would warrant.

HALFWAY HOUSES

This approach has a long history with rehabilitation programs in the mental health and alcoholism field. Application to the drug abuse field has been uneven. The halfway house approach appears to function most effectively when it is affiliated with a larger treatment resource and when used very selectively.

METHADONE MAINTENANCE

In this approach a synthetic opiate is substituted for heroin to facilitate the use of other treatment techniques to achieve rehabilitation of the narcotic addict. Although the addict continues to be addicted, this treatment has great attractiveness today because it appears to reduce antisocial behavior. Major questions still unanswered are the long-term consequences of the drug, its real therapeutic efficacy, and its impact on the heroin economy. Lifetime costs per patient may in fact exceed other modalities with greater short-term costs. This has been the most effective modality in engaging large numbers of addicts in treatment in a brief period of time.

None of the above modalities by itself can effectively meet the need of *all* heroin addicts let alone all drug abusers. Those treatment centers which offer the greatest variety of modalities at the community level are able to retain in treatment a larger percentage of individuals who come for help. Those centers who offer only one form of treatment often retain less than 50 percent beyond the first 3 months of treatment.

Treatment related research is sometimes deprecated as being less than the worthy pursuit of truth. However, from these applied efforts we expect to develop the accepted treatment techniques of tomorrow.

NARCOTIC ANTAGONISTS

Perhaps the ongoing research with the greatest potential for direct clinical application is the search for improved narcotic antagonists. These are drugs which will occupy the sites on the nerve cell which heroin would ordinarily occupy. If these can be blockaded by safe agents, the "high" which heroin produces can be blocked. Naloxone and cyclazocine have already been developed and are in use, but they suffer the disadvantages of being relatively short acting and of producing undesirable side effects in some addicts. The precise nature of the narcotic binding site is being intensively studied. The more we can learn about how opiates interact with the nerve cell, the better the chances for a rational approach.

Research is being conducted to develop a device representing a combination of polymer plastic and a morphine antagonist to be implanted in order to permit slow release of the antagonist over an extended period of time. Such a device used in the treatment of narcotic addicts would greatly extend the effective duration of cyclazocine and other antagonists and make repeated medication less necessary. A breakthrough in the area of nontoxic removable implants that can release a narcotic antagonist slowly would be a valuable addition to the armamentarium of present treatment methods. Such a removable device is viewed as, in principle, far superior to a depot injection method of drug administration.

Work is also being supported for the development of new and improved long-acting narcotic antagonists with little or no additional pharmacological action beyond blocking opiate action.

Quite apart from opiate antagonists, there is a need to develop specific antagonists to other drugs of abuse so as to permit both emergency and long-term treatment of other types of drug abuse. The possibility of immunizing individuals against a specific drug's effects remains a more distant and yet tantalizingly promising one for the longer-range future.

There has been a rapid proliferation of methadone maintenance programs following reports of the success of such programs in socially rehabilitating addicts. The Institute has had continued concern that this promising therapy not be adopted uncritically and that there be adequate evaluation of it. It is particularly important that we have a thorough understanding of the implications of this treatment for all aspects of the individual's functioning. Under NIMH support investigators are studying the sleep behavior of patients selected for methadone treatment who have been withdrawn from narcotics while being institutionalized for periods up to one year. Sleep studies are being conducted while the patient is drug free, while he is in

the process of stabilization on methadone, and after he leaves the hospital and is taking an average daily dose of 100 mg of methadone. The same research team is also studying the sleep characteristics of a group of normal women at different stages during the menstrual cycle, to gain baseline data for a comparison study of women in the methadone treatment program. In a subsample, researchers are comparing the sleep patterns of women who are taking oral contraceptives with those who are not.

Other studies are concerned with various aspects of the psychological and physiological implications of ongoing use of methadone--all have the objective of better understanding the implications of this treatment both for the individual and the larger society.

A potentially important development in methadone maintenance therapy is the introduction of L-alpha-acetyl methadole (LAAM), a long-acting methadone which will last 48 or even 72 hours instead of the present 24 hours that methadone administered orally is presumed to act. This will provide a much more convenient, and in many cases, more desirable substitute for the present drug which requires daily clinic visits and a take-home supply over weekends. The Institute has obtained a limited supply of LAAM and is encouraging its research evaluation. A recently approved grant will study the chronic psychosocial, physiological and cognitive effects of methadone and LAAM in the treatment of heroin addicts.

DETECTION OF DRUGS IN URINE AND URINE MONITORING IN TREATMENT OF ADDICTION

The effectiveness of daily urine monitoring in detecting narcotic drug use and inpatient management has been evaluated in an addict group of patients over whom mandatory supervision could be maintained. This approach was found to be feasible and meaningful and may be a preamble to other forms of treatment concerned with the management of the addict. An overwhelming majority of the participants viewed the program as being supportive. Continued daily knowledge of the absence of narcotics use provided reassurance to the employer, relief to the parolee's family, and the basis for a better relationship between the parole agent and his charge. The prompt confrontation and assistance given on occasions when narcotics use had occurred, prevented an accelerated regression into another cycle of narcotic dependence in many subjects. The fact that no patient became addicted while participating in the program, and that the number of arrests were relatively small for a group as highly recidivistic as addicts was a very encouraging finding.

Because of the widespread use of chemical monitoring programs in connection with the treatment of addiction, improved techniques for detecting drugs of abuse in body fluids are badly needed. Researchers at Boston University School of Medicine have developed new thin layer techniques for the detection of drugs in human urine, a technique using ion-exchange resins rather than ion-exchange paper for the extraction procedure.

Previous chemical procedures for detecting drug abuse required essentially separate analyses for different types of drugs. One investigator has developed an efficient screening procedure, using a single solvent system, to extract simultaneously from urine, acidic (barbiturates), neutral (glutethimide) and basic drugs (morphine, amphetamine).

Another grant has been awarded to examine and evaluate (on a comparative basis) the most commonly used methods for the detection of drugs in the urine for specificity, sensitivity and validity. Opiates, sedative hypnotics, stimulants, and hallucinogens are being studied.

The accurate, sensitive and simplified method of detecting urinary metabolites of opiates, sedatives and stimulants is so important that the Institute's Addiction Research Center has undertaken a complete review of all techniques now in use. They are also studying this problem and attempting to improve upon existing methods of urinary detection of drugs.

There are four treatment issues which continue to be debated in our country. On most of these issues the core drug abuse professionals are arriving at a reasonable accommodation in order to sustain the public trust. Meanwhile individuals who deal in social policy and public discussions in the mass media continue to express divergent views on these issues.

METHADONE MAINTENANCE

Methadone is an addicting synthetic narcotic which, when taken by mouth, produces a minimum euphoria, obscures most of the pleasurable effects of narcotics injected during the duration of the drug effect and suppresses the craving for other narcotics. It has been used historically for the short-term relief of pain, cough suppression, and withdrawing addicts from heroin. Since 1964 there has been a steady increase in the use of methadone in maintenance therapy, until today it is estimated by the Food and Drug Administration that up to 40,000 persons may be receiving the drug at maintenance dosage.

Experts in the field agree that by itself methadone is not a miracle drug and does not cure the economic, psychological, social and criminal problems of the addict. They further

agree that it is beneficial for methadone treatment programs to include a variety of supporting social, occupational, legal and health services.

Methadone maintenance is criticized on a number of grounds:

- 1) It does not "cure" the addict of his addiction.
- 2) It is motivated by a desire to prevent antisocial behavior rather than treating the addict.
- 3) Precise long-term safety and efficacy of the drug are unknown.
- 4) The drug can be and is diverted into illicit channels from programs not carefully supervised.
- 5) Accidental deaths in children have occurred from methadone.
- 6) Some addicts on methadone are known to abuse heroin, alcohol, barbiturates, or amphetamines and to engage in criminal activity.
- 7) It is not an appropriate treatment for all heroin addicts or experimenters, especially adolescents.

Proponents of methadone maintenance argue that:

- 1) Methadone maintenance is like the treatment of any chronic disease such as diabetes or epilepsy: the medication ameliorates rather than cures the disease.
- 2) The program aims not only at reducing antisocial behavior, but also at providing the addict with the help necessary to solve or cope with his psychological, interpersonal, and vocational problems so that he leads a life more satisfying to himself and more productive.
- 3) Thousands of patients have been treated with methadone and no serious medical side effects have been reported; moreover, a large percent of the patients treated seem to have benefited greatly from the program as measured by a variety of outcome criteria.
- 4) Careful supervision will prevent diversion of the methadone.

- 5) More children have died from aspirin poisoning than from any other kind. One must weigh the social benefits of any medication against the social risks. Steps can be taken to protect children and others from accidental ingestion of methadone.
- 6) While methadone maintenance is not suitable for or helpful to all addicts, it should not be denied to those who can benefit from this kind of program.
- 7) The economic and social benefits of changing addicts from welfare recipients, supporters of criminal sources of drug supplies, and in some cases criminals, into productive citizens are enormous and far outweigh the costs of treatment.

THE ROLE OF COMPULSION IN TREATMENT

In the United States narcotic addicts can be forced by certain legal procedures termed "civil commitment" to submit to treatment. The individual can be civilly committed by a relative or he can elect civil commitment in lieu of facing trial for a crime with which he is charged. The individual can also volunteer for commitment for treatment if he feels his motivation will not persist for the length of time treatment might take. Moreover, addicts convicted of crimes can be sentenced to treatment institutions rather than to ordinary prisons.

In some states (such as California) civil commitment may mean treatment in a residential facility for up to 7 years. On the Federal level it means that the addict first undergoes an evaluation to determine whether he is likely to benefit from treatment. If he is likely to benefit, he is given 3 to 6 months of residential care followed by outpatient aftercare services in his home community up to a total of 42 months of treatment. If he is not likely to benefit, he is not accepted for treatment.

There are, generally speaking, two ways of viewing involuntary civil commitment. The "medical model" stresses preserving health and treating any person with a serious illness or an illness dangerous to the community, even without the patient's consent. This view has historical links to quarantining people having or suspected of having dangerous infectious diseases. The "legal model" stresses preserving the individual's civil liberties (constitutional rights) and insists that civil commitment procedures pass two tests: 1) that the individual's rights to a fair hearing, legal representation and so on are preserved, and 2) that leaving the individual free would constitute a clear and present physical danger to himself or others.

The two models are not mutually exclusive, but each has a different stress and priority: the medical model stressing health and the needs of society, the legal model stressing civil liberties and the rights of the individual.

Those who question civil commitment are concerned with the following kinds of questions: Is this invasion of individual liberty warranted by the danger the individual poses to himself, the public health, or the public welfare? How does one measure degrees of danger? Do the commitment procedures safeguard his right? Can one justify committing an individual to a facility which cannot reasonably assure his rehabilitation? In instances where civil commitment is an alternative to criminal punishment, should society be allowed to commit an individual for a period longer than he would have been jailed if he had been found guilty of a crime? Is civil commitment aimed at "getting the addict off the street" or at providing the best treatment possible? Is the cause of addiction closely related to the idea of a contagious disease, or is it more closely related to human misery and hopelessness? If contagion is a small factor, public health procedures, e.g., quarantine, become less defensible.

Those who favor civil commitment or other forms of involuntary treatment make the following points:

In the early history of voluntary programs, many addicts left treatment long before rehabilitation was achieved and often after only a few days. Second, some individuals who want treatment may have conflicting desires or may lack the will power to stay in treatment; compulsory treatment helps them stay. Patients who are initially unmotivated may become motivated after being in the treatment situation for a period of time. Third, several studies have shown that patients who receive parole supervision after a period of institutional treatment have higher rates of abstinence from drugs than those not under supervision; this suggests that some compulsion benefits addicts. Fourth, civil commitment can be carried out in a manner which protects the individual's rights. Fifth, since effective treatments are available, and since the addict does constitute a danger to himself and in some cases to society, he should be required to accept treatment.

THE USE OF EX-ADDICTS AS STAFF IN TREATMENT PROGRAMS

The ex-addict has several assets which may make him a valuable member of a treatment program. His personal experience with drugs and his familiarity with the drug culture and social milieu make him effective in public education activities, in

training health, mental health and social service personnel who must deal with addicts, in counseling, and in leading group therapy sessions.

There is some disagreement, however, about the proper relationship of the trained ex-addict to health, mental health and social service professionals. Questions arise as to who should administer the program, who bears responsibility for directing the treatment modalities. There is also the feeling that ex-addicts tend to underutilize health and mental health professionals in times of health and mental health emergencies.

THE RELATIVE EFFECTIVENESS OF INSTITUTIONAL VERSUS OUTPATIENT CARE

Those who favor a period of institutional care argue that rehabilitation can more effectively be carried out away from the stresses and seductions of the addict's home community. Moreover, since rehabilitation services for addicts differ in some respects from those for mental patients, a specialized institution may serve their needs better than a general mental hospital.

Proponents of outpatient care point to the fact that some patients can be successfully withdrawn or treated with methadone or psychotherapy on an outpatient basis. Moreover, this form of treatment may aid the addict to master the stresses in his living situation and allows interested friends and relatives to become involved in the addict's rehabilitation. Proponents also point out that outpatient care is much less expensive than institutional care.

No definitive studies demonstrate the marked superiority of either form of treatment. At present it appears that both forms of treatment should be available to meet the differing needs of selected groups of addicts.

THE EFFECT OF 6-HYDROXYDOPAMINE ON MORPHINE ABSTINENCE SYNDROME IN RATS

by

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Some authors have reported that morphine tolerance and abstinence syndromes are related to brain catecholamines (3, 5, 9). On the other hand, some authors have reported that there is no relationship between the addiction cycle and the levels of brain catecholamines (1, 8).

Systematically administered, 6-hydroxydopamine (6-OHDA) produces a selective degeneration of adrenergic nerve terminals in peripheral sympathetically innervated organs (12). The compound 6-OHDA produces a long-lasting depletion of brain noradrenaline (NA) and dopamine (DA) when injected into the lateral ventricle of the rat brain. After treatment with large doses of 6-OHDA, in the central nervous system are restricted to NA and DA containing neurones, and there is no recovery for periods of up to 142 days after treatment [*sic*] (2, 14).

Previously we have shown that 6-OHDA inhibits the analgesic and hyperthermic effects of morphine in rats (13). In the present study we report the action of 6-OHDA on the nalorphine-induced abstinence syndrome of rats.

MATERIAL AND METHODS

Male white rats (130-150 g) were used in these experiments. Twenty μ l of a solution of 6-OHDA hydrobromide (containing 250 μ g free base) was injected into the lateral ventricle of the brain as described by Uretsky and Iversen (14). After 6 hours of 6-OHDA, the morphine injections were begun.

Morphine hydrochloride was administered (i.p.) at 12-hour intervals 7 days a week. The initial dose of morphine hydrochloride was 40 mg/kg per day and was gradually increased to 200 mg/kg per day at the end of the 14th day.

At the end of the 21st day of morphine injections the rats received (i.p.) 10 mg/kg nalorphine hydrochloride. Before nalorphine injection and 45 minutes after nalorphine, the rats were weighed and rectal temperature measured. Also for a period of 45 minutes, starting with nalorphine injections, their faeces were collected and weighed (6). The rectal temperature was measured with an electrical thermometer.

Mean values and standard errors were calculated and compared by Student's "t" test.

RESULTS

After 5 days of chronic treatment, rats receiving doses of 80 mg/kg per day showed a marked increase in activity after each injection, which was noticeable 10 to 15 minutes after morphine administration and lasted approximately 60 to 80 minutes. The 6-hydroxydopaminized rats which received the first dose of morphine (20 mg/kg) showed obvious excitation and aggressivity. The rats which received only 6-OHDA showed some excitation. On consecutive days, during the first few hours after receiving morphine, motor activity and rearing were much increased, and the animals were extremely sensitive to tactile stimuli and noise. They were more irritable on handling than the normal, morphine-treated and 6-OHDA control rats.

The rectal temperatures of the 6-hydroxydopaminized rats were found lower than the morphine-treated and intact rats. The administration of the 10 mg/kg nalorphine to normal rats and 6-hydroxydopaminized rats significantly increased the rectal

temperature. When nalorphine was given to chronic morphine-treated rats, the rectal temperature significantly decreased. No significant difference was found between the chronic morphine-treated and the chronic morphine-treated-6-OHDA rats' faeces weight.

All the test results are shown in the following table:

THE EFFECT OF 6-HYDROXYDOPAMINE ON THE RECTAL TEMPERATURE AND THE FAECES WEIGHT OF THE RATS

Group	Rectal Temperature Mean S.D.C.		Faeces (mg) P	n
	Before Nalorphine	After Nalorphine	Mean + S.D.	
Normal rats	38.8+0.15	39.1+0.08	350+ 42	0.025 9
6-OHDA control rats	37.6+0.07 ^a	39.4+0.10 ^a	315+ 37	0.0005 4
Chronic morphine	38.1+0.27 ^a	37.2+0.11 ^a	2545+353 ^a	0.0005 20
Chronic morphine + 6-OHDA	37.9+0.09 ^{ac}	37.7+0.10 ^a	2369+287 ^{ac}	0.05 9

a: p < 0.005 when compared with normal rats.

b: p < 0.0025 when compared with chronic morphine group

c: p Nonsignificant when compared with chronic morphine group.

