EVALUATION OF DEPENDENCE LIABILITY AND DEPENDENCE POTENTIAL OF DRUGS

Report of a WHO Scientific Group
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WHO SCIENTIFIC GROUP ON EVALUATION OF DEPENDENCE LIABILITY
AND DEPENDENCE POTENTIAL OF DRUGS

Geneva, 4-9 November 1974

Members:

Dr J. Engel, Department of Pharmacology, University of Göteborg, Sweden
Dr J. A. O'Donnell, Professor of Sociology, University of Kentucky, Lexington, KY, USA
Dr F. Hoffmeister, Professor and Director, Bayer AG Institute of Pharmacology, Wuppertal, Federal Republic of Germany (Rapporteur)
Dr J. Jacob, Professor of Pharmacology and Toxicology, Institut Pasteur, Paris, France
Dr D. Jasinski, Chief, Clinical Pharmacology Section, Addiction Research Center, National Institute on Drug Abuse, Lexington, KY, USA
Dr P. Kifholz, Professor and Director, University Psychiatric Clinic, Basle, Switzerland
Dr H. W. Kosterlitz, Professor and Director, Unit for Research on Addictive Drugs, University of Aberdeen, Scotland (Vice-Chairman)
Dr M. O. Olatawure, Department of Psychiatry, University College Hospital, Ibadan, Nigeria
Dr C. R. Schuster, Professor of Psychology, Department of Psychiatry, University of Chicago, IL, USA (Chairman)
Mr C. Schneider, Head of Pharmacology, Research Department, Miles Laboratories Ltd., Stoke Poges, Buckinghamshire, England
Dr J. P. Smith, Assistant Director for International Activities, National Institute on Drug Abuse, Rockville, MD, USA (Rapporteur)
Dr M. I. Souef, Professor of Psychology and Chairman, Department of Psychology, University of Cairo, Egypt
Dr C. Vinar, Head, Department of Psychopharmacology, Research Institute for Psychiatry, Prague, Czechoslovakia
Dr T. Yanagita, Director, Division of Medical Sciences, Central Institute for Experimental Animals, Kawasaki, Japan

Representatives of other organisations:

United Nations:

Dr O. J. Braenden, Chief, Scientific and Technical Section, Division of Narcotic Drugs, United Nations, Geneva, Switzerland

* Unable to attend: Dr W. R. Martin, Chief, Addiction Research Centre, National Institute on Drug Abuse, Lexington, KY, USA.
Mr J. L. Gomez del Prado, Drug Demand and Information Unit, Division of Narcotic Drugs, United Nations, Geneva, Switzerland

Dr M. L. Ibañez-Martin, Scientific and Technical Section, Division of Narcotic Drugs, United Nations, Geneva, Switzerland

Dr M. Klibardy, Chief, Drug Demand and Information Unit, Division of Narcotic Drugs, United Nations, Geneva, Switzerland

International Narcotics Control Board:

Mr R. Angarola, Treaty Research and Information Section, International Narcotics Control Board, Geneva, Switzerland

Mr A. Babi, Chief, Drug Requirements and Quota Section (Estimates), International Narcotics Control Board, Geneva, Switzerland

Dr S. Kazmakçalı, Chairman, Department of Pharmacology, Medical School, University of Ankara, Turkey

International Council on Alcohol and Addictions:

Dr H. Halbach, Honorary Professor of Pharmacology, University of Munich, Federal Republic of Germany

International Union of Pharmacology:

Dr F. Hoffmeister, Professor and Director, Bayer AG Institute of Pharmacology, Wuppertal, Federal Republic of Germany

Department of Justice, Washington, DC, USA:

Dr Th. Harwood, Chief Pharmacologist, US Drug Enforcement Administration, Washington, DC, USA

Department of Health, Education and Welfare, Washington, DC, USA:

Dr J. S. Kennedy, Pharmacologist, Food and Drug Administration, Rockville, MD, USA

Department of Health and Welfare, Ottawa, Canada:

Dr I. W. D. Henderson, Policy Adviser, Non-Medical Use of Drugs Directorate, Ottawa, Canada

Secretariat:

Dr T. L. Chruscieł, Senior Medical Officer, Office of Mental Health, WHO, Geneva (Secretary)