DISCUSSION

The roles of catecholamines in morphine tolerance and abstinence syndrome are still not clearly established. In the rat, the administration of morphine resulted in supranormal levels of brain NA. This rise was observed irrespective of the frequency of treatment. When rats were abruptly withdrawn from long-term morphine treatment there appeared to be no decrease in brain NA (4,5,7,11). Akera and Brody reported (1) that there is no relationship between the addiction cycle and the levels of brain catecholamines in rats. Also Maynert reported (8) that the concentrations of brain stem NA and surrenal adrenaline do not decrease in nalorphine-induced narcotic withdrawal of rats. Our results are in accord with these authors.

Our findings indicated that chronic morphine treatment stimulates motor activity in the rats. Also chronic morphine treatment caused obvious excitation and aggressivity in 6-hydroxydopaminized rats. These observations suggested that catecholamines in the brain play an important role in the regulation of motor activity by the chronic administration of morphine. We could not find any relation between nalorphine-induced abstinence syndrome and brain catecholamines in rats.

According to Simmonds and Uretsky (10), the acute hypothermic response to 6-OHDA may be related to a release of DA in the brain. Also previously we have shown that on the rats which received 6-OHDA 25 days before the test, the temperature was significantly decreased when compared to the normal rats. When morphine was given to 6-hydroxydopaminized rats the temperature was increased significantly (13). In this experiment we observed also that nalorphine increased the temperature on 6-hydroxydopaminized rats. Destruction of the catecholamine neurons with the use of 6-OHDA may result in a relative increase in the brain serotonin level, thus causing hypothermia and morphine, or nalorphine may prevented the serotonin receptors against to the serotonin [sic].

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INTERACTION BETWEEN MORPHINE AND LITHIUM

by

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INTRODUCTION

Lithium has been used successfully in the treatment of manic-depressive disease for almost 20 years (35,36). Since 1960, especially for the last few years, there has been increased interest in lithium among clinicians and among those engaged in basic research. During recent years some experiences showed that there is an interaction between lithium salts and brain monoamines. Several authors have stated that lithium influences brain noradrenaline (NA) metabolism (6,17,23,24,32,33,39). On the other hand, some other authors have reported that lithium also influences brain 5-hydroxytryptamine (5-HT) metabolism (9,11,20,23,24,25,34,37).

However, there is confusion about the mode of action of morphine as well as lithium on brain monoamines. But it has been shown that morphine analgesia is closely related with the brain monoamines (7,26,27,40,42,46,48,49).

Considering this mutual effect, we decided to investigate the interrelation between morphine and lithium on the thermo-regulation and analgesia by the route of brain monoamines, performing experiments on rats.

METHODS

For these experiments, white male rats weighing between 150-175 g were used. The analgesic effect was tested with the hot plate method at 57.3-0.2°C and the rectal temperature was measured with an electrical thermometer. The ambient temperature was 22-24°C. Student's "t" test was used for statistical analyses.

The rats were divided in 12 groups as follows:

1) *Control Group*: 20 rats were given intraperitoneally (i.p.) 0.2 ml saline. After 45 minutes their rectal temperature and pain thresholds were measured.

2) *Morphine control group*: 10 rats were given (i.p.) 6 mg/kg morphine hydrochloride and after 45 minutes their rectal temperature and analgesic reactions were measured.

3) *Lithium control group*: 10 rats were given (i.p.) 400 mg/kg lithium hydrochloride and 6 to 8 hours later the same parameters were measured.

4) *Lithium+morphine group*: 20 rats were given 400 mg/kg lithium hydrochloride and 6 to 8 hours later 6 mg/kg morphine was injected and 45 minutes after the last injection they were tested.

5) *Reserpine control group*: 10 rats were given (i.p.) 5 mg/kg reserpine and 38 to 40 hours later they were tested.

6) *Reserpine+lithium group*: 10 rats were given 5 mg/kg reserpine and 38 to 40 hours later they were given 400 mg/kg lithium hydrochloride and 6 to 8 hours later they were tested.

7) *Reserpine+lithium+morphine group*: 20 rats were prepared like group 6, and were given 6 mg/kg morphine 45 minutes before the test.

8) *Reserpine+morphine group*: 10 rats were given 5 mg/kg reserpine, 48 hours later 6 mg/kg morphine was injected and they were tested 45 minutes later.

9) *6-Hydroxydopamine (6-OHDA) control group*: In this group 10 rats were given 250 µg 6-OHDA intraventricularly, 25 days later they were tested with the same methods.

10) *6-OHDA+lithium group*: 12 rats which were given 6-OHDA like group 9, were given 400 mg/kg lithium hydrochloride 25 days later and were tested 6 to 8 hours after lithium injection.

11) *6-OHDA+lithium+morphine group*: 12 rats were prepared like groups 9 and 10, and were given 6 mg/kg morphine and 45 minutes after morphine injections were tested with the same methods.

12) *6-OHDA+morphine group*: 12 rats were prepared like group 9, and were given 6 mg/kg morphine and 45 minutes after morphine injections they were tested.

RESULTS

Apart from the 6-OHDA groups, we observed a depressive state in all the rats 1 to 2 hours after lithium injections. The depression was more obvious in the reserpenized rats. We also observed diarrhea in almost all the rats which received lithium.

When lithium was given to 6-hydroxydopaminized rats, they showed an initial depression for about 2 hours, but later they showed excitation; they became irritable for external stimuli (e.g. handling and sound). They quarrelled with each other and squeaked. When morphine was administered during this condition their excitation became more obvious.

The administration of the 6 mg/kg morphine to normal rats significantly increases the analgesia and the rectal temperature. The administration of lithium on normal rats significantly decreases the temperature but increases the analgesia. In the rats which received lithium-morphine, the rectal temperature decreased but the analgesia was significantly increased compared to the morphine alone.

In the rats which received 6-OHDA 25 days before the test, the analgesia was significantly reduced and the temperature was decreased, but this was not significant when compared to the normal rats. When morphine was given to the 6-hydroxydopaminized rats, neither the analgesia nor the temperature was increased. According to these results, 6-OHDA inhibited both the analgesic and the hyperthermic effects of morphine.

When lithium was given to 6-hydroxydopaminized rats, it caused a fall in temperature and slightly increased the analgesia. If morphine and lithium were administered together, both analgesia and temperature increased significantly.

After 38 to 40 hours of 5 mg/kg reserpine, the analgesia and the hyperthermic effects of morphine [sic]. When lithium was given to reserpinized rats the temperature was significantly decreased and the analgesia was increased. Reserpine-morphine-lithium treatment significantly increased the analgesia when compared to the normal rats, but did not alter the temperature.

All the test results are shown in Tables 1 and 2.

Table 1. THE EFFECTS OF LITHIUM, RESERPINE, MORPHINE, 6-OHDA AND THEIR COMBINATIONS ON THE ANALGESIA AND TEMPERATURE OF RATS

Group	Rectal Temperature Mean \pm S.E.($^{\circ}$ C)	Analgesia Mean \pm S.E. (Seconds)	Number of Animals(n)
Normal control	39.1 \pm 0.08	4.9 \pm 0.16	20
Lithium control	39.4 \pm 0.63 ^a	6.2 \pm 0.23 ^a	10
Reserpine control	39.3 \pm 0.12 ^d	4.7 \pm 0.21 ^d	10
6-OHDA control	38.3 \pm 0.29 ^b	4.0 \pm 0.34 ^a	10
Morphine control	39.9 \pm 0.05 ^a	8.4 \pm 0.30 ^a	10
Reserpine + lithium	37.2 \pm 0.15 ^{a,e}	5.4 \pm 0.20 ^{c,e}	10
Reserpine + morphine	39.4 \pm 0.07 ^b	3.9 \pm 0.17 ^a	10
Lithium + morphine	39.1 \pm 0.26 ^{d,e}	15.1 \pm 1.22 ^{a,e}	20
6-OHDA + morphine	39.0 \pm 0.32 ^d	4.9 \pm 0.39 ^d	10
6-OHDA + lithium	37.2 \pm 0.22 ^{a,f}	4.3 \pm 0.37 ^{c,e}	12

a: $p < 0.0005$ when compared with normal control group.

b: $p < 0.005$ when compared with normal control group.

c: $p < 0.05$ when compared with normal control group.

d: Nonsignificant when compared with normal control group.

e: $p < 0.005$ when compared with lithium control group.

f: Nonsignificant when compared with lithium control group.

Table 2. THE EFFECTS OF THE COMBINATION OF DRUGS ON THE ANALGESIA AND TEMPERATURE OF RATS

Group	Rectal Temperature Mean \pm S.E.(°C)	Analgesia Mean \pm S.E. (Seconds)	Number of Animals
Lithium + morphine	39.1 \pm 0.026	15.1 \pm 1.22	10
Lithium + morphine + reserpine	39.2 \pm 0.13 ^b	14.6 \pm 0.91 ^b	20
Lithium + morphine + 6-OHDA	40.4 \pm 0.18 ^a	10.3 \pm 1.06 ^a	12

a: $p < 0.005$ when compared with lithium + morphine group.

b: Nonsignificant when compared with lithium - morphine group.

DISCUSSION

As can be seen from these results, if lithium is used alone it has a hypothermic and analgesic effect on the rats. But if it is given together with morphine it enhances the analgesic action of morphine but inhibits its hyperthermic action. The experiments performed by the others so far with lithium or morphine have not yet demonstrated the mode of action of these drugs. Since different authors have used different methods, different doses and different species, there is no agreement about the mode of action of lithium or morphine.

While some authors reported that catecholamines enhance the analgesic effect of morphine or that the central catecholamines had an effect on the analgesia produced by morphine (18, 27, 29, 41, 46, 47, 48, 49), some authors reported that 5-HT increased the analgesic effect of morphine (7, 26, 31, 38, 40, 42).

It is certain that these two amines have an effect on the analgesia and thermo-regulation. Some authors observed that different amines have different effects on different species. NA was found to decrease the temperature in cats (5, 13, 14, 15), but to increase the temperature in rabbits, sheep and goats (1, 3, 8, 19). On the other hand, 5-HT was found to increase the temperature in cats (13, 14, 15) and to decrease the temperature in sheep, mice rabbits and rats (1, 4, 8, 10, 12, 21).

Feldberg and Lotti (16), as well as Myers and Yarksh (28), found that intraventricular injections of NA caused hypo-

thermia or hyperthermia, depending on the dose used, whereas intraventricular injections of 5-HT always caused hypothermia in rats. Bruinvels (4) also reported that injections of 5-HT into the cisterna magna of rats resulted in a dose-dependent decrease in body temperature. According to Feldberg and Myers (15), body temperature is regulated in the hypothalamus of homoiothermic animals by the balance between the monoamines NA and 5-HT.

It is reported that reserpine inhibited the analgesic effect of morphine (7,30,38,40,46,48,49). 6-OHDA, if given intraventricularly, causes long lasting degeneration of the central NA neurons (22,43,44,45). In our department it was observed that 6-OHDA significantly inhibited the analgesic effect of morphine (2). Recent results also confirm these findings.

Although the mode of action of lithium is not known definitely, it was observed that its effect was related to the brain monoamines. It was reported that lithium decreased the level of the brain NA or increased the turnover rate of brain NA (6,17,32,33,39), and also some other authors reported that it increased the turnover rate and brain level of 5-HT (11,34,37), but some claimed that it decreased the 5-HT level in the brain (9,20,25).

Stern *et al.* (39) found that lithium significantly increased the NA turnover in the rat brain, and the plasma and brain lithium concentration reached an equilibrium after about 8 hours. Sheard and Aghajanian (37) reported that lithium treatment increased the brain 5-HT and 5-HIAA levels in the rat and probably this was due to the increase of 5-HT synthesis. Cruet *et al.* (11) also reported that chronic lithium treatment increased the brain 5-HT and 5-HIAA levels and 5-HT synthesis on rats.

According to our results the analgesic and the hypothermic effects of lithium may be due to the release of both 5-HT and NA from the rat brain. Reserpine is depleting both 5-HT and NA and inhibiting the analgesic and hyperthermic effects of morphine. When lithium and morphine are used together on reserpinized rats, the analgesic effect of morphine is restored but neither morphine hyperthermia nor lithium hypothermia is observed.

All these findings suggest that lithium has a synergetic effect on morphine analgesia and an antagonistic effect on morphine hyperthermia. Probably lithium also increases the synthesis and the level of 5-HT in the brain causing the hypothermia. Our findings are in accordance with (11,34,37) as far as the 5-HT release or its increase in the brain by use of lithium is concerned, also with (1,8,10,12,21) that serotonin causes hypothermia.

On the other hand, the destruction of the NA neurons with the use of 6-OHDA may result in a relative increase in the 5-HT level, thus causing hypothermia and decreased analgesia. We think that the analgesic effect is mainly due to NA, but the thermo-regulation is under the influence of 5-HT. In the actions of morphine and the lithium on analgesia and temperature both these amines play a combined role, but the resulting effect is not due to their separate actions but depends on their respective ratio.

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THE EFFECT OF LITHIUM ON MORPHINE ABSTINENCE SYNDROME IN RATS

by

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The rats were made tolerant to morphine with twice daily injections. The starting dose was 20 mg/kg per day and on the 21st day it reached 200 mg/kg per day. Another group received the same dose of morphine as described above, and in addition to morphine, they also received lithium chloride 100 mg/kg i.p. daily.

Some animals received 100 mg/kg i.p. p-chlorophenyl-alanine (pCPA) for the last three days of morphine injections. Some other animals received only saline and served as the control group.

The behaviour, rectal temperature and amount of faeces were recorded during the tolerance and nalorphine-precipitated abstinence syndrome. The results of faeces and rectal temperature of the abstinence syndrome are shown in the tables below.

The details of behavioural changes and other parameters will be presented and discussed in relation to central monoamines.

Table 1. THE CHANGES IN RECTAL TEMPERATURE DURING THE NALORPHINE-PRECIPITATED ABSTINENCE SYNDROME. TEMPERATURE $^{\circ}\text{C} \pm \text{SE}$

Group	Before Nalorphine	After Nalorphine	P	Number of Experiment (n)
Morphine	38.1 ± 0.27	37.2 ± 0.11	0.005	20
Morphine + Lithium	38.3 ± 0.07	37.7 ± 0.10	0.005	17
Lithium	39.0 ± 0.07	39.0 ± 0.15	N.S.	10
Saline Control	38.8 ± 0.15	39.1 ± 0.08	0.025	10
pCPA + Lithium + Morphine	36.5 ± 0.30	35.8 ± 0.25	0.0005	8

Table 2. THE CHANGES IN THE AMOUNT OF FAECES DURING THE NALORPHINE-PRECIPITATED ABSTINENCE SYNDROME

Group	Faeces (mg \pm SE)	Number of Experiment (n)
Morphine	2545 ± 353	20
Morphine + Lithium	3761 ± 328^a	17
Lithium	220 ± 45^a	10
Saline Control	270 ± 95^a	10
pCPA + Lithium + Morphine	2392 ± 309^a	8
pCPA + Morphine	1279 ± 396^a	5
pCPA	465 ± 54^a	5

a: $p < 0.005$ when compared with morphine group.

b: $p < 0.005$ when compared with morphine + lithium group.

THE POSSIBLE ROLE OF MAST CELLS IN THE ACTION OF MORPHINE

by

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The literature on the mechanism of the action of morphine has been thoroughly reviewed by Wikler, Domino and Martin (9,2,5). The effects of morphine on animals and man may be classified in three major groups:

- 1) Peripheral effects exerted either directly by the action of morphine on the smooth muscles of the gas-

tro-intestinal tract or indirectly by release of histamine (3,6).

- 2) Peripheral effects induced indirectly via the central nervous system, such as hypersalivation, lacrimation, miosis, or midriasis according to the animal species, increased motility of the gastro-intestinal system in certain animal species, etc.
- 3) Central nervous system effects, such as analgesia, changes in mood, sedation (dog, monkey), excitation (cat), or hypermotility (mice).

Schmidt and Livingston (8) were the first to describe the symptomatology induced by an i.v. injection of morphine in dogs. We have reinvestigated the acute effects of the intravenous injection of morphine in unanesthetized dogs (1) in an effort to further understand the possible role of mast cells in morphine action.

The intravenous administration of 10 mg/kg of morphine sulfate (Table 1, Group 1), induced after a lapse of 30 seconds, induced struggling, howling and screaming as if the animals were in great pain or distress. Also, after a latency of 30 seconds, a precipitous fall in the blood pressure was recorded; the blood pressure remained reduced for 1 to 2 hours. The circulatory effects of i.v. injections of morphine in dogs have been attributed to the release of histamine (3,6). During and immediately following the initial phase of agitation, the animals urinated, defecated and salivated profusely. These dogs also scratched themselves, particularly on the ears. Vomiting occurred in instances where the animals had been fed before the injection. This stage of agitation lasted only 1 to 2 minutes, after which the animals became quiet and preferred to remain quietly in a corner; they were apparently still in distress, apprehensive and alert. After a period of approximately 5 minutes, sedation gradually supervened; the animals' posture became relaxed, their attentiveness diminished, but profuse salivation persisted; respiration was shallow and accelerated.

A second i.v. injection of morphine (10 mg/kg) 90 minutes after the i.v. administration of morphine (10 mg/kg) deepened the already present sedation and induced only minor changes in respiratory and circulatory functions (Table 1, Group 2).

In contrast to the effects of a single i.v. injection of 10 mg/kg of morphine, the same dose administered subcutaneously failed to induce the pattern of struggling, restlessness, hypotension, etc.; moreover, such subcutaneous pretreatment also failed to prevent the symptomatology induced by subsequent i.v. administration of morphine (Table 1, Group 3).

Table 1. THE ACUTE EFFECTS OF THE INTRAVENOUS ADMINISTRATION OF MORPHINE AND OF 48/80 IN NONANESTHETIZED DOGS

Experimental Group	Pretreatment	Treatment (i.v.)	Initial Agitation*	Sedation (lasting for 1 to 2 hours)	Persistent Shallow Tachypnea	Hypotension +
1	-	Morphine 10 mg/kg	++	+	+	+
2	Morphine 10 mg/kg, i.v. 90 min. before	Morphine 10 mg/kg	-	++	+	-
3	Morphine 10 mg/kg, s.c. 30 min. before	Morphine 10 mg/kg	+	++	+	+
4	-	48/80 0.5 to 1 mg/kg	++	-	+	+
5	48/80 0.5 mg/kg, i.v. 90 min. before	48/80 0.5 mg/kg	-	-	-	-
6	48/80 0.5 mg/kg, i.v. 90 min. before	Morphine 10 mg/kg	-	+	+	-
7	48/80 0.5 mg/kg, i.v. 3 weeks before	Morphine 10 mg/kg	++	+	+	+

* Screaming, restlessness, irregular respiration, profuse salivation, defecation, urination, etc., beginning after a 25-30 sec. latency and lasting for 1-2 minutes

+ After a 25-30 sec. latency and lasting for 1-2 hours.

The i.v. administration of 0.5 to 1 mg/kg of 48/80, a potent histamine releaser, produced acute effects (Table 1, Group 4) similar to those induced by morphine as described above (Table 1, Group 1); after a latency of about 30 seconds, a similar phase of agitation occurred as well as all the other acute effects described, with the exception of sedation and the persistent shallow and accelerated respiration.

Ninety minutes after the initial injection of 48/80, a subsequent administration of the same drug (Table 1, Group 5) failed to induce the syndrome obtained initially. This phenomenon can be explained by the fact that the initial injection of 48/80 depletes the stores of histamine and other active substances of the mast cells so that any subsequent injection cannot release the active substances responsible for inducing the fall in blood pressure, salivation, itching, etc. (04).

The i.v. injection of morphine to dogs whose mast cells had been previously depleted by injection of 48/80 (Table 1, Group 6) failed to produce the characteristic syndrome of morphine, except for its sedative and respiratory actions.

When morphine was administered 3 weeks after the 48/80 (Table 1, Group 7), it once again produced the same effects as in nonpretreated animals; it is known that the histamine content of mast cells has completely recovered to normal levels by 14 days after 48/80-induced depletion (7).

These observations suggest that some of the acute peripheral effects of morphine such as salivation, urination, defecation, scratching, vomiting and fall in blood pressure are neither centrally mediated, nor due to a direct effect of morphine on effector organs. Rather, these experiments serve as pharmacological evidence indicating that morphine affects the same target cells as 48/80, the mast cells, thereby causing the release of either histamine or other active substances.

Further experiments were conducted, using morphine-addicted dogs. To induce addiction, each of the dogs received 20 mg/kg of morphine sulfate twice daily for 6 weeks. During the 4th week, one of these two daily injections was omitted; the animals showed some signs of the abstinence syndrome such as hypersalivation, lacrimation, or change in mood. (The animals which failed to show signs of abstinence were excluded from the experiment.) To further ascertain that the dogs were addicted to morphine, at the end of the 6th week a randomly selected group of dogs were injected i.v. with 0.5 mg/kg of nalline (n-allylmorphine). This antimorphine compound precipitates an acute withdrawal syndrome (10).

There are some similarities between the symptoms of the nalline-precipitated withdrawal syndrome in addicted dogs (Table

2, I) and the effects of the i.v. injection of morphine in non-addicted animals (Table 1, Group 1).

The administration of 48/80 (1 mg/kg) to morphine-addicted dogs (Table 2, II) induced a pattern similar to that observed after nalline in these animals. It is extremely important to note the fact that in these addicted dogs, 48/80 causes a deep sedation (following the brief initial period of restlessness) as if an excess dose of morphine had been administered, whereas sedation was not induced by 48/80 in nonaddicted animals.

Table 2. THE EFFECTS OF 48/80 ON THE WITHDRAWAL SYNDROME PRECIPITATED BY AN I.V. INJECTION OF NALLINE TO THE MORPHINE-ADDICTED DOGS

Signs	I Nalline 0.5 mg/kg i.v.	II 48/80 1 mg/kg i.v.	III 48/80 1 mg/kg i.v. 24 hours after first exhibition of 48/80	IV Nalline 0.5 mg/kg i.v. 30 min. after second exhibition of 48/80
Lacrimation	+	+	-	-
Rhinorrea	+	+	-	-
Salivation	+	+	-	-
Urination	+	+	-	-
Defecation	+	+	-	-
Emesis	+	+	-	-
Restlessness	+	+(1)	-	+
Yawning	+	-	-	+
Mydriasis	+	-+	-	+
Tachycardia	+	-+	+	-
Hyperthermia	+	-+	-	?
Hyperpnea	+	-+	-+	-

(1) Later, deep sedation.

Twenty-four hours after the injection of 48/80 to addicted dogs, a second injection (Table 2, III) failed to elicit most of the responses originally obtained with nalline or 48/80. Presumably, the lack of effects was due to the depletion of the mast cells. The injection of 0.5 mg/kg i.v. of nalline (Table 2, IV) to these same dogs 30 minutes after the second injection of 48/80 also failed to produce most of the signs of acute withdrawal, such as lacrimation, rhinorrhea, salivation, urination, defecation, emesis, tachycardia and hyperpnea.

These results indicate that the peripheral signs of the precipitated withdrawal syndrome produced by nalline are due to the release of pharmacologically active substances from the mast cells in a manner similar to that accomplished by the i.v. injection of morphine in nonaddicted dogs.

It is important to note that the administration of 48/80 also mimicked many of the effects of morphine withdrawal with the important exception that it induced deep sedation similar to that produced by morphine itself; whereas nalline did not induce sedation. In an attempt to determine whether or not the morphine stored in the body may in any way be involved, we determined the blood levels of morphine before and after the administration of 48/80 (Table 3) using the method described by Kupferberg, Burg-holter and Way (1964). The marked increase in morphine blood levels induced by 48/80 suggest that this compound can release morphine, concomitantly with other active substances, from its tissue stores, presumably from the mast cells.

We may consider that chronic administration leads to an accumulation of morphine in the mast cells and that these cells become more sensitive to a lack of morphine and to the morphine's antagonists. Thus, these morphine antagonists release abundantly from the mast cells pharmacologically active substances, which in turn are responsible for the peripheral signs of acute, drug-induced withdrawal syndrome in the dog.

We can summarize our view as follows: a significant proportion of morphine is stored in the periphery by the mast cells, while a certain portion reaches the central nervous system producing effects such as analgesia or respiratory depression, as well as centrally mediated peripheral actions as illustrated schematically in Fig. 1. When mast cells are confronted with a massive dose of morphine in a short time, there is a release of biologically active substances such as histamine, serotonin (5-HT), bradikinin and slow reacting substance (SRS), from the tissue stores. These compounds in return reach the target organs (microcirculation, exocrine glands and smooth muscles). If morphine is administered chronically to the dogs, the mast cells' capacity for morphine storage increases. Morphine antagonists release this stored morphine as well as other active

Table 3. THE BLOOD LEVELS OF MORPHINE ($\mu\text{g/ml}$)
IN ADDICTED DOGS BEFORE AND AFTER AN
I.V. INJECTION OF 0.5 MG/KG OF 48/80

	Before 48/80		After 48/80		
Dog. No.	Blood level of Morphine $\mu\text{g/ml}$	Average \pm S.E.	Blood level of Morphine $\mu\text{g/ml}$	Average \pm S.E.	t
1	1.04		2.60		
2	2.30	1.58 ± 0.1844	3.00	2.83 ± 0.05916	3.185
3	1.40		2.90		

$p < 0.05$.

substances, thus causing the central nervous system signs of abstinence syndrome.

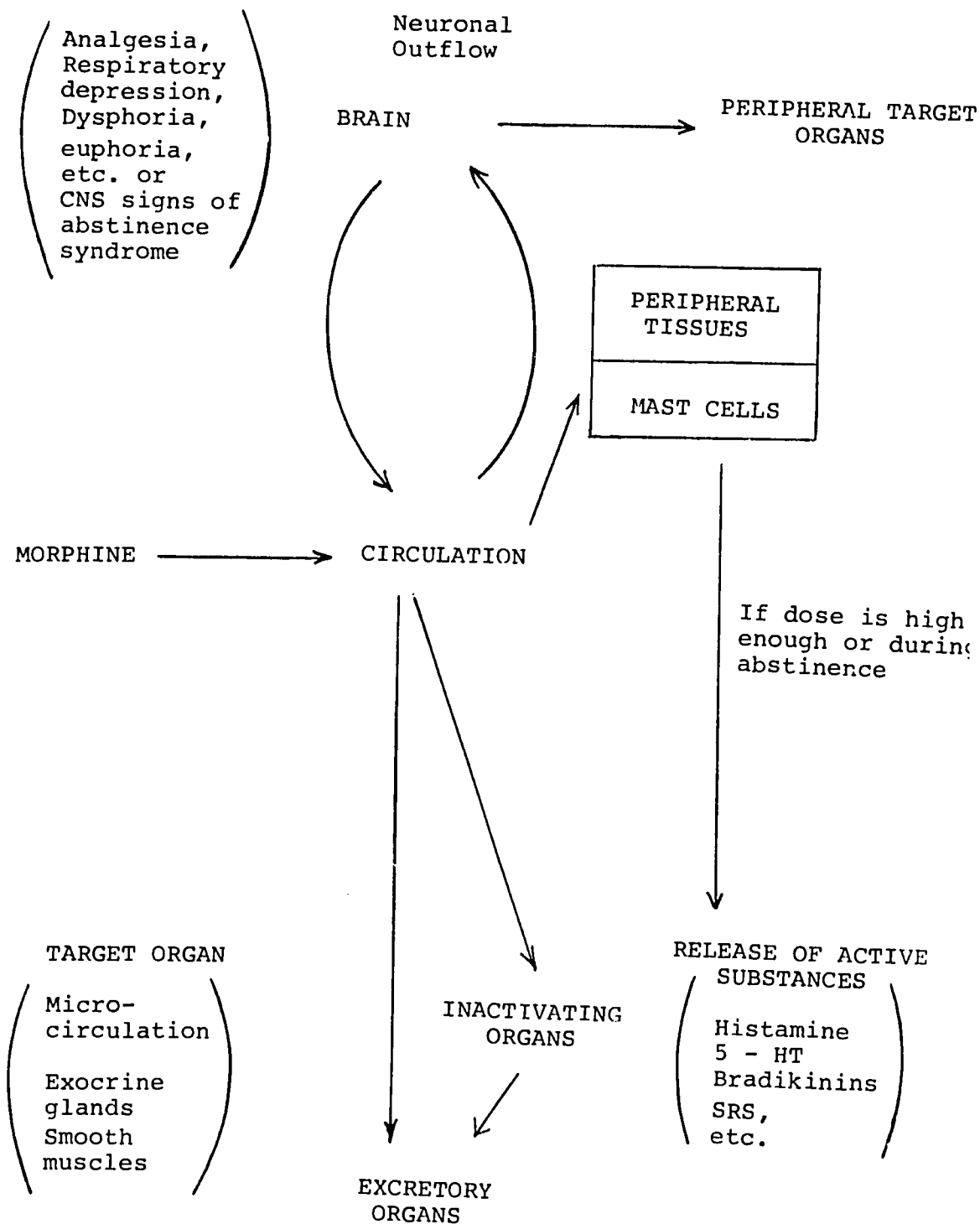
In summary, the depletion of mast cells by the administration of the histamine releaser 48/80 markedly modified morphine effects and addiction as follows:

1) Morphine plasma levels increase, thereby inducing sedation (an effect which cannot be observed by 48/80 injections in nonaddicted dogs).

2) The i.v. injection of morphine fails to produce the fall in blood pressure, struggling, howling, salivation, defecation, emesis and urination; instead only sedation (central nervous system effect) is observed.

3) Nalline does not induce most of the classical signs of the withdrawal syndrome.

FIGURE 1. DIAGRAMATIC ILLUSTRATION OF THE DISTRIBUTION OF MORPHINE IN THE BODY



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A STUDY ON MORPHINE DEMONSTRATING THE PHENOMENA OF PHARMACOLOGIC TOLERANCE, BEHAVIOURAL TOLERANCE AND BEHAVIOURAL HABITUATION IN RATS

by

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Changes in an animal's behaviour are generally measured as an indication of the effects of psychoactive drugs. The return to normal parameters of behaviour in spite of continued drug employment becomes one indication of tolerance development to such drugs. Behavioural parameters, however, are subject to continuous modulation by numerous internal and external stimuli. In studies dealing with tolerance development to psychoactive drugs, the modifying effects of external stimuli, in particular, must be distinguished from those resulting merely from the repeated administration of the drug. Among the external factors which can influence the measurement of tolerance is the effect of repeatedly testing the animal while it is under the influence

of the drug. This drug-test interaction, which has been referred to as "behavioural tolerance" has been implied to occur with a variety of psychoactive drugs (5).

Another factor which can affect drug-behaviour research is repeated exposure of animals to the same test environment even in the absence of drug. A diminution in response to a drug brought about by repeated exposure to a test procedure in the absence of drug has been referred to as "behavioural habituation" (11). This phenomenon has been demonstrated to develop to amphetamine and to barbiturates (9) and to an amphetamine-amobarbital mixture (11,12,13).

Previous studies have demonstrated that a behavioural tolerance to morphine, as well as a pharmacologic one, develops in rats (1,8). Behavioural habituation was not observed in these studies. However, the number of doses administered and/or tests given were limited to five. Since it is known that behavioural habituation develops when other psychoactive drugs are used, it is possible that behavioural habituation can be observed following morphine if animals receive more experience in the test procedure. Thus, an experiment was designed to investigate specifically whether or not behavioural habituation to morphine can develop in rats tested on the hot plate. Also investigated were: 1) the effect of the dose (or test) interval on the development of behavioural habituation and tolerance, and 2) the temporal relationship between behavioural tolerance, pharmacologic tolerance and behavioural habituation.

METHODS

Animals

Young adult male Holtzman rats having an initial weight of 120-140 g were utilized as the experimental animals. Throughout the experiments, the animals were kept in constant environmental conditions with free access to water and commercial food. At least 5 days were allowed for acclimation in this environment before use in the experiments. On the day of an experiment, the animals were transported in cages to a separate room for testing.

Drugs

Morphine sulfate was dissolved in normal saline to provide a concentration of either 2.5 mg/ml, or 5 mg/ml of the free base. A dose of 5 mg/kg, or 10 mg/kg was administered subcutaneously in the midline of the back. A corresponding volume of nor-

mal saline, 2 ml/kg, was administered in a similar manner to the saline treated animals.

Basic Analgesic Testing Procedure

The hot plate method of Eddy and Leimbach (2) as modified by Johannesson and Woods (7) with one alteration was used to measure analgesia. The alteration consisted of replacing the use of a "prone hand" with a 10-in. square perforated plexiglass plate cover for the restraining cylinder. Throughout an experiment, the surface temperature was maintained as $55.0 \pm 0.5^\circ\text{C}$. The experiments were conducted by two persons. The first dropped the rat onto the plate and placed the plexiglass atop the cylinder. The second person, unaware of the drugs and/or dosages administered, determined the animal's response latency with a stopwatch. Response latency was measured as the interval from the moment the animal was dropped onto the surface of the hot plate until it reacted to the heat stimulus, or until 60 seconds elapsed. The responses used as end points were either licking of the paws or jumping up the side of the restraining cylinder. The great majority of the animals responded to the stimulus by licking their paws. For analgesic testing, each animal was tested twice on the hot plate: the first (the control response latency) took place immediately before the administration of experimental agents (morphine or saline) and the second took place 30 minutes after the first test. The difference between these two response latencies was recorded as change in response latency.

These experiments were conducted, differing only in the dosage of morphine and in the frequency of both drug administration and analgesic testing.

Experiment 1: Drug administration and/or analgesic testing were employed *once each day* for 11 days. The dose of morphine was 10 mg/kg.

Experiment 2: Drug administration and/or analgesic testing were employed *once each day* for 11 days. The dose of morphine was 5 mg/kg.