Dr G. M. Ling, Senior Medical Officer, Office of Mental Health, WHO, Geneva

Dr R. Stetch, Professor of Psychology, Department of General Experimental Psychology, University of Ottawa, Canada (Temporary Adviser)

Dr J. E. Villarreal, Director, Miles Research Laboratory, Mexico City, Mexico (Temporary Adviser)
EVALUATION OF DEPENDENCE LIABILITY
AND DEPENDENCE POTENTIAL OF DRUGS

Report of a WHO Scientific Group

1. INTRODUCTION

A WHO Scientific Group on Evaluation of Dependence Liability and Dependence Potential of Drugs met in Geneva from 4 to 9 November 1974. Dr W. H. Chang, Assistant Director-General, opened the meeting on behalf of the Director-General and welcomed the participants, the representatives of the Secretary-General of the United Nations, the International Narcotics Control Board, the International Council on Alcohol and Addictions, the International Union of Pharmacology, and the observers from the Non-medical Use of Drugs Directorate of the Department of Health and Welfare of the Government of Canada and from the Departments of Justice and of Health, Education, and Welfare of the Government of the United States of America. Dr Chang noted that WHO has been concerned since its inception with the problems associated with drug dependence. In 1963, WHO convened a Scientific Group to review the laboratory and clinical procedures in use at that time for identifying drugs with dependence-producing properties. The vast amount of research work carried out in the field since then has resulted in significant advances in the development of concepts on the nature of drug dependence. This research work has also greatly improved the techniques and methods reviewed 11 years ago and produced new and powerful techniques for assessing the dependence liability of drugs. In view of these developments, interests in the evaluation of new drugs and of their dependence liability has increased considerably.

The Seventeenth World Health Assembly adopted in 1974 a resolution requesting the Director-General "to undertake with the assistance of the Advisory Committee on Medical Research the formulation of generally accepted principles and requirements for the evaluation of the safety and efficacy of drugs." In response to this request a number of scientific groups have been convened on such topics as preclinical testing of drug safety testing for teratogenicity, carcinogenicity and mutagenicity, clinical

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evaluation, and bioavailability of drugs." Most recently, a WHO Scientific Group on Guidelines for Drug Evaluation considered all aspects of the evaluation and testing of drugs in the light of increasing knowledge, and formulated proposals and guidelines for present and future research in this field. 

The present meeting was convened to review the methodological criteria for predicting and assessing the dependence liability and dependence potential of drugs, to discuss in detail the progress achieved so far in relevant preclinical and clinical methods, and to formulate proposals and guidelines for present and future research strategies and activities. Recognizing that social, economic, and legal factors can also determine excessive drug consumption, the World Health Organization also requested the Group to discuss methods that may serve to detect the existence of drug problems in society.

The methods for assessing dependence liability are useful not only in preventing the exposure of man to dangerous drugs but also in developing better and safer medicaments.

The proper examination of problems of drug dependence requires the consideration of its multiple aspects falling within the domains of various disciplines. It was therefore fitting that the Group, representing a number of disciplines, should be invited to review the progress in methods and techniques for the evaluation of dependence liability and dependence potential of drugs and to make recommendations on research.

2. REVIEW OF PREVIOUS WORK OF THE WORLD HEALTH ORGANIZATION CONCERNING METHODOLOGY OF EVALUATION OF DEPENDENCE LIABILITY AND DEPENDENCE POTENTIAL OF DRUGS

The terms used to describe the condition of dependence and the methods available for the determination of dependence liability have evolved over the last several decades. During this time, various WHO expert committees have drawn attention to these changes, recognizing the need for scientific evaluation.

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* The dependence potential of a substance consists of those intrinsic pharmacological properties that can be measured in animal and clinical testing procedures. The evaluation of the liability of a substance to produce dependence ("dependence liability") must take into account the dependence potential of the substance and the extrapharmacological individual and societal factors that may lead to dependence.
studies. In 1963, WHO convened a Scientific Group on the Evaluation of Dependence-producing Drugs. The report of this meeting described the methods of evaluating drug dependence for morphine and substances with morphine-like effects, barbiturates and other sedatives, amphetamines, cocaine, hallucinogens, and cannabis. The applicability of the then available methods was discussed and none was considered conclusive as regards predictive value. In its concluding remarks, the Group noted: "Whatever the agent, recognition of psychic dependence is for the most part a matter of observation and judgement when it is actually used by man. The experimental approach to the assessment of psychic dependence in both animals and man is just beginning and no definitive statement regarding techniques or their predictive value can as yet be made."*