Experiment 3: Drug administration and/or analgesic testing were employed *once each week* for 11 weeks. The dose of morphine was 5 mg/kg. In each experiment, the rats were randomly divided into two categories (Table 1), those designated as *experienced* and those as *naive* animals. Animals in these catego-

ries were divided into two subcategories, those receiving morphine on a *chronic* basis and those receiving morphine only *acutely*. By "experienced" is meant that the animal's response on the hot plate was measured prior to and following each injection of the experimental agent (either morphine or saline). Naive rats, although receiving the experimental agent (either morphine or saline) were not subjected to the analgesic testing until the final day they were in the experiment. The experienced rats receiving morphine chronically (designated as chronic morphine-experienced) were injected and tested daily (or weekly) eleven times. The experienced rats receiving an acute dose of morphine (designated as acute morphine-experienced) were further subdivided into ten groups (Table 2). The first group received saline and was subjected to the analgesic testing on the 1st day (or week). On the 2nd day, it received an acute dose of morphine and analgesic testing, and was then discarded. The second group received saline and analgesic testing on days 1 and 2; a dose of morphine along with the analgesic testing on day 3 and was then discarded. The remaining groups were similarly treated such that on the 11th day (or week) of the experiment, the tenth group had received ten injections and ten analgesic testings under saline and one injection and one testing under morphine. The procedure utilized with the naive animals receiving an acute dose of morphine (designated as acute morphine-naive) was very similar with that of the acute morphine-experienced category. The only difference between experienced and naive-acute morphine groups was the analgesic testing; the naive rats received analgesic testing concomitantly with morphine *only*. Likewise, the naive animals receiving morphine chronically (chronic morphine-naive) were divided into ten groups and were subjected to the same procedure as acute morphine-naive groups except that they received morphine at all times.

Table 1. CLASSIFICATION OF EXPERIMENTAL GROUPS

	Experienced		Naive	
	Chronic Morphine	Acute Morphine	Chronic Morphine	Acute Morphine
Number of Groups*	1	10	10	10

Each group consisted of 10 animals.

Table 2. EXPERIMENTAL DESIGN FOR THE ACUTE
MORPHINE-EXPERIENCED GROUPS*

Number of Groups	D a y s o r w e e k s										
	1	2	3	4	5	6	7	8	9	10	11
1	S	M									
2	S	S	M								
3	S	S	S	M							
4	S	S	S	S	M						
5	S	S	S	S	S	M					
6	S	S	S	S	S	S	M				
7	S	S	S	S	S	S	S	M			
8	S	S	S	S	S	S	S	S	M		
9	S	S	S	S	S	S	S	S	S	M	
10	S	S	S	S	S	S	S	S	S	S	M

*Only difference between acute morphine-experienced and acute morphine-naive groups is the analgesic testing. S animals received saline; M animals received morphine.

Calculations

The control response latencies were analyzed using an analysis of variance, and the means were compared using Duncan's New Multiple Range Test (17) in all experiments for each experimental day or week. Changes in response latencies from control were analyzed for each experimental day or week as described below.

Experiment 1: Since most of the animals in the groups of acute morphine-experienced and acute morphine-naive did not respond to the heat stimulus within the cut-off time (60 seconds) a quantal data analysis was employed using Fisher's Exact Probability Test (16) when any of these two groups were compared. When comparisons were made between chronic morphine-experienced and chronic morphine-naive groups, it was found that these two groups always had unequal variances; therefore, statistical analysis of these two groups was performed utilizing the Mann Whitney U Test (4).

Experiments 2 and 3: It was found that variances of the chronic morphine-experienced groups were always significantly smaller than those for the other three groups, thus causing a heterogeneity of variance when an analysis of variance applied to all four groups. Therefore, the data of all groups, less the chronic morphine-experienced category, were analyzed utilizing an analysis of variance and means were compared using Duncan's New Multiple Range Test. Statistical comparisons of the chronic morphine-experienced with the acute morphine-experienced and with the chronic morphine-naive groups were calculated using the Mann Whitney U Test. In all cases, $p \leq 0.05$ was chosen as the level of significance.

RESULTS

Daily Administration of 10 mg/kg of Morphine

The mean control response latencies obtained prior to a 10 mg/kg morphine dose during eleven daily trials on the hot plate are illustrated in Figure 1A. When animals were exposed to the test procedure repeatedly (the acute morphine-experienced and chronic morphine-experienced groups); their control response latencies became shorter than those animals subjected to testing for the first time (the acute and chronic morphine-naive groups). A significant difference between the experienced and naive-acute morphine groups was first observed on the 5th day and remained significantly different thereafter. A significant reduction in the mean control response latency of the chronic morphine-experienced group, as compared to the chronic morphine-naive group was developed by the ninth test.

Changes in response latency from the daily control time throughout experiment 1 are summarized in Figure 1B. As can be seen from this figure, tolerance developed most rapidly and most completely in those animals which received both morphine and testing on a chronic basis (chronic morphine-experienced group). Even on the 2nd day, the analgesic effect of morphine was significantly less in this group than in those experienced animals

receiving morphine for the first time (the acute morphine-experienced group). Tolerance also developed, but to a less rapid and complete extent, in those animals receiving chronic morphine but naive to the testing procedure. In addition, an examination of the data obtained from the acute morphine-experienced groups shows that repeated testing alone appears to diminish the responsiveness to morphine. This reduced analgesic effect became significantly different from that of the acute morphine-naive group by the 8th day of testing.

Daily Administration of 5 mg/kg of Morphine

The mean control response latencies attained prior to a 5 mg/kg morphine injection during eleven daily trials on the hot plate are illustrated in Figure 2A. Again, repeated daily trials in the hot plate procedure reduced the rats' control response latencies. This was illustrated by significant differences between the experienced and naive groups on days 4 through 11.

Changes in response latency from the daily control time throughout experiment 2 are summarized in Figure 2B. Again, tolerance developed most rapidly and completely in those animals which received both morphine and testing on a chronic basis. In contrast, tolerance developed considerably more slowly (and less completely) in the chronic morphine-naive animals. In this group, significant tolerance development was not observed until the seventh dose of morphine. As in the previous experiment, repeated testing alone diminished the responsiveness to morphine. This was apparent by the 7th day of testing (compare the acute morphine-naive groups vs. the acute morphine-experienced groups).

Weekly Administration of 5 mg/kg of Morphine

The effects of weekly hot plate trials on the mean control response latencies are summarized in Figure 3A. While significant differences between the experienced and naive groups were observed on some of the trials, these differences were not persistent once they first occurred, as was the case during the daily experiments.

Changes in response latency from the weekly control time throughout experiment 3 are summarized in Figure 3B. As in the previous experiments, tolerance developed most rapidly and com-

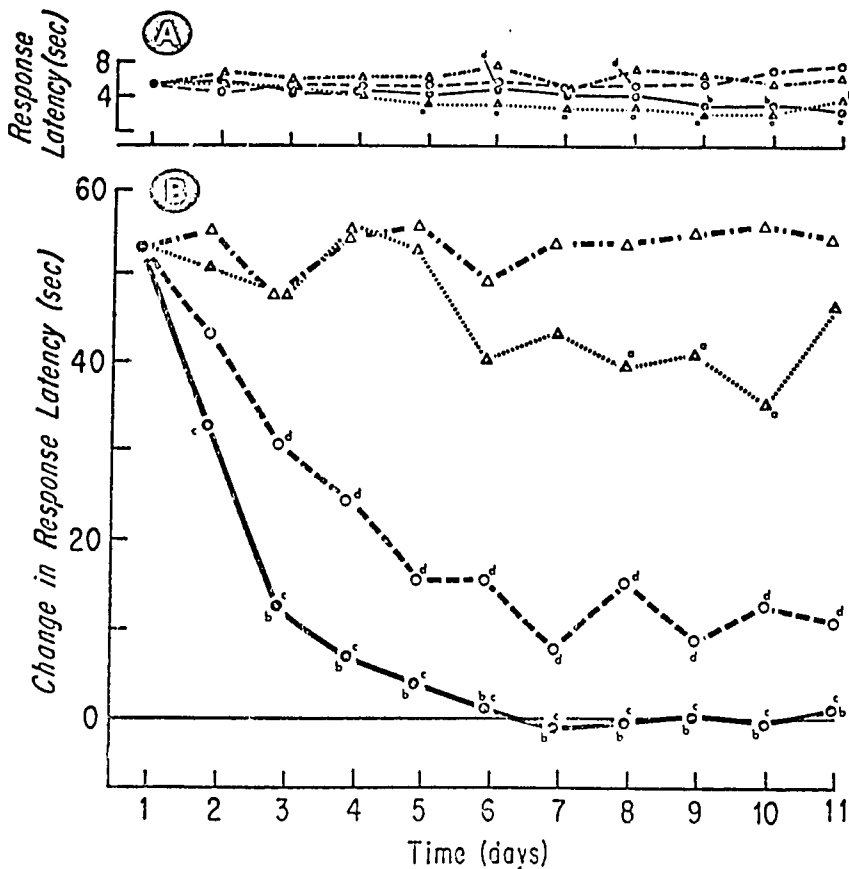


Figure 1. Daily administration of 10 mg/kg of morphine.

- A. Control response latencies (in seconds) immediately before morphine administration.
- B. Changes in response latency (in seconds) from the control time 30 minutes after morphine injection.

Each point indicates the mean control response latency or the mean change in response latency in the chronic morphine-experienced (●—●), chronic morphine-naive (○---○), acute morphine-experienced (▲---▲), or in the acute morphine-naive (Δ---Δ) animals. The solid lines indicate that the same animals were used throughout the experiments, and the dotted lines indicate that a different group of animals were tested each day. The number of animals in each group was 10. A statistically significant difference at $p \leq 0.05$ is denoted by an "a" between the acute groups, by a "b" between the chronic groups, by a "c" between the experienced groups and by a "d" between the naive groups. For further details see text.

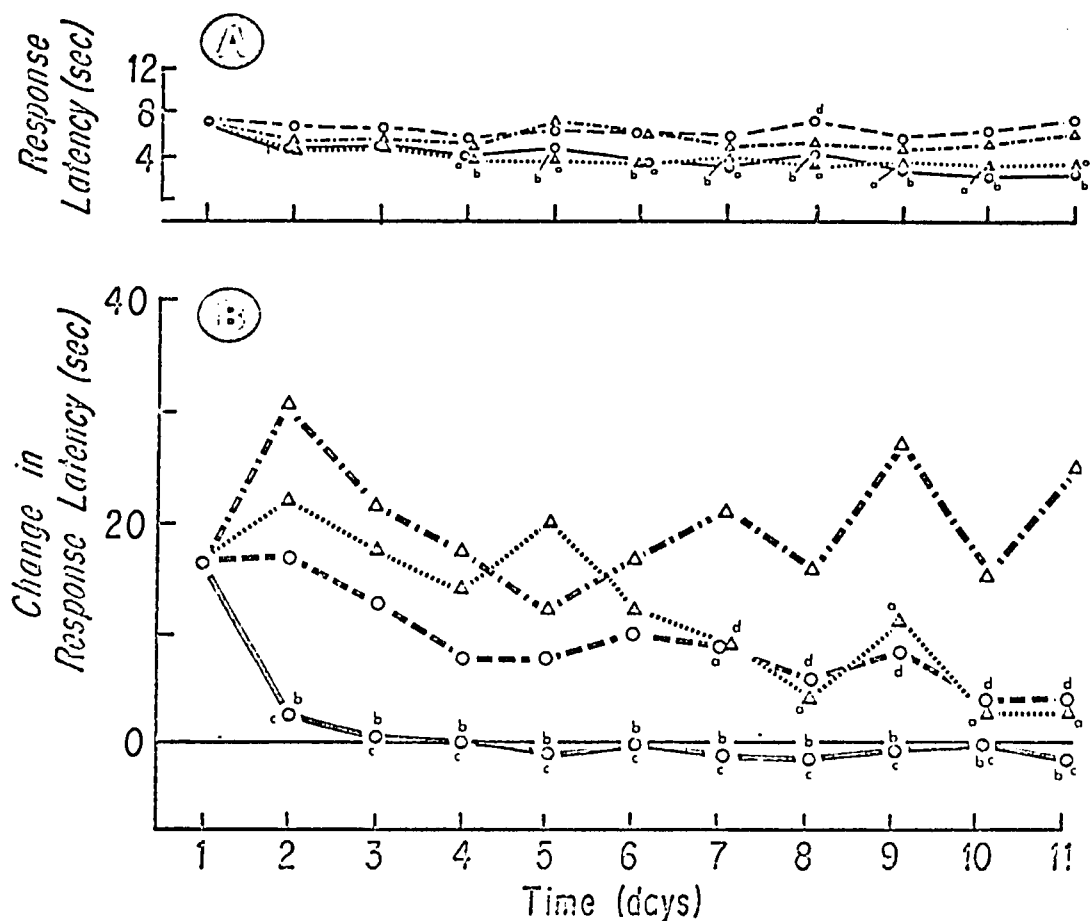


Figure 2. Daily administration of 5 mg/kg of morphine.

- A. Control response latencies (in seconds) immediately before morphine administration.
- B. Changes in response latency (in seconds) from the control time 30 minutes after morphine injection.

Each point indicates the mean control response latency or the mean change in response latency in the chronic morphine-experienced (●—●), chronic morphine-naive (○—○), acute morphine-experienced (▲—▲), or in the acute morphine-naive (△—△) animals. The solid lines indicate that the same animals were used throughout the experiments, and the dotted lines indicate that a different group of animals were tested each day. The number of animals in each group was 10. A statistically significant difference at $p \leq 0.05$ is denoted by an "a" between the acute groups, by a "b" between the chronic groups, by a "c" between the experienced groups and by a "d" between the naive groups. For further details see text.

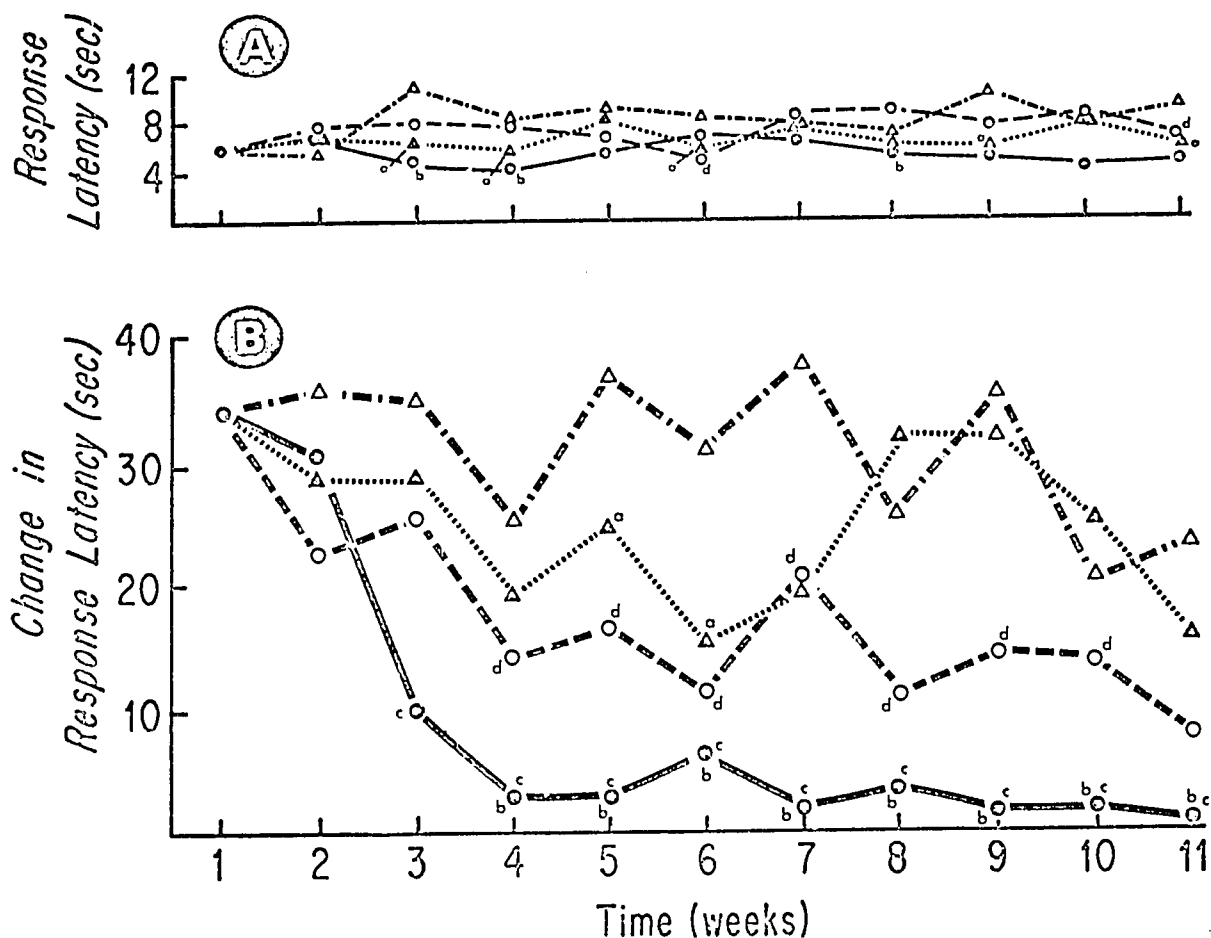


Figure 3. Weekly administration of 5 mg/kg of morphine.

- A. Control response latencies (in seconds) immediately before morphine administration.
- B. Changes in response latency (in seconds) from the control time 30 minutes after morphine injection.

Each point indicates the mean control response latency or the mean change in response latency in the chronic morphine-experienced (●—●), chronic morphine-naive (○---○), acute morphine-experienced (▲---▲), or in the acute morphine-naive (△---△) animals. The solid lines indicate that the same animals were used throughout the experiments, and the dotted lines indicate that a different group of animals were tested each week. The number of animals in each group was 10. A statistically significant difference at $p \leq 0.05$ is denoted by an "a" between the acute groups, by a "b" between the chronic groups, by a "c" between the experienced groups and by a "d" between the naive groups. For further details see text.

pletely in the chronic morphine-experienced group. In contrast to the results of the two previous experiments; however, there was no measurable tolerance development in this group until the third dose of morphine was administered. In the chronic morphine-naive animals, significant tolerance development did not occur until the fifth dose and the degree of this tolerance remained less than that seen in the chronic morphine-experienced group. Also, in this experiment no evidence for an effect of repeated testing alone on the responsiveness to morphine was obtained, since no consistent differences were observed between the acute morphine-naive and acute morphine-experienced groups.

DISCUSSION

The results of these experiments have once more demonstrated that repeated testing on the hot plate reduces rats' control response latencies as was shown previously (3,8). An interesting point, however, and one which had not been observed in these previous studies, is the fact that repeated testing in the absence of drug can also cause a diminished analgesic response to an acute dose of morphine. This phenomenon, termed behavioural habituation (see Introduction), was observed in the animals tested daily. In the daily studies, it was not observed until the 7th or 8th day of testing. This explains why it was not seen in the previous studies, since in these studies testing occurred only for 5 days. It is also of interest to note that behavioural habituation was not consistently observed in those animals tested once each week. Thus, it appears that the time interval between testing has an influence on the development of behavioural habituation. Indeed, it has been pointed out (19) that repeated evocation of a response pattern can influence subsequent measurements of the same behaviour and this can be prevented if intervals between measurements are of sufficient length. Our data suggest that an interval of one week between testing on the hot plate is a sufficient length to prevent the occurrence of behavioural habituation, but not long enough to prevent the decrease in control reaction time which occurs with repeated testing, since even in the group tested weekly, the control response latencies were significantly less in the experienced than the comparable naive animals after the 4th week.

It also appears from these data that the interval between tests (and/or morphine administration) is important in the development of behavioural tolerance. Behavioural tolerance developed by the 2nd day in the daily experiment but not until the 3rd week in the weekly experiment.

An indication of the rate of pharmacologic tolerance (i.e., tolerance due to the repeated administration of the drug,

per se) is given by the chronic morphine-naive animals in these experiments. Examination of these data show that the development of pharmacologic tolerance is less rapid and less complete than the development of behavioural tolerance. This was shown by the fact that no analgesia was detectable after two or three doses of morphine in the chronic morphine-experienced animals, whereas, in the chronic morphine-naive animals, some analgesia remained even on the last dose.

Gebhart *et al* (3) postulated a mechanistic scheme for the development of behavioural tolerance. According to this scheme: 1) a recently acting drug inhibits an enzyme system which produces a product from a substrate, 2) this product is necessary for, and is released during, some behaviour, 3) the repression of the system results in an impairment of behaviour, and 4) repression of the enzyme system leads to a compensatory derepression of the system and consequently returns the impaired behaviour toward "normal." This scheme extends the expansive theory of drug tolerance and physical dependence advanced by Goldstein and Goldstein (6) and Shuster (15) and applies it to the behavioural tolerance which has been demonstrated to develop to many centrally acting drugs. The exposure of an animal to perform some task while under the influence of a drug will enhance the development of tolerance to the drug since both the drug and behaviour decrease the level of product and depress the enzyme system more rapidly than any of them alone. Therefore, behavioural tolerance occurs more rapidly and completely than pharmacologic tolerance. The phenomenon of behavioural habituation will also fit this scheme. In this case, the partial depletion of product occurring through repeated testing at sufficiently short intervals would produce a partial depression of the system thus resulting in greater enzyme activity than normal. Consequently, the drug is less effective in this case of heightened enzyme activity than when the enzyme activity is present at normal levels. This hypothesis, albeit speculative, is nonetheless consistent with the data and is of value since it does suggest new approaches to the study of behavioural habituation and behavioural tolerance.

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BEHAVIOURAL TOLERANCE TO MORPHINE IN RATS AND ITS EFFECT ON DETERMINING THE TIME-RESPONSE CURVE

by

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ABSTRACT

Rats tested on the hot plate following morphine showed marked attention in their analgesic response to morphine in the subsequent test (30 minutes later). This attenuation is the result of a drug-test interaction, referred to as behavioural tolerance, and has important consequences in determination of the time-response curve when psychoactive drugs are investigated.

In studies concerned with the analgesic effect of morphine and other narcotic drugs in laboratory animals, time-response curves are often used for evaluation of the data (1). In order to obtain these time-response curves, an animal's response is measured in the algesimetric procedure at least once before and then several times after the administration of the drug at various time intervals. Studies from this laboratory have demonstrated that experience in the testing procedure acquired while the animal is under the influence of morphine can accelerate the rate of tolerance development to the drug (2). In one study, it was observed that this drug-test interaction occurred within 6 hours following morphine administration (3). Time intervals shorter than 6 hours were not studied, however. The question arises, therefore, as to how rapidly this phenomenon can occur.

Specifically, it is of interest to know whether or not time-response curves generated by repeatedly testing the same animals are different from those obtained using different groups of animals for each time interval.

Four groups of experimental animals (male, Holtzman rats, 120-180 g) were utilized, with 16 rats in each group. Initially, all rats were subjected to the hot plate procedure (4), and thus their control response latencies were determined. Immediately after the test, they received a subcutaneous dose of 5 mg/kg morphine (equivalent amount of morphine sulfate was dissolved in normal saline to give a concentration of 2.5 mg/ml). Group A animals were tested again on the hot plate 30, 60, 90 and 120 minutes after the drug; group B 60, 90 and 120 minutes after; group C 90 and 120 minutes after; and group D 120 minutes after. Response latencies for each group and control response latencies for all groups were analyzed using an analysis of variance and the means were compared, utilizing Duncan's New Multiple Range Test (5). At the 60, 90 and 120-minute time intervals, the means of groups B, C or D, respectively, were compared to that of group A. Since there were always unequal variances between the compared groups, a tabulated t' value was computed (6) instead of the Student's t Test. Table 1 shows the data obtained from this experiment. Analgesia was present in group A at 30 and 60 minutes after morphine administration, although the degree of analgesia at 60 minutes as compared to 30 minutes was significantly reduced. No analgesia was present at 90 and 120 minutes after the drug in this group. In contrast, when groups B, C and D were tested for the first time after morphine at the 60, 90 or 120-minute intervals respectively, a significant degree of analgesia was observed and the magnitude of this response was always greater than that for group A at the corresponding time period.

In order to investigate whether or not this marked attenuation in the analgesic response of the group A animals might be due to more exposure of the animals to the heat stimulus than the other groups, another experiment was conducted. In this experiment, each group was again tested on the hot plate for determination of their control response latencies. However, one-half of the animals from each group were not removed from the plate after this measurement until 60 seconds had elapsed from the time the animals were dropped onto the heated surface. They constituted the A' and B' groups respectively. Response latencies for each group and control response latencies for all groups were analyzed as described in the first experiment. There were unequal variances between the A and A' groups at 30 minutes and, therefore, the means for these groups were compared as described in the previous experiment. At 60 minutes groups were analyzed, using an analysis of variance and the means were compared, utilizing Duncan's New Multiple Range Test. Table 2 summarizes the results of this experiment. As was observed in the

Table 1. THE EFFECT OF REPEATED ANALGESIC TESTING AFTER
DOSE OF MORPHINE IN RATS¹

Groups	Control ²	Minutes after Morphine			
		30	60	90	120
A	7.6±0.6	24.8±2.8 ⁴	13.2±1.6 ⁴	7.2±0.7	6.7±0.5
B	8.5±0.7	-	38.3±4.7 ^{3,4}	20.5±4.6 ⁴	10.5±1.8
C	8.5±0.6	-	-	16.2±1.9 ^{3,4}	8.9±0.9
D	7.4±0.7	-	-	-	9.4±0.7 ^{3,4}

1. The mean response latencies (in seconds) ± standard error. Number of animals in each group is 16.
2. There is no significant difference among the groups during control.
3. Significantly different from that of group A within the same time interval and from their control.
4. Significantly different from the control.
P ≤ 0.05 in all cases.

Table 2. THE EFFECT OF PROLONGED EXPOSURE TO THE
HOT PLATE ON THE ANALGESIC RESPONSE TO
MORPHINE IN RATS¹

Group	Response Latencies (in Seconds) Minutes after Morphine		
	Control ²	30	60
A	7.2±0.8	26.9±2.9 ⁴	15.7±2.9 ⁴
B	8.6±0.4	-	35.6±6.9 ^{3,4}
A'	9.3±1.1	48.2±6.0 ^{3,4}	39.1±8.1 ^{3,4}
B'	7.2±0.7	-	38.7±6.2 ^{3,4}

1. The mean ± standard error. Number of animals in each group is 8.
2. There is no significant difference among the groups during control.
3. Significantly different than that of group A within the same time interval and from their control.
4. Significantly different from the control.
p ≤ 0.05 in all cases.

previous experiment, group A showed significantly less analgesia than group B at 60 minutes and less than its own response during the 30-minute period. The effect of heat in groups A' and B' was also examined. As can be seen from Table 2, group A' had a significantly greater response than group A at both the 30 and 60-minute periods. Group B' did not show any significant difference from B at the 60-minute period. However, group B' had a significantly greater response than that seen in group A at 60 minutes.

These results demonstrate that the animal's exposure to the testing procedure, while it is under the influence of morphine, can reduce its response to the drug even within a period of 30 minutes, and markedly alters the time-response which is apparently the result of a drug-test interaction and has been termed "behavioural tolerance" (7). It has been reported to occur with other psychoactive drugs (8) as well as with morphine (4). Therefore, the consequences of the results obtained in this study must be considered not only in studies dealing with narcotics, but also with other psychoactive drugs when time-response curves have to be constructed.

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CHARAS ABUSE AND PSYCHOSIS

by

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Cannabis has long been used in the East without attracting much attention. Since the drug invaded the West and came in time to be incorporated in the "Green Revolution" the controversy started. More knowledge of the immediate and long-term effects of cannabis smoking on the human mind and body will determine the place this chemical is to attain in future.

The adverse reactions associated with cannabis range from a transitory perceptual distortion to toxic psychosis. The purpose of this paper is to present a profile of psychotics using cannabis and compare them with a matched group of psychotics. It is also intended to present a hypothesis linking the perceptual processes in psychosis and the use of cannabis.

Cannabis preparations are variously named in different parts of the world. Depending on the potency and the mode of administration they are known as charas, bhang and ganja (Indo-Pakistan subcontinent), hashish and dagga (Africa) and of course marihuana, pot or merely grass.

It has been shown that Cannabis sativa, the plant and flowering tops of the female, secrete the most potent and concentrated resins, called hashish or charas. Among the four cannabinoids, delta-9-tetrahydrocannabinol is believed to be responsible for the psychoactive properties (5).

In West Pakistan cannabis grows wild in the northern part of the Punjab, the North West Frontier Province, Swat and Baluchistan. The charas is prepared illegally on a large scale, and the huge quantities often impounded indicate that a brisk and profitable trade is flourishing underground. It is believed that most of it is smuggled out of the country. The easy availability at cheap prices also shows that there is an ample supply. The use of charas in West Pakistan was limited for a long time to a group of mystics, dervishes, pirs and their disciples. It is a common sight, even today, at the famous and the not so famous shrines and dargahs, to find people sitting, lying or reclining, quite oblivious to their surroundings. In fact, they had and have cultural sanctions and in practice "legal immunity" because their indulgence in charas is well known, yet ignored, accepted, defended and even dreaded.

To understand and appreciate such cultural sanctions it is necessary to mention briefly the history of mysticism in Islam-Sufism. It was in the 2nd century (Hijri) that the foundation was laid when groups of ascetics started meeting to recite the Holy Quran aloud which took liturgical character--dhikir, and this later evolved into sama (6). During the 4th and 5th centuries the movement grew.

Although Sufism was firmly based on the Quran and moral teachings of Islam, there was a tendency to neglect the ritual

and at times run contrary to the traditional teachings of the Ulemas. For Sufis the cognitive capacities available, like sense perception for the awareness of reality, were not enough and the spiritual experiences were considered more important.

It is fair to assume that marihuana may have provided a shortcut to such an experience and thus in time became a part of the mystic way of life and more so of the pseudomystics. Thus the controversial grass achieved a "sacred" place in a predominantly Muslim population.

In the absence of any worthwhile survey, it is on the basis of common experience that today charas is believed to be widely used by the peasants in villages and the working class people in the cities of West Pakistan.

In the last few years a lot of work has been done on the immediate effects of cannabis smoking. Weil reported (11) in a double-blind control study that marihuana-naive persons demonstrated impaired performance on simple intellectual and psychomotor tests, while the performance of regular users did not show any impairment, and in some, improvement was noticed on smoking marihuana. Baker, in a retrospective study (1), found that the most serious acute syndrome would appear to be a toxic confusional psychosis with disorientation and hallucinations.

The long-term effects of marihuana and its relationship with psychosis is not very clear. The Indian Hemp Drugs Commission 1893-94 (8) set out to clarify the impression that excessive consumption of hemp drugs produced insanity. They eventually reported cannabis consumption could be considered to be a factor in not more than 7 to 15 percent of the cases. One study reported that 25 percent of some 2,300 men admitted to psychiatric hospitals were diagnosed as cannabis psychotic (2). Chopra observed (4) that 58 percent of a group of 200 cannabis users were weak, unstable and borderline personalities, while 5 percent had frank psychotic episodes previously. It appears, therefore, that the "acute cannabis psychosis" described in Eastern literature is similar to acute toxic psychosis currently being reported at lower doses in less chronic marihuana users in the Western world. But "the Western experience has involved a level of cannabis usage substantially below that of the Eastern studies and the associated psychic disturbances are not generally comparable" (9).

In view of the potency of charas and the pattern of smoking in terms of frequency, it is essential to make a scientific study of the situation in this part of the world.

Table 1. DEMOGRAPHIC CHARACTERISTICS OF CHARAS AND CONTROL GROUPS OF PSYCHOTICS

No.	Age in Years		Employment Status		Number of Siblings and Birth Order		Marital Status		Offspring		Family History of Mental Illness	
	Charas	Control	Charas	Control	Charas	Control	Charas	Control	Charas	Control	Charas	Control
1.	24	21	++	++	6/5	7/3	M	S	2	-	-	+
2.	32	35	++	++	7/6	1/1	M	M	None	8	+MGF	-
3.	23	20	+-	++	8/3	8/7	S	S	-	-	-	+M
4.	23	24	++	+-	5/3	9/9	S	S	-	-	-	-
5.	22	31	+-	+-	1/1	8/7	S	S	-	-	-	-
6.	24	20	+-	--	6/1	6/1	S	S	-	-	-	-
7.	24	24	+-	++	8/1	9/4	S	S	-	-	+F&S	+M
8.	26	25	+-	++	4/1	1/1	S	S	-	-	+GF	+M&MGF
9.	22	26	+-	++	5/5	2/1	S	S	-	-	+F	+M&B
10.	26	21	+-	++	6/2	8/3	S	S	-	-	-	-

++ Employed before and at the time of examination.
+- Employed before but no job at the time of examination..
-- Never worked.

MATERIALS AND METHODS

The data were collected from a larger study on schizophrenia. The basic criteria for the project were: age 17 to 35 years, duration of illness less than 3 years, and adequate support available from the family. Between December 1969 and December 1971, 186 patients were registered (133 male, 53 female). A history of addiction was recorded in 20 patients (male 17, female 3), out of which 14 were smoking charas. Complete data on 10 were available and all of them were males. Ten psychotics were randomly selected as controls, matched for age, sex, education, occupation and social status.

This is admittedly a biased sample. A large number of psychotics and addicts were excluded in view of the criteria used in the selection of cases by the larger study. It was decided to analyze the symptomatology of the two groups and find out the relationship between history of charas smoking and the onset of psychosis.

RESULTS

The mean age of the two groups was more or less the same (charas 24.9, control 24.7). Only one patient in the control group was married, with eight issues, three of whom had died, while two patients from the charas group were married; one had no issue, the other had two children. A positive family history of mental illness (which also included grandparents and first cousins) was found in four of the charas group and five in the control group. In the charas group all were employed before, but seven had no jobs when seen by us. On the other hand, one of the control group had never worked, while nine had been employed before, and all except two had retained their jobs (Table 1).

Six symptoms of schizophrenia were compared in the two groups. They were: lack of energy (charas 7, control 3), withdrawal (charas 6, control 7), disorientation (charas 0, control 1), hypochondriasis (charas 1, control 3), hallucination (charas 4, control 3), and delusion (charas 5, control 3).

Personality tests (MMPI) could not be administered to all the patients because most of the patients were either illiterate or could read and write Urdu only.