Expert committees meeting after 1964 continued the discussion of theory and methods, commenting on criteria for control of drugs and problems of definition and assessment of subjective drug reactions; *consideration of specific drugs, and classification of drugs recommended for control; *the social context of drug problems, the nature of society's response, etiological factors in onset and continuation of drug-seeking behaviour, the goals of prevention, and treatment and evaluation; *approaches, methods, and priority areas of research in epidemiology; *and the general prevention of problems associated with drug use." Lastly, general considerations for evaluating drugs for therapeutic use were discussed by a WHO Scientific Group on Guidelines for Drug Evaluation *that met in Geneva from 14 to 19 October 1974.

3. GENERAL CONSIDERATIONS

Drug dependence is a condition produced by the interaction between the drug, the organism, and the environment—a condition that can be studied experimentally. Studies of this phenomenon have various purposes: to increase understanding of the process of dependence, to develop possible therapeutic agents for the treatment of dependence, and to

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provide educational information for health professionals and the public. However, such studies have special significance as instruments for (a) the protection of public health and (b) the development of newer psychoactive drugs with less dependence-producing properties than currently available compounds. Moreover, these studies should provide reliable information on the properties of drugs so that sound evaluations of their dependence potential and liability as well as accurate predictions of possible harm to individuals and society can be made. For this purpose, knowledge of the dependence potential of a drug is not by itself sufficient. For evaluation of liability in man it needs to be integrated with information on such aspects as the drug's general pharmacology and toxicology, psychotropic and psychotokinetic effects, therapeutic efficacy, availability, and cost. The scope of this report is limited to methods for the assessment of dependence potential and dependence liability of drugs.

In order to understand the nature of the conclusions that are drawn from laboratory or clinical tests, it is necessary to distinguish between testing and evaluating. In testing, the properties of drugs are determined through experiments that use physical, chemical, biological, or behavioural methods. Evaluation, on the other hand, is the appraisal of the validity of specific results, the significance of the overall pharmacological picture of a specific drug, and the prediction of events in specific human and social situations.

4. GENERAL METHODOLOGICAL PRINCIPLES

The most direct way to determine whether or not a particular drug is producing dependence at a certain level is by the epidemiological assessment of known cases of dependence after exposure of a sufficiently large human population to the drug. Since it would be unethical to institute experiments of this sort in man, predictive test procedures are required to evaluate the risk of induction of dependence.

In the initial stages of evaluation the characterization of the general pharmacological profile of a drug may be useful. At later stages, there is a progressively greater need for procedures that measure responses regarded, on the basis of scientific evidence, as being intimately related to the induction of compulsive drug-taking in man.

Production of dependence is not an all-or-none phenomenon. Nevertheless, evaluations and decisions have to be made in research laboratories about the development of drugs and about their control in regulatory agencies on the basis of data from preclinical, clinical, and epidemiological studies.
Many drugs are taken in excessive amounts and on a long-term basis for a variety of reasons. The objective of the techniques of study described here is to identify drugs with such strong reinforcing effects that, primarily because of their pharmacological properties, their consumption leads to dependence and poses a universal risk to public health.

Drugs without dependence-producing potential are sometimes used in excessive quantities. Non-pharmacological factors—such as fashion or behavioural or environmental pathology—or psychopathological states can stimulate and sustain drug-seeking behaviour. Knowledge of the extraneous factors leading to this form of excessive consumption is not extensive enough at this time to permit laboratory replications for testing. Behavioural research in this area is progressing, however.

As in other fields, tests for dependence-producing properties have to be evaluated to their specificity, practicability, reliability, and predictive value. Since all pharmacological tests have some limitations, evaluation of the dependence-producing potential of particular drugs has to be made on the basis of the accumulated evidence from multiple tests. Reliability of tests is increased when multiple measures are taken of a range of responses in the same subject.

Using multiple tests, it is desirable to match the profile of action of new drugs with reference drugs known to be dependence-producing. If the profile of action of a new drug is very similar to that of the appropriate reference drug, the probability that the new drug will also produce dependence is very high.