Electroencephalographic recordings (EEG) were done in the charas and control groups. The results recorded were "abnormal" or "within normal limits." The EEG in the charas group had four abnormal and six within normal limits. The control group had two patients with abnormal EEG and eight within normal limits (Table 2). The abnormalities noticed were high voltage slow waves or theta activity, mostly in the frontal and temporal regions.

Table 2. EEG FINDINGS IN PSYCHOTICS SMOKING CHARAS AND CONTROL

Group	Within Normal Limits	Abnormal	Total	Remarks
Psychotics smoking charas	6	4	10	Slowing in frontal region in three and temporal region in one
Psychotics in Control group	8	2	10	Immature pattern in one and paroxysmal, diffuse, high voltage 5-6 c/s. in one

The number of charas cigarettes smoked per day and the duration of the habit varied widely. The information was gathered from the patient, reliable family members, or friends. At the time of the interview or in the recent past the minimum number of charas cigarettes consumed was one to two, at least once a week, while the maximum was 10 to 20. The minimum period of smoking charas was found to be one month, and the longest was up to 10 years. Four patients were reported by the relatives to have become psychotic within weeks of giving up charas smoking. One became psychotic 6 months after leaving a habit of 6 years. The relatives of three believed that the psychosis was the result of oversmoking charas. One of the patients became disturbed after one month and the other after 6 months of acquiring the charas habit (Table 3).

Table 3. DURATION AND AVERAGE NUMBER OF CHARAS CIGARETTES
SMOKED AND THE ONSET OF PSYCHOSIS

No.	Duration of Smoking in Years	Number of Cigarettes per Day	Relationship with Psychosis
1.	1	6-8	On leaving +
2.	1	2-5	On leaving -
3.	6/12	3-8	Oversmoking ++
4.	1/12	1-2	On starting +
5.	3	4-6	6/12 starting+
6.	10	10-20	Oversmoking ++
7.	1	2-5*	On leaving -
8.	6	1-2 occasionally	6/12 leaving --
9.	5	3-5	On leaving -
10.	10	4-5	Oversmoking ++

*Not every day, maximum gap one week.

DISCUSSION

In the absence of any reliable survey in Karachi, it is fair to conclude that a larger percentage among psychotics smoke charas as compared to the general population. Fourteen out of 186 patients amount to 7.5 percent. Secondly, the habit is restricted mostly to males, which can be explained on the basis that females culturally do not smoke, but chewing tobacco (in pan) is quite acceptable. The attitude towards work and lack of ambition among the charas group is quite consistent with the "amotivational" syndrome. All of them have had jobs before, but seven were unemployed when seen by us. On the other hand, among the control group, one never worked, while nine had jobs before, and seven were still employed.

Of the six symptoms observed between the two groups, lack of energy and delusion were found to be more frequently present in the charas group than in the control group. A careful observation differentiating the lack of energy and psychotic withdrawal, and the former being more frequent among the charas group, can be broadly attributed to the recognized effects of the drug.

The electroencephalographic findings can be interpreted as signs of immaturity and psychopathy.

The number of charas cigarettes or the duration of smoking and the onset of psychosis has not shown any definite pattern. It is quite likely that the level of disorganization determines the attraction towards charas or giving up the habit. When the disturbance is minimal the charas helps them to cross into the psychotic world, though temporarily, but once the psychosis sets in, it is no longer necessary to use such means.

The sample presented here is small and highly selective but sufficient to support our hypothesis.

Hypothesis

Weil mentions (11) toxic psychosis and believes it to be self-limiting and not dangerous. But the disturbance noticed in those who gave a previous history of psychosis led him to believe that marihuana may constitute a stress that pushes the patient in the direction of derealization. In persons with a low threshold for psychosis, the drug precipitates true psychotic breakdown. He quotes Smith and Mehl who comment: "The psychosis is characteristic of personality structure of the user (not of the drug). The intoxication merely triggers the psychosis as is seen with a variety of other drugs including alcohol, amphetamine and LSD." This explanation is quite safe and more or less generally acceptable. But we wish to put forward the same line of argument with a different explanation.

One theory of the basis of schizophrenia is that this is "a perceptual abnormality, that is, schizophrenics act oddly because the sensory data processing equipment he possesses is faulty" (7). Other observations are that the schizophrenics have concrete thinking and show overinclusiveness. There is an inability to preserve conceptual boundaries resulting in inclusion of irrelevant ideas leading to vagueness (3). The time perception in schizophrenics is also disturbed. Hallucinatory experiences during sensory deprivation are also well known (10).

Weil's threshold for psychosis and Smith and Mehl's personality structure in fact means prepsychotic or schizoid personality. Although such persons may not seek psychiatric attention, they do exhibit concrete thinking, overinclusiveness and disturbance of time perception. This produces vagueness and even a "vacuum" in the thought process because they cannot translate the sense perception into meaningful thinking. This is a painful situation. Thus it is not simply a question of intoxication triggering the psychosis when such persons are exposed to drugs. It is postulated that the experience of intoxication in such persons is entirely different. From a painful situation they enter into a different world. Thus a chance experimentation may provide them means to escape from a painful prepsychotic state. They continue to smoke. In this process a few break down into frank psychosis and do not need charas, i.e., they give up smoking.

It is, therefore, suggested that there are two different groups who take to charas. Those who experiment occasionally with pleasant results constitute the first group and they smoke either for "kicks," a break from dull routine, or group identification. The second group consists of those who continue to smoke persistently to complete the psychosis. In the latter group there may be wide variations. A few need the drug to cross into a temporary psychotic state, and in addition identify with a group where perceptual distortions are appreciated, accepted and looked for; some find it horrifying but keep trying at intervals, and yet others give up smoking after they have completely dissociated from reality. Here perceptual disturbance is complete and no longer painful or agonizing as it was in the prepsychotic phase.

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BACKGROUND PAPERS

TREATMENT OF NARCOTIC AND NON-NARCOTIC DRUG DEPENDENCE : THE NEED FOR RESEARCH *

by

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INTRODUCTION

The treatment of drug-dependent individuals has been the subject of debate for many years, particularly in the United States of America where the problem has remained large, and where, since it is an affluent society, it might have been thought that a concentrated effort could have been made to deal with the problem and to carry out an evaluation of treatment. Unfortunately, the law enforcement aspects of the problem achieved prominence, and only in the past few years has a start been made on such evaluation.

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Ed. by Richard V. Phillipson, Butterworths, London, 1970.

Perhaps the greatest handicap in assessing treatment results has been a failure to set up adequate controls in the methodology of the studies. The difficulty in obtaining random samples is well known, but the temptation to generalize from selected samples and the errors of extrapolating findings from the American scene to other countries has led to confused thinking. This is particularly relevant considering that the vast majority of heroin users in the U.S.A. come from ghettos and are deprived, Negro, Puerto Rican and Mexican populations in contradistinction, for instance, to the British picture which does not include this group. Furthermore, differences in law enforcement practices in the different countries create a different milieu for the addict and influence the pattern of behaviour, and the methods of treatment used (employing the word treatment here in its widest sense).

Since this book is concerned with "Modern Trends" only brief reference will be made to older methods of treatment and the main attention will be given to new methods which have been developed during the past few years.

GENERAL ASPECTS OF TREATMENT

Treatment of drug dependence has been split up into various phases (10) where the following phases were defined in relation to amphetamine-dependence treatment: 1) treatment of the withdrawal phase, 2) treatment of the early abstinent phase, 3) long-term treatment.

Since it was then assumed that amphetamine withdrawal had to take place in hospital, and since more recently attempts have been made to withdraw patients from narcotics on an outpatient basis, this concept of phases of treatment requires extending in the light of modern knowledge and in reference to all drugs of dependence. Furthermore, the expression "long-term" treatment infers medical supervision of a long-term nature, whereas the concept of rehabilitation which is now considered a vital one may not be thought to be properly included under long-term treatment since much rehabilitation may have little to do directly with medical practice. A more useful definition of the phases of treatment might be as follows:

- 1) Referral to an outpatient clinic or centre where assessment of the initial problems and the optimum method of treatment can be formulated.
- 2) Outpatient treatment. This to include a withdrawal method, or a maintenance method using the drug of dependence or a substitute.

3) Inpatient treatment which will include:

- a) withdrawal from the drug or replacement of the drug by another, such as in the methadone programmes to be described later
 - b) the early abstinent phase. This will also include full assessment of the underlying problems after withdrawal, recognizing that the body physiology and psychology may not become normal or nearly normal for some weeks or even months after the drug has been withdrawn. This assessment will be vital in that suitable rehabilitation approaches can then be selected and the need or otherwise for further outpatient medical supervision evaluated.
- 4) Rehabilitation. This will include the complex process of helping to re-establish the erstwhile drug-dependent person in the community either when withdrawn from drugs or when under a maintenance programme. This requires close liaison between medical and many other social agencies whether they be attached to law enforcement facilities, voluntary bodies or other social services. It is now generally recognized that whatever the system of medical treatment, whether it be complete abstinence, replacement therapy or specific therapy, inadequate rehabilitation provision is likely to vitiate the earlier efforts of patients, doctors and other staff. Thus programmes which are set up in the absence of adequate rehabilitation facilities are likely to show evidence, early on, that such rehabilitation facilities must indeed be provided if the time and expense of hospital treatment or other treatment is not to be wasted.

WITHDRAWAL FROM DRUGS IN HOSPITAL

Heroin and Other Opiates

The principle of withdrawal usually used is that of replacing heroin or another opiate directly with methadone, and once withdrawal symptoms are controlled, to reduce methadone by 10 mg every 24 hours so that withdrawal is effected in 7 to 14 days. Wikler (63) describes this method and agrees with Blachly (5), who has also written in detail, that the following are methadone equivalents:

1 mg methadone = 3 mg morphine sulphate
 1 mg heroin
 1/2 mg dihydromorphinone (dilaudid)
 20 mg meperidine (demerol, pethidine)
 30 mg codeine
 4 mg hydrochlorides of opium alkaloids (pantopon)
 7-8 ml paregoric (contains 0.4 mg morphine per ml but less than half absorbed 15 ml)
 1/2 mg levorphanol (levo-dromoran)

These equivalents are based on a large number of experiments carried out in Lexington over many years.

Blachly distinguishes abstinence signs in sequential appearance in time after the last dose of narcotic, in patients with well established parenteral habits and places them in five grades (0-4). It is doubtful whether in voluntary hospitals it would be possible for patients to tolerate the degree of withdrawal symptoms mentioned. Blachly notes that the system was developed at Lexington (61). He gives 10 mg methadone orally initially when grade 2 signs are present. These are an increase of grade 1 signs (yawning, perspiration, lachrymation, rhinorrhoea, "yen" sleep), and the development of mydriasis, gooseflesh (pilo-erection), tremors (muscle twitches), hot and cold flashes, aching bones and muscles and anorexia. If the patient vomits, 10 mg methadone is given parenterally and 20 mg repeated in 12 hours. If, however, debilitating illness is present a slower withdrawal is recommended at 5 mg each 24 hours.

Blachly warns that the presence of severe restlessness, anxiety and insomnia in the absence of autonomic symptoms characteristic of opiate abstinence may indicate that the patient is dependent on barbiturates. In this case an appropriate barbiturate-withdrawal regimen must be instituted. Insomnia is a universal complaint after the second to third day, notes Blachly (5), and pentobarbitone 100 to 200 mg is given at night to combat this. Extra fruit juices are given in the diet and hot soaks in a bath if there are muscular cramps.

Wikler (63), using a similar method of substitution with methadone or with subcutaneous morphine as a system of rapid withdrawal, emphasizes the need for a lower regime in cases of debilitating disease, active pulmonary tuberculosis or cardiac

insufficiency. He advocates the use of codeine in the final stages of withdrawal and the use of aspirin 10 grains (600 mg) if there are aches and pains. Barbiturates (100 to 200 mg) are given at night for insomnia.

It is clear from these reports that some withdrawal symptoms are expected and it is of interest to note that Thigpen, Thigpen and Cleckley (53) advocate the use of electric convulsive therapy in morphine, meperidine and related alkaloid addictions to "eliminate the adverse manifestations of withdrawal, in an effort to help patients progress through this period without severe emotional and physiologic disturbance." This method does not appear to have found support in subsequent medical practice.

Goodman (27) suggests the use of diphenoxylate hydrochloride (lomotil) which is an exempt narcotic (nonaddictive opium derivative) in the U.S.A., and which also contains atropine sulphate; thus it can be used more easily there from the medico-legal standpoint. There was a considerable dropout of subjects, but a preliminary study of 20 patients suggested that neither the patients nor the staff reported symptoms of withdrawal syndrome apart from slight leg cramps and minor discomforts in the first 3 days of treatment. Barbiturates, phenothiazines and glutethimide were used if tranquilization was necessary. It should be emphasized that this is only a preliminary report and further work using diphenoxylate requires to be carried out on a research basis before this method is used as a routine practice.

Blachly (5) notes that in the U.S.A. it is rare for addicts to require more than 40 mg methadone in a 24-hour period. This is because the average dose of heroin used by American addicts is now low, and of the order of one grain (60 mg) a day. Bewley (3) observes that larger doses of heroin are taken in the U.K. so that more methadone may be required to prevent symptoms of withdrawal. He prefers to give the patient doses of heroin below those normally taken in order to estimate the severity of withdrawal symptoms and then to change over gradually to methadone. Thereafter he proceeds in the same way as does Blachly.

Bewley also notes that larger doses of methadone may be needed, up to a total of 100 mg in 24 hours or more and that withdrawal takes place over a period of 14 days. One patient said to be taking 1,080 mg heroin daily was withdrawn in this time. Before following the routine of Blachly, then the regime, Bewley's use initially in the high dosage cases is as modified from Table 1.

Table 1. REGIMEN USED FOR EFFECTING WITHDRAWAL
FROM HEROIN (Eewley 1968)

	Heroin Total	Methadone Total	Frequency of Administration
Admission day	750 mg	-	2-hourly
2nd day	360 mg	360 mg	4-hourly
3rd day	180 mg	540 mg	4-hourly
4th day	-	720 mg	4-hourly
5th day	-	700 mg	6-hourly
6th day	-	600 mg	6-hourly
7th day	-	500 mg	6-hourly
8th day	-	400 mg	6-hourly

Prolonged sleep therapy described by Schlomer (50) was used on the basis of the scope it offered to discontinue the drug abruptly without causing the patient any suffering. Schlomer observes that this method was first tried in 1924 and has proved its worth. The method he describes includes medication every 3 hours for the first 24 hours using phenobarbitone (luminal 5 grains) and--provided that the patient can swallow--paraldehyde in alternate doses. Paraldehyde (6 ml intramuscularly) is given later if required and the object of the treatment is to keep the patient drowsy so that there is amnesia for the period of acute withdrawal. No morphine is given after admission. During the third and fourth days--the height of the withdrawal symptoms--"The patient will moan, show signs of great restlessness and thrash about violently even while sound asleep. During the fifth day he will quieten down, respiration will become even and regular and the patient will give the impression of someone sleeping comfortably." This marks the end of the acute withdrawal symptoms and sleeping drugs are discontinued by day from this point.

Owens and colleagues (45) in Birmingham, England, have used a sleep-withdrawal approach recently by employing modern tranquilizers such as chlordiazepoxide.

It has seemed to the present writer that bearing in mind that patients have usually been taking the narcotic for a long time before they come to withdrawal, there has been an undue preoccupation with the need to withdraw the drug as quickly as possible. So far as prolonged sleep therapy is concerned there are risks attendant on giving drugs to promote continuous sleep or

drowsiness and skilled nursing is required. It is doubtful whether these risks warrant the use of such a method unless long-term research demonstrates a higher rate of success in terms of "cure" of the addict or a more successful rehabilitation which can be clearly attributed to the method of withdrawal.

Pethidine

Withdrawal from pethidine should be treated in a different way from withdrawal of other opiates, since if methadone or morphine is substituted, excessive sedation tends to occur. Wikler (63) suggests that if a patient is dependent on a dose level greater than 2,000 mg, he may develop withdrawal fits which may be followed by extreme restlessness, profuse sweating and isolated muscle twitches. If the patient is then given the accustomed dose of pethidine, the cycle may be repeated. He therefore suggests a withdrawal regime using pethidine by intramuscular injection in diminishing doses, given 3-hourly for the first week.

Barbiturates

There are differing views concerning the best method to be used to effect withdrawal of barbiturates from a chronic user. These are presented by Wulff (64) on the one hand and Hamburger (28) and Blachly (4) on the other.

Wulff's regimen is one of abrupt withdrawal. Neither hypnotics nor sedatives are given after admission to hospital. Mild withdrawal symptoms such as restlessness, sleeplessness, reflex hyperirritability as well as a single convulsion do not, in Wulff's view, constitute an indication for administration of barbiturates. However, with the first signs of a withdrawal psychosis (such as confusion, disorientation and hallucinations) or the development of more than one fit, phenobarbitone is given immediately. A dose of 0.2 grammes at least three times a day is recommended and this dose is maintained until psychotic symptoms have disappeared when the dose is diminished gradually over 10 days, by which time no phenobarbitone is being given. No additional or further hypnotics or sedatives are given. Wulff favours abrupt withdrawal for diagnostic and therapeutic reasons. He stresses that, unlike the experimental conditions obtaining at Lexington Hospital, where the gradual withdrawal method has been worked out in detail, diagnosis is often a problem in psychiatric hospitals. The abrupt method thus allows a diagnosis to be established. The diagnostic reason for which method would not

obtain if daily estimations of body fluids to determine the presence of drugs--using modern laboratory methods--were carried out[sic]. Unfortunately, few hospitals have these laboratory facilities. From the therapeutic standpoint, however, Wulff considers that gradual withdrawal strengthens the patient's belief that he cannot exist without barbiturates, so he resists final withdrawal. This aspect of his argument requires validation. Wulff also advocates the use of a long-acting barbiturate (phenobarbitone) in controlling major withdrawal symptoms because he found that none of his nine cases, dependent on long-acting barbiturates, developed seizures or delirium. He hypothesizes, therefore, that intoxicating the patient first with short-acting barbiturates, as is done at Lexington Hospital, is an added risk which might produce the very withdrawal symptoms which the treatment is designed to prevent. The validity of this hypothesis remains to be tested by large-scale controlled trials.

It must be stressed, at this point, that the standard method for barbiturate withdrawal used throughout the world is the method developed at Lexington Hospital as a result of research on experimental intoxication and withdrawal of barbiturates in volunteer ex-morphine addicts. The aim of the methods was to prevent the major symptoms of barbiturate withdrawal (delirium, convulsions and occasionally death). This method has been described (21,22,31) and further amplified (4).

Blachly (4) notes that many acute intoxications may be on the basis of chronic addiction and require that the intoxication threshold be determined regardless of history. He chooses pentobarbitone for withdrawal because it has a moderate duration of action and because most addicts use either this drug or secobarbitol. He advises against the use of phenobarbitone since its long action prevents flexible manipulation of dosage. He notes that the determination of blood barbiturate level is of value only if the patient is intoxicated or comatosed; not if he is agitated or convulsing. Wulff, however, found such estimations useful for forecasting fits which were likely to occur if there was more than a 20 percent fall in 24 hours.

If the patient has a fit and can swallow, Blachly recommends that pentobarbitone in a dose of 200 mg should be given 2-hourly until the patient is intoxicated. The dose should then be reduced by 100 mg daily. If the patient cannot swallow, phenobarbitone should be given in a dose of 250 mg intramuscularly. He further modifies the regime to apply to three groups of patients, those who have normal tolerance, those highly tolerant and those with debilitating illness (4).

James (34), in discussing the recognition and management of addiction and chronic intoxication with sedative drugs, prefers to withdraw the drug concerned over the space of a few days

and to control the withdrawal symptoms with chlorpromazine or with chlordiazepoxide. He gives phenytoin to patients with barbiturate intoxication for the first 3 weeks--when the dosage of this drug is tailed off. Chlorpromazine and chloral hydrate are given at night for insomnia, but he recommends that chloral hydrate be withdrawn as soon as possible to prevent a substitutive addiction. Jaffe (32) notes that Essig and Carter (20) found that diphenylhydantoin (phenytoin) and selected anticonvulsants are ineffective in suppressing the general depressant withdrawal syndrome in dogs and are probably without value in man.

Non barbiturate Hypnotics

Essig (19) notes that there do not appear to be any controlled trials in man to determine the best method of withdrawal from drugs such as meprobamate, glutethimide, ethchlorvynol, methyprylon and chlordiazepoxide. He suggests that the principles of barbiturate withdrawal are applicable. Where the drug and its previous daily dose are known, withdrawal at the rate of one therapeutic dose per day is suggested. If, however, the patient becomes apprehensive, tremulous or suffers from insomnia, he recommends that dosage reduction should be discontinued for one or two days or until symptoms disappear. If, on the other hand, the drug and the daily dose are unknown (and cannot be determined) he recommends that barbiturates be substituted for the drug. He notes that convulsions and delirium have been reported in patients dependent on meprobamate, glutethimide, ethinamate, ethchlorvynol, methyprylon and chlordiazepoxide.

Amphetamines

Abrupt withdrawal of amphetamines--because of the absence of severe physical withdrawal symptoms--has been advocated (8,9). The withdrawal symptoms met with are those of sleepiness and depression, the latter often being severe and leading to a definite risk of suicide. For this reason hospitalization is usually advisable.

Where a patient is admitted in an acute amphetamine psychosis, abrupt withdrawal can be combined with medication by a tranquilizer, such as chlorpromazine, in order to diminish the restlessness and overactivity as well as the fear attendant on paranoid delusions.

Kramer, Fischman and Littlefield (35) regard the sudden withdrawal of amphetamines from a patient who has taken large doses intravenously as an "abstinence syndrome" since they feel that the depth and length of withdrawal sleep cannot be ex-

plained by chronic fatigue alone, and because of other evidence including physiological dysfunction lasting for some weeks as shown by sleep EEG records (43).

Since the rate of excretion of amphetamines is dependent on the pH content of the urine (1), acidifying the urine by giving the patient ammonium chloride has been advised (10).

REHABILITATION

There is virtually no literature devoted to a consideration of the assessment of the addict in terms of the early abstinent phase. Such a consideration should include assessment of the basic problems in terms of individual difficulties, family difficulties and social difficulties in the widest sense. It may well be that the problem, as initially assessed, when the patient is either still on drugs or is being withdrawn, is markedly different from the basic problems revealed by a thorough assessment subsequent to withdrawal. Possibly, also, since it may be several months before the body physiology returns to normal, the problems remaining then may differ from those in the early period of complete abstinence and those during withdrawal. There is a need for comprehensive evaluations at these different stages. A recent attempt (23) to evaluate addicts in terms of personality types in relation to social concepts is interesting and possibly important in mapping out long-term treatment needs.

Follow-up studies have been sparse and of a retrospective rather than a prospective design. Results have tended to be poor in terms of the ideal concept of "cure" being a patient off drugs and socially competent in terms of work and personal adjustment. The general view of poor outcome has been recently challenged by the findings of Vaillant (55) that much better outcome might be related to a system of regular and firm parole. The development of methadone maintenance and of "self-help groups" such as those of Synanon, Daytop Village, Phoenix communities and the like have raised new hope. The latter approach combines a concept for the individual who commits himself to be off drugs of "treatment" and of rehabilitation. Since these self-help groups are one of the main developments in the modern approach to drug addiction, they will be dealt with in some detail.

SELF - HELP GROUPS

Synanon

The first of the self-help communities was the Synanon Foundation Incorporated of Santa Monica, California. This--a

private, non-profit making, rehabilitation organization--was founded in 1958 by its own member-participants for the purpose of mutual self-treatment of drug addiction and, to a lesser extent, of alcoholism. This foundation has opened other houses throughout the U.S.A. and plans to expand further. The moving force behind this development was Charles (Chuck) Dederich, who was himself a former alcoholic.

Synanon is supported by private donations and by funds from a number of businesses owned by the foundation and operated by the members themselves. These businesses include petrol service stations, garages, machine shops, a pencil-manufacturing business and carpentry shops which provide practical and realistic work and rehabilitation outlets for members.

Holzinger (29) reported on the functioning of Synanon after he, a psychologist, had spent a week there as a special guest observer--being interested in claims of a 50 percent recovery rate. He lived in during his stay there.

Holzinger noted that the great majority of the members were narcotic addicts or former amphetamine or barbiturate addicts, the rest being a small number of alcoholics.

He describes the programme as a busy one with 6:30 a.m. rising. "Synanon sessions" were held on three evenings a week and were compulsory. Psychodrama was enacted once a week by members who had been with Synanon at least 2 years. Administrative staff were recruited from the members, and the day was a busy one and highly organized. A high school curriculum and vocational and other educational help were provided where feasible. New entrants were screened and expected to suffer withdrawal without any covering medication. Holzinger witnessed two such withdrawals in which two frail and sickly girl entrants passed smoothly through this ordeal. He does not comment, however, about the level of dosage of the drug previously used or whether they might have gradually withdrawn themselves before acceptance by Synanon--because of prior knowledge that "cold turkey" withdrawal was required. Synanon, says Holzinger, appears to explain this withdrawal--which does not show classical withdrawal symptoms--in terms of "a psychological investment of which they (the new entrants) can be proud." Evidence is required, however, that a barbiturate addict is not subject to seizures since Synanon does not wish to be regarded as a hospital and does not have the facilities to cope with medical problems. It is difficult to assess what is meant by evidence that an individual is not subject to seizures, and it would be surprising if some barbiturate addicts who join while still taking large doses of barbiturates did not have fits or barbiturate-withdrawal psychosis.

Holzinger notes that the Synanon sessions seem to be a special kind of group psychotherapeutic situation. Each group comprises 8 to 12 members. The total group members rotate as time goes on so that everyone can expect to meet everyone else at some time during the sessions. The group leader, sometimes called the "Driver," is "usually informed by the administration about certain observations concerning members of his group." The sessions are devoted, in the one and one-half hours available, to verbal discussion which involves not polite discussion, but emotionally intense verbal exchanges in which individuals have roles "both as aggressors and aggrieved." The aim would appear to be to find out the truth about oneself and to express hostilities or feelings without regard to the sensitivities of others. Physical aggression is not, however, permitted. Since no individual in a group escapes, Holzinger notes that "all show signs of relaxation because they have been able cathartically to express their feelings even if they were of a negative type."

New entrants are required to involve themselves at Synanon for a minimum period of 2 years and usually stay longer. There are those, says Holzinger, "particularly in the beginning but sometimes later who fail to benefit from the treatment programme; and as they are discovered they are presented with the ultimatum either to leave or to be subjected to a sort of trial by their peers, who then decide what disposition to make." Members are not paid for their work but receive pocket money.

Holzinger concludes that at Synanon there is a kind of tribal family which re-educates its members and--because of the goal-directed life and the possibility of status advance--members have a purpose and develop an intense loyalty towards the Synanon movement. The Synanon sessions, although appearing "unmerciful and even sadistic, seem to constitute effective guidance and punishment administered by a basically loving 'family'."

Daytop Lodge

This was founded by an ex-member of Synanon and is similar. According to Bewley (3) "It is a rather more open community than Synanon and a larger number of people who pass through the programme return to the community." Recently, there have developed schisms within this facility.

The Phoenix House Programme and Phoenix Houses of New York Incorporated

This private foundation, Phoenix Houses of New York Incorporated, was established to support the Phoenix House Programme of the Rehabilitation Division of New York City's Addiction Services Agency. The first house was set up in the spring of 1967. In the description of the programme put out by the foundation, it was noted that the Mayor of New York appointed Dr. Efren Ramirez (a physician and psychiatrist who had established and operated a successful treatment and rehabilitation programme at Rio Pedras in Puerto Rico), to head the Office of the Coordinator of Addiction Programmes. The approach is based upon the Puerto Rican experience and the Synanon and Daytop Village experiences. Dr. M.S. Rosenthal, who had experience of Synanon, is in charge of rehabilitation. In January 1968, the Office of the Coordinator of Addiction Programmes was transferred into a major city department, the Addiction Services Agency of the Human Resources Administration. The programme rapidly grew from the 10 addicts who formed the nucleus of the first Phoenix House to the present figure of approximately 560 addicts spread through a number of Phoenix Houses throughout New York.

The private assistance derives partly from the fact that New York City's welfare money to each addict--some \$2,000 a year per person--is pooled together by the addicts, who are almost all voluntary residents; the rest comes from gifts and donations. Among other activities the private organization buys buildings; this, it was found, could be done much more quickly than if the usual governmental channels had to be used. Thus a combination of city and private funding has led to a flexible and rapidly expanding programme.

Ramirez (47) defines the scope of the total programme of New York City. This includes not only the Phoenix House Programme, but the whole field of addiction, including consultant advice to public, voluntary and private agencies, education programmes directed towards the public, train-in programmes for persons in public, voluntary and private agencies and the evaluation of present and proposed research designs, demonstration projects, services programmes and so on.

The theoretical assumptions defined by Ramirez include several concepts: 1) that drug addiction is a symptom of personality malformation and aberrations, 2) that treatment especially designed to deal with characterological deviations must therefore be developed, 3) that the addict unless psychotic is responsible for the consequences of his behaviour, 4) that the role of the therapeutic personnel involved in the process is not the conventional one, and 5) that the treatment and prevention of addiction cannot be accomplished merely through the rehabilitation of addicts.

Three major phases are delimited in the process of rehabilitation.

Phase I - Induction

In this phase the addict learns to become a patient. The first stage of the induction is an "encounter" in which the addict is challenged, usually by an ex-addict, "to examine the myths which he uses to justify his own pathological behavior." The notion that he can be cured is put to him. The phase of induction lasts about a month and is carried out in a "day-evening care centre." The addict must be abstinent while attending this centre.

Phase II - Treatment

This phase requires that the addict reside in a Phoenix House where he "undertakes the difficult and rigorous task of reconstructing and reorienting his attitudes." This, Ramirez notes, may take 6 to 8 months, but the writer has reason to believe that the average period is likely to be more than this. Addicts are required to be free from drugs and honest and non-violent.

There are two types of "encounter." The basic one (49) is the "floor encounter." This is especially for newcomers. "Emotional catharsis is the goal and the accuracy of psychological confrontation or interpretation is not important. It is a sort of training ground where the newcomer can both loosen up and toughen up psychologically, learn that he can yell or be yelled at without anything happening to him or to anyone. There is no appointed leader. The more advanced encounter is the staff tutorial encounter. Here there is an appointed leader. He controls a group of experienced participants. He commands a powerful force. He can spearhead an attack and harness the energy, insight and experiences of the group, bringing it into focus in turn on each participant. The impact is tremendous. Participants are also instructed as to the process of the group and individual defences employed."

Phase III - Re-entry

"Treatment now completed, the addict still faces anticipated and real difficulties in making the transition from a relatively isolated, supervised environment to everyday life in the open community. In order to expedite this return, the re-entry candidate usually transfers to a re-entry house" (47). There the ex-addict becomes gradually integrated into the community. He

may receive training in vocational skills and preparations for further professional schooling. There are five levels of functional progress. These include working in detoxification wards, day-evening care centres, therapeutic aid in the therapeutic community and being a co-leader in intensive treatment group sessions, and thence to work in the community itself.

This comprehensive programme is still too recently initiated for adequate evaluation and has, in common with other self-help groups, the goal of personality reorientation and reorganization.

METHADONE MAINTENANCE

Recognizing that many addicts are unable to keep free from drugs following withdrawal and some may be better on a drug such as methadone rather than continue to be addicted to heroin--a very poor drug for maintenance purposes--methadone has been used in two ways. The first is to replace heroin with methadone either by inpatient treatment initially and then outpatient maintenance, or by outpatient treatment from the beginning. The second is the method of "Narcotic Blockade" devised in 1964 (18).

Methadone Maintenance - Low Dose

Paulus (46), in a retrospective follow-up study, compares a regular 12-day methadone-withdrawal regime with prolonged methadone withdrawal. The patient in the latter regime "may be maintained on methadone, a synthetic narcotic, until such time as he, or she, can either function without a narcotic or other factors warrant discontinuation of medication....prolonged methadone then provides a stepping stone to a more desirable way of life--less damaging to the addict and to the community." Methadone is prescribed on a continuing basis over a period of weeks or months, the maximum daily dose has been 40 mg orally in 10 mg tablet form.

Paulus found that prolonged withdrawal is more likely to keep the patient in therapy; more of the patients were over 30 years of age, more were male and more were capable of doing skilled rather than unskilled jobs. More patients on methadone maintenance could work, fewer had to sustain their habits by illegal means and consequently were less likely to be apprehended and convicted. Thus he suggests, "Maintenance methadone equals less crime." A closer look at the age range showed that men over 50 years of age responded well and the under 40 group quite well, but the hard core 40 to 50 group did not do so well. Although

Paulus recognizes that his sample and the retrospective nature of the study, even though nearly all persons in the study were interviewed, makes definitive conclusions somewhat hazardous, his findings do warrant a closer look at methadone maintenance on low dosage in a longitudinal, prospective research survey. Others have also used a methadone low-dose method with encouraging results (33).

Methadone Maintenance - High Dose (Narcotic Blockade)

Dole and Nyswander (14), noting that psychiatric treatment had consistently failed as a treatment for chronic addiction to heroin, though paying tribute to "devoted and well trained physicians, assisted by competent nurses, social workers, probation and enforcement agents," considered that it seemed "reasonable to look for some medication to block the abnormal reactions of addicts to heroin and permit them to live as normal citizens in the community." Such medication must meet a number of criteria to be of any practical value. These, suggest Dole and Nyswander, are:

- 1) It must eliminate the euphoric appeal of heroin and the abstinence syndrome that draws addicts back to drug use.
- 2) It must be sufficiently free from toxic or dysphoric effects for patients to continue with treatment.
- 3) It must be orally effective, long acting, medically safe and compatible with normal performance in work and at school and with responsible behaviour in society.