There are two problems inherent in this research strategy. One problem is the selection of characteristics on which to base the comparison of profiles. For example, as Fraser et al. have pointed out, the profile of action of propoxyphene in dependence tests is very similar to that of morphine, and yet the actual incidence of dependence on propoxyphene is significantly less than that of morphine, the suggestion being made that the low incidence of abuse of propoxyphene results from its side effects and its strong local irritating properties.\(^a\)

The second type of problem is that there are many new drugs whose pharmacological profile is different from that of available reference dependence-producing drugs. Drugs with a new profile of action are less likely to be classified correctly. Therefore, caution must be exercised to avoid errors of classification, especially those of the false negative type.

5. PRECLINICAL METHODS

5.1 Assessment of a drug's reinforcing properties

Over the past decade, powerful procedures have been developed to analyze the behavioural aspects of drug dependence in animals. This analysis is based upon conditioning principles widely used by experimental psychologists and behavioural pharmacologists. For the analysis of drug-seeking behaviour, conditions are arranged so that a behavioural response is followed by the administration of a drug. If the response increases in frequency, then the drug is defined as a positive reinforcer for the behaviour leading to its administration. A wide variety of psychoactive drugs have been shown to serve as positive reinforcers in both rats and monkeys.\(^a\)\(^b\)\(^c\)\(^d\)\(^e\) In general, drugs that serve as positive reinforcers in animals are those that produce dependence in man.\(^a\) It would thus appear that this procedure has predictive value for assessing a new drug's dependence potential. Although numerous routes of administration have been used in drug reinforcement experiments, the most widely used for water-soluble compounds is the intravenous route. Experiments employing the intragastric route for self-administration of water-insoluble compounds have been described by Yanagita & Takahashi.\(^c\) Techniques have been developed for the chronic catheterization of veins in monkeys, so that long-term experiments lasting many months can be carried out.\(^d\)\(^e\) Further, the electrical and mechanical equipment both for providing the automatic delivery of drug reinforcement and for recording the data has reached a high degree of sophistication.

The most widely used drug reinforcement experiments can be divided into three categories: (a) continuous self-administration of drugs, (b) the cross-self-administration procedure, and (c) quantitative methods for the assessment of a drug's relative reinforcing effects.

5.1.1 The continuous self-administration test

In this test animals are allowed to self-administer a drug without time or dose limitation 24 h a day for several weeks. This procedure permits

assessment of the reinforcing effects of a drug, the pattern of drug-taking characteristics of the individual, and the manifestation of pharmacological effects of a drug at self-medicated dose levels.

The experimental protocol involves, first, the self-administration of saline, or other control agents, to determine the baseline response rate. If a significant increase in response rate is observed following substitution if the test drug, the observation is continued. Later, the drug is withdrawn for 24–48 h and any manifestations of withdrawal are observed. If no increase in response rate is seen with the test drug, forced programmed injections are given and response rates during and after this period are observed.

Subjects experienced in self-administration can be used effectively when the reinforcing effect of a drug appears to be weak or non-existent, since they are known to be more susceptible to the effect than inexperienced animals. However, naive monkeys or monkeys trained in responding to another reinforcer should then be used if the drug is shown to act as a reinforcer.

5.1.2 Cross-self-administration of drugs

Of several procedures that have been employed to assess the reinforcing effects of new drugs, the cross-self-administration technique has the advantage that well-trained animals can be exposed to different drugs and dosages over the course of relatively few test sessions. The rate of self-administration is first established and maintained by response-produced infusions of a standard drug; other test drugs are then substituted for several consecutive sessions to determine the extent to which self-administration of the substituted drug in maintained in comparison with saline substitution as a control procedure.

Although research has shown that the rate of drug self-administration depends to a certain extent upon factors other than the reinforcing effects of the drug, reliable and reproducible results have been achieved. The main disadvantage of this method is the lack of quantitative data referring to relative potencies of reinforcing properties of drugs. On the other hand results achieved with cross-self-administration techniques in which drugs are offered as positive reinforcers can be controlled by cross-self-administration procedures for assessing the negative reinforcing properties of drugs.

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Comparison of the results of both techniques gives further evidence upon which to judge the reinforcing properties of a drug as a whole.\footnote{Hoffmeister, F. & Witzke, W. Psychopharmacologia (Berl.), 33: 247 (1973).} \footnote{Hoffmeister, F. J. Pharmacol. exp. Ther., 193: 468 (1973).}  
Nevertheless, other procedures are needed to supplement information derived from the cross-self-administration experiments.

5.1.3 Quantitative methods of assessing the relative reinforcing efficacy of drugs

Although cross-self-administration and combined self-administration procedures yield valuable results on reinforcing properties of drugs the results are not quantitative. Therefore, techniques that may yield better quantitative data to establish the intensity of reinforcing effects need to be developed.

5.1.3.1 Drug choice procedures

Drug choice procedures can be used to avoid the influence of the rate-modifying effects of drugs if discrete trials are spaced appropriately. The procedure permits monkeys to indicate a preference for one of two drug solutions. The experimental protocol may be exemplified as follows:

In order to deliver two different solutions independently, a double-lumen intravenous catheter is connected to two separate infusion pumps. The experimental cubicle contains two levers; external stimuli control each response. A daily session consists of sampling trials and choice trials. In sampling trials, the subject samples each of the two drug solutions separately. During choice trials, the subject is allowed to choose the preferred drug solution by pressing the appropriate lever associated previously with that drug during sampling trials.\footnote{Johnson, C. E. & Schuster, C. R. J. Pharmacol. exp. Ther., 193: 676 (1975).}

5.1.3.2 The second-order schedule procedure

Recently, the patterns of responding maintained in rhesus monkeys under a second-order schedule by intramuscular injections of morphine or cocaine has been studied.\footnote{Goldberg, S. R. et al. In: Report of the 36th Annual Meeting of the Committee on Drug Dependence, 1974, Washington, DC, National Research Council, Commission on Drug Dependence, 1974, p. 592.} Under this schedule, every tenth key-press response (FR 10) during a fixed interval of time produced only a brief light. The first FR 10 component completed after a 60-min interval had elapsed produced the light, which then remained on until the monkey had been given an intramuscular injection of either morphine or cocaine. Since the drug injection occurred only at the end of each session, it is
possible to study the effects of morphine and cocaine in maintaining
behaviour, independently of their other pharmacological effects. The
intravenous route has also been used in the study of second-order schedules.\cite{Goldberg1973}

5.1.3.3 The progressive ratio test

In this test an attempt was made to determine the intensity of the rein-
forcing effect of drugs through the persistence of animals' drug-seeking
behaviour by lever-pressing.\cite{Yamagita1973} For example, a drug can be replaced by
saline, and observation is continued until the animal reduces the number
of daily injections to less than half for the standard drug. At this point,
self-administration of the test drug is introduced at a fixed ratio of 100 re-
sponses for 24 hours. The ratio is then doubled after a fixed number of
injections. When the time interval between injections becomes longer
than 48 h (24 h for the short-acting drugs) the ratio performed for the last
dose is regarded as the final ratio of the test.

Recent investigations have combined choice and progressive ratio pro-
cedures to assess the reinforcing effects of psychomotor-stimulant and
sedative-hypnotic drugs. A progressive ratio method has been used in
baboons as a means of rank-ordering the reinforcing properties of drugs
in a given class. The test differs from that described above mainly in
timing. The animal is given an opportunity to initiate self-administration
of a drug on a fixed-ratio basis every 3 h. At regular intervals (about a
week apart) the fixed ratio requirement is doubled until the animal initiates
drug self-administration lasting less than 25% of the time. The fixed ratio
at this point is called the response cost. A range of response costs has
been generated for both sedative-hypnotic and psychomotor stimulant
drugs.\cite{Griffith1975}

Since relatively few drugs have been studied using drug choice and pro-
gressive ratio and second-order schedule procedures, further evidence is
needed to establish their value as quantitative methods for assessing the
reinforcing effects of drugs. The currently available data were derived mainly
from cross-self-administration and continuous self-administration tests.

5.2 Physical dependence

5.2.1 Conceptual background

Historically, the emergence of the concept of physical dependence has
had a profound impact on teaching in this field. Chronic administration of

\begin{itemize}
  \item \textit{Griffith, R. R. et al.} Psychopharmacologia (Berl.), \textbf{28} (1975, in press).
\end{itemize}
dependence-producing drugs (usually opiates and their alternates) was found to produce changes such that the removal of the drug would lead to a number of severe physiological and behavioural disturbances designated as the abstinence syndrome. Further administration of the opiate was found to relieve this syndrome. In addition to restoring the organism to its previous condition, continued administration of the drug led to the maintenance of physical dependence. This cycle was thought to be responsible for a "hunger" for drugs, which explained the craving of the addict for narcotic analgesics. Accordingly, physical dependence was considered to be the defining characteristic of "addiction".

Later, it was acknowledged that factors other than physical dependence play a very important role in the initiation and maintenance of drug-seeking behaviour. Removal of the physiological need for narcotic analgesics does not necessarily eliminate the desire for these drugs. Strong drug-craving persists long after detoxification and withdrawal. Further, drugs such as cocaine and some other stimulants lack the ability to produce physical dependence and yet may produce a strong craving.

The findings of laboratory and clinical studies now support the view that physical dependence is neither a necessary nor a sufficient condition for the production of compulsive drug-taking behaviour. Thus, nalorphine and cyclazocine produce some degree of physical dependence but do not initiate drug-seeking behaviour in animals or in man. Further, the analgesics profadol and pentazocine readily lead to self-administration behaviour in the monkey under conditions in which physical dependence is not readily observable.

In the case of the classical morphine-type drug, however, physical dependence is generally regarded as a strong contributing factor to the strength and the persistence of drug-seeking behaviour. This is one reason for the continued emphasis on studies of physical dependence properties of new analgesics. Another reason is that physical dependence and the suppression of the morphine abstinence syndrome are the most specific pharmacological properties of drugs of this type. In fact they are the defining characteristics of this class of substances since their other effects—such as analgesia and respiratory depression—are not found exclusively in narcotic analgesics. The capacity of a compound to produce physical dependence of the morphine type is strongly predictive of its ability to induce and maintain drug-seeking behaviour.

Barbiturate-like drugs and alcohol also produce physical dependence, although of a different type. The abstinence syndrome connected with these compounds can be severe and even lethal. Physical dependence on these drugs may present serious problems of clinical diagnosis and management. In contrast to the situation with the morphine-like drugs, the contribution of physical dependence to drug-seeking behaviour in the case of barbiturate-like drugs is not clear. For example, physical dependence is produced by the long-acting barbiturate phenobarbital, yet this drug has only minimal liability to produce drug-seeking behaviour in man.  

For ethical reasons, studies in man on the physical dependence capacity of drugs can be carried out only on a limited scale. Therefore, there is a special need for adequate reliability and validity in preclinical studies involving the newer techniques of assessment.

5.2.2 Opiates and synthetic alternates

Procedures for the evaluation of new compounds of this type have been described in detail elsewhere.  

Briefly, the physical dependence induced by these substances may be tested directly by administering them at appropriate intervals for prolonged periods. The presence of physical dependence is assessed by producing abstinence with (a) the administration of morphine antagonists and (b) abrupt termination of the chronic treatment with the test drug. The need for continuous appropriately high levels of the drug in the organism must be stressed as a requirement for a valid test. In direct studies of physical dependence, there have been numerous instances of false negative results because short-acting drugs have been administered at intervals that are longer than the duration of drug action. Problems of experimental design and of interpretation of results also arise with the tests for the precipitation of abstinence with narcotic antagonists. For example, it must be proven that the reactions produced by the antagonist are indeed signs of abstinence and not non-specific effects.

In interpreting the results of experiments in which antagonists are administered to determine whether or not physical dependence has been produced, it must be borne in mind that the presence of morphine-like

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physical dependence is reflected in characteristic changes in the dose-response curve of the antagonist—a marked shift to the left of the curve and a higher maximum point.

Compounds should also be tested in the "single-dose suppression test", a procedure more convenient than the direct physical dependence study. This procedure is based on the well-established principle that drugs suppressing morphine abstinence are themselves capable of producing morphine-like physical dependence on chronic administration. Criteria for the identification of compounds with specific morphine-like properties in single-dose suppression tests have been discussed in detail elsewhere. Briefly, these criteria are based on the pattern of the signs that are suppressed by morphine-like drugs and cannot be obtained with other central depressants. The criteria also refer to the fact that dependence-producing analgesics have two major effects: (a) they suppress some aspects of behaviour that increase during abstinence, and (b) they restore behaviour characteristics that decrease or disappear during abstinence (e.g., eating, climbing, non-aversive social interaction).

5.2.2.1 New approaches: subacute and acute dependence and protracted abstinence

Physical dependence of the morphine type has been demonstrated in man and various other species by the precipitation of abstinence after short-term administration of morphine-like drugs (acute physical dependence). By