Noting that the addict taking heroin intravenously is usually in a "high" state or a "sick" state and rarely in a "straight" (normal) state, Dole and Nyswander demonstrate the effect of stabilizing a patient on methadone by gradually increasing the methadone dosage to inpatients and thus producing methadone tolerance and also showing that the "patient is firmly buffered in the zone of normal function." Methadone itself did not make the patient high or cause any other narcotic effect. The test of the blockade was a test by intravenous injection of heroin, hydromorphone hydrochloride, morphine, methadone, or saline. The patient did not know what he was receiving; nor did the physician. A blockade was produced by a maintenance dose of 100 mg methadone, no euphoric action was noted after doses of 80

mg or more of heroin--"an amount equivalent to the drug contained in several illegal 'bags' in New York." Rehabilitation and common sense support are stressed (15).

In a later paper (17) it is made clear that "methadone can be used as an anti-narcotic agent, blocking the euphorigenic action of narcotic drugs rather than substitution for them." It is also stressed that medical supervision is necessary and that methadone has a definite abuse potential. Methadone is given to patients orally, diluted in fruit juice, in the hospital or clinic and "only after they have proven themselves sufficiently reliable are they permitted to take out limited amounts of methadone in fruit juices for consumption at home."

Strict criteria are used for selecting cases for the Dole and Nyswander Methadone Maintenance Programme (14). These include a period of at least 4 years heroin addiction, the absence of psychiatric illness, and the absence of use of other drugs. A recent evaluation (18) has shown that by March 1968, 871 patients had been admitted to the programme. Of these, 119 (14 percent) had left the programme--87 (10 percent) having been discharged, 3 percent dropped and one percent having died. One thousand addicts now on the street or in jail were awaiting admission to the programme. Results showed 59 percent to be working, 29 percent to be socially acceptable and 12 percent to be failures. Reduction in criminality was demonstrated by a 90 percent reduction in the rate of convictions.

Other workers (33,60,24) have used this approach with similar findings, although with smaller numbers of cases. It can therefore be stated that this method of treatment does make a large contribution to the problem of rehabilitating the addict in the community.

Of some interest, but open to considerable controversy, are the views that heroin addiction is a metabolic disease and that "addict traits" are a consequence, not a cause of addiction (16). These views are based on the success of narcotic blockade by methadone.

NARCOTIC ANTAGONISTS

The use of narcotic antagonists in the treatment of heroin addiction is being explored (38,37). Freedman and colleagues (24) report this use and note that cyclazocine is a synthetic analgesic related to nalorphine hydrochloride. It antagonizes both the central and systemic effects of opiates. It has a long duration of action, few undesirable effects, can be taken oral-

ly, and, if a patient is receiving cyclazocine and then takes heroin, no euphoria is produced.

The method used includes detoxification of addicts on an inpatient basis using a rapid methadone withdrawal procedure. Cyclazocine induction was commenced after a drug-free period of a week. Cyclazocine in a dose of 0.2 mg a day was given and this was increased by 0.2 mg each day for 10 days. If this was tolerated, cyclazocine dosage was increased to 0.4 mg maintenance dose--the completed induction dose, being reached in 15 days when administration was changed to a single 4-mg dose each morning.

A narcotic challenge was used on volunteers who had been told that the narcotic would fail to produce the usual euphoric or systemic effects. The challenge was cyclazocine, heroin or saline in different sequences. Using a 15-mg dose of heroin, the euphoric effect was suppressed in many patients. In one patient who reported a high, the increase of cyclazocine to 5 mg daily blocked subsequent euphoric reactions to a narcotic challenge. No tolerance to the heroin-blockading effects of cyclazocine was observed 6 months after attainment of induction, and evidence suggests that the effective duration of antinarcotic activity of a single 4-mg dose on daily administration was at least 20 hours, waning rapidly after 28 hours.

Side effects were noted. These included complaints of increased libido, constipation, elation, anxiety, dizziness, headaches, restlessness and insomnia which were reported in half to two-thirds of the subjects. These were most frequent during the initial days of treatment and gradually abated after several days except for increased libido and constipation. Less frequent were complaints of depression, crampy abdominal pains, lethargy, increased appetite, muscular twitches and paranoid ideas. Two patients reported visual hallucinations, though one had hallucinated prior to cyclazocine treatment.

Withdrawal from cyclazocine caused, in some patients, increased irritability, headaches, suspiciousness, depression and paranoid ideas. Six patients described "electric shocks" on withdrawal--sudden stabbing pains in the neck and back, lasting a few seconds, and leaving no sequelae. These did not interfere with the patients' regular activities. There were no unusual demands for additional medication during the period of withdrawal.

Although it is early to assess the results of this approach, the preliminary report (24) suggests that results, although not quite as good as those for the methadone maintenance method, are encouraging. This method has the advantage of the use of a narcotic antagonist rather than a narcotic itself, such as methadone, for treatment.

PRESCRIBING CLINICS

Much discussion has taken place about the propriety of prescribing drugs of addiction to the addict. Considerable heat has been engendered, but one fact seems generally agreed. This is that a prescribing clinic which has minimal supervision or control of the amounts of drug prescribed is likely to spread addiction.

Thus, quite apart from the law enforcement attack on doctors running such clinics in the 1920's in the U.S.A., it seemed that these clinics failed because of lack of supervision, lack of definition of the goals of treatment, and because of the ability of addicts to coerce doctors who were not clear what they were doing, to give excessive doses of the drugs.

Similar experience has been recently reported from Sweden (25,26) where doctors allowed to prescribe phenmetrazine to addicts, but not under any strict supervision or control system, found that patients became unmanageable and the addiction spread.

A notable exception to this lack of success of prescribing clinics has been referred to by Paulus (46) and Straus (51), both of whom obtained data from Terry and Pellens (52). The latter book is unfortunately unobtainable at the present time so that the data to be presented now are not first hand. Paulus notes that some experiments "especially those by Dr. Butler in Shreveport, Louisiana, showed promising results," but no systematic assessment of the results of these clinics was ever carried through. Straus notes that between 1919 and 1923 more than 40 clinics were in operation. Many of these survived the threat of Federal prosecution for only a few weeks, and eventually the Treasury Department closed them all. One such clinic survived, however, for a period of 4 years. This was run by Dr. Willis P. Butler at Shreveport, Louisiana, who "insisted from the outset on instituting precisely those controls that were missing in the activity of other clinics. A thorough physical examination of each addict determined what dosage of narcotics was necessary to keep him fit for gainful employment. And every man capable of working had to do so as a condition of his treatment; clinic inspectors made sure he did."

The patient had to sign a pledge not to sell, give, lend or borrow any of the prescribed medicine. His fingerprints were taken in quadruplicate--one set being sent to Leavenworth, Kansas, for identification and classification. The addict came 3 days a week for his morphine and had to be neat and tidy. "No vagabonds or loafers are tolerated." Doses varied from one to twelve grains (60 to 720 mg) a day. A monthly record sheet carefully noted the amount of morphine dispensed to each addict,

when it was dispensed and how much was paid for the prescription. Straus, again quoting Terry and Pellens, notes that the U.S. Marshal for the Western District of Louisiana said: "We cannot speak too highly of the thoroughness of Dr. Butler and his methods of handling this class of case, of the suffering and misery which has been averted, and of his practical and common-sense administration of this institution." More specifically, the city's Director of Public Safety maintained that "from a police standpoint, the City of Shreveport is greatly benefited by its being here. It has practically eliminated the bootlegger who deals in narcotics, and in this way alone has reduced the number of possible future dope users."

Another clinic which also succeeded in this approach is mentioned by Straus, but no details are given. This clinic was at Jacksonville and "illicit drug peddling was almost completely eliminated." When the clinic was discontinued, illicit traffic immediately reappeared.

These experiences are all important since they suggest that even in the presence of a well established criminally organized drug supply system, a prescribing method, suitably controlled, can get rid of such a system. There are no data available to the present writer from which to evaluate whether or not the numbers of addicts in the communities served by these clinics increased, diminished or remained the same. These facts are essential if adequate appraisal is to be made, but the impression is gained that at least the problem did not increase.

More recently prescribing of heroin to heroin addicts has been instituted in special clinics in Great Britain, but principally in the London area, where the main problem of drug abuse exists. In Great Britain heroin is still prescribed for medical conditions. Discussion about centres for treatment of drug addiction has taken place (3,7,11,44). The Dangerous Drugs Act (13) confines the prescribing of heroin and cocaine to addicts to doctors who have a special licence to so prescribe--this licence being renewable yearly. Every doctor who comes into a professional relationship with an addict is required to notify certain details such as age, date of birth, name and address, to the Chief Medical Officer of the Home Office and details of physical attributes such as scars, tattoo marks, and colour of eyes are also recorded. Addicts are required to attend the special clinic at least weekly or fortnightly, when an assessment is made and a prescription sent to the designated pharmacy to which the patient must go each day for his daily supply of heroin.

The rationale of this approach has been described in detail, and some of the possible difficulties and dangers enumerated (12). Briefly, the experience in Great Britain has been

that if doctors are freely allowed to prescribe heroin to addicts when there is a socio-cultural pressure in the community to take drugs, there will be a small number (less than 10) who will overprescribe and spread the problem of heroin addiction. In Great Britain there is no criminally organized black market in heroin, and the heroin available due to overprescribing by doctors is in the form of one-sixth grain (10 mg) tablets. A main aim of the new system is to prevent the development of a criminally organized black market, while at the same time containing the problem of heroin addiction and preventing its spread. Such clinics, it is argued, will obviate the necessity of the addict indulging in criminal activities to obtain money to purchase the drug since it is available free (apart from a very small prescription charge) on the National Health Service. Furthermore, the obligatory attendance at a special clinic will enable the addict to see a doctor regularly, and this may assist in the development of a relationship which will eventually lead the addict to desire withdrawal from the drug or other forms of treatment. The addict is regarded as a sick person who properly comes within the ambit of medical practice.

The new law did not come into operation until April 1968, and it is still too early to make definitive statements as to the success or failure of the above aims. Preliminary figures, however, would suggest that the situation is being contained, and that addicts will attend such clinics for their drugs and for help from social workers and others. The number of new cases (not yet notified to the Home Office)--having risen rapidly before, during and after implementation of the new act--has started to fall. It remains to be seen whether there will be a further rise or whether the great majority of addicts are now attending the clinics so that no new notifications will be necessary. There are no data yet as to the numbers, if any, of individuals who have become addicted for the first time subsequent to the implementation of the Dangerous Drugs Act. This will be an important aspect to bear in mind in assessing the value of the approach. At the present time, also, there are no compulsory methods to deal with addicts by hospital admission just because they are addicts. Only if there is some mental condition covered by the Mental Health Act (39) can such a person be admitted to hospital against his will, and drug addiction *per se* is not included.

DISCUSSION

The foregoing thumbnail sketch of developments in the field of treatment of drug dependence is by no means complete. Space has not allowed the presentation of the full range of facilities provided by the New York City Programme (47) nor are such facilities as "A Counselling Center for Drug Addicts" (42)

or half-way houses described. The setting up of theoretical frameworks within which to plan treatment programmes such as that presented by Brotman, Meyer and Freedman (6) has not been covered--since the essential findings will be the success or otherwise of treatment methods based upon these theoretical concepts. Nor have the conditioning theories of Wikler (62) been discussed or the attempts to decondition by the use of scoline aversion (54).

Perhaps one of the most important papers to achieve publication recently has been that by Nagahame (40), who describes the measures taken in Japan since World War II to combat the serious problems of amphetamine abuse which developed there. A combination of stricter laws to ban the drugs and their precursors, more severe penalties, the setting up of treatment facilities in mental hospitals to which addicts could be admitted against their will, and also the creation of a general headquarters for the campaign against amphetamine abuse--with the function of organizing treatment, strengthening control systems, educating the public, acting as a clearing house of information about methods of treatment and fostering awareness of the need to improve economic and social conditions--has led to a diminution in the number of persons dependent on amphetamine from over 1,000,000 at the peak to a negligible number. This approach would appear to be a truly comprehensive one and represents an immense investment of money, personnel, hospital facilities and so on. The paper does not give many details and does not say what has happened to the previously amphetamine-dependent individuals. Have they, for instance, turned to barbiturates? Similarly, methods to deal with the much smaller number of heroin abusers along the same lines appear to have produced a dramatic change.

It is therefore difficult to draw accurate conclusions on the basis of Nagahama's paper, but on the face of it the results are almost unbelievable. Further study will answer the question as to whether such methods are applicable to other countries and whether ex-amphetamine addicts are indeed free from drugs and socially rehabilitated.

Looking at the whole field of treatment of drug dependence the reader cannot fail to realize that there are few areas which are well defined, and that almost all areas are ripe for further research. The field of treatment by hospital withdrawal, for instance, is still not fully worked out. The studies at Lexington, which are brilliantly conceived and executed, do not really answer the question as to whether a group of addicts from the street, not under compulsory detention, and springing from a different community, would show the same phenomena. Why is it, for instance, that some patients on quite large doses of heroin when placed in a cold turkey situation in prison, perhaps, show

only minimal or even no physical withdrawal signs. Is the practice of withdrawing a patient as quickly as possible really the best way, or would it be better if the patient were withdrawn more slowly, particularly in a voluntary setting--if only to allow longer exposure to the therapeutic influences of the withdrawal unit? Does it matter at all which method is used in terms of long-term success, and how can one set up a study to evaluate such factors? Is Wulff's method of barbiturate withdrawal, so carefully worked out, superior to and as safe as the traditional methods developed at Lexington and are his interesting hypotheses, as noted earlier, tenable?

Follow-up studies have been criticized (41) and most have shown poor outcome. More recent studies have defined the problems more clearly (55,56,57,58,48) and the successes in terms of social rehabilitation referred to under the methadone and cyclazocine programmes are most encouraging.

The self-help groups such as those at Synanon, Daytop Village and Phoenix Houses have the disadvantage of not incorporating research, and are clearly strongly emotional belief systems. Claims of successes are impossible to evaluate without adequate research data. Nevertheless, the goal of producing personality change is an ambitious one, and the fact that the protagonists of these self-help groups believe in what they are doing and tend to talk as though success was just round the corner and their method was the best, should not lead to a sceptical rejection of the methods. The Phoenix Houses, in particular, should be able to produce some answers since there is a mass of documentation and close follow-up of patients. Perhaps the belief system which is common to self-help groups and methadone maintenance programmes is an essential part of the treatment.

It seems sad that methods such as the "methadone maintenance programme" and the Phoenix House Programme should become the subject of political diatribe in which they are regarded as constituting an either/or situation. The question one should be asking is, "Which kind of addict is best handled by the methadone programme and which by the Phoenix House Programme, the cyclazocine programme, or other programmes?" It is unlikely that one method will be successful with all patients. It should, in my view, be obligatory that all new approaches, which require financing from public monies, should be carefully thought out and should have provision for research built into them. It is one of the tragedies of life that where a problem is massive, as with the drug-dependence problem in the U.S.A., the pressure for services takes precedence over the need to evaluate that service. This is true of other areas presenting problems, such as those of delinquency and child psychiatry.

A particular omission from this chapter is a reference to the civil commitment programmes of California and New York State. These programmes are an attempt to deal with the problem under a therapeutic label, but if the addict regards this in the same way as prison, there is unlikely to be much change in outcome unless therapy and rehabilitation are really effective and supervision is much closer than has previously obtained. Kramer and colleagues (36) have concluded "that commitment programmes for addicts can be considered at this time an interim procedure between a totally punitive and evolving non-punitive approaches to the issues of drug-dependence, though perhaps they will persist as an alternative for those who are not helped by other programmes."

What is the best treatment for amphetamine addicts? Amphetamines, after all, are causing concern throughout the world (25,26,59).

Finally, in this wide review of modern developments, only short reference has been made to the developments in Great Britain. Perhaps enough has been said about these to show that the situation is being closely watched, that it is a situation which could lend itself to evaluation by research, and that in due course publications will indicate whether or not the new method can be continued and whether the problem is being successfully dealt with. Furthermore, what measures, if any, are required to deal with amphetamine dependence, barbiturate dependence, or dependence on other drugs not within the scope of the new Dangerous Drugs Act may be delimited.

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- 43. Symposium on Hydrology and Water Resources Development, 1966
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- 46. Summer Training Program in Geological Mapping, 1966
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48. Symposium on Mine Health and Safety, 1966
49. Conference on Engineering Education, 1966
50. Conference on Agricultural Extension, 1967
51. Traveling Seminar on Processing and Marketing of Fruit and Vegetable Products, 1967
52. Summer Training Program in Geological Mapping, 1967
53. Conference on National and Regional Agricultural Development Policy, 1967
54. Symposium on Agricultural Statistics, 1967
55. Traveling Seminar on Marketing of Livestock and Livestock Products, 1967
56. Conference on Combating Malnutrition in Preschool Children, 1968
57. Symposium on Development and Utilization of Mineral Resources, 1968
58. Conference on Industrial Vocational Education, 1968
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60. Report of the Ad Hoc Working Party on Fertilizers, 1968
61. Decade of Development, a Ten-Year Compendium, 1959-69
62. Symposium on Demographic Statistics, 1968
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64. Geology and Ore Deposits of the Lakan Lead-Zinc District, Iran, 1968
65. Symposium on Manpower Planning and Statistics, 1969
66. Conference on National and Regional Livestock Development Policy, 1969
67. Geology and Ore Deposits of the Sizma-Ladik Mercury District, Turkey, 1969
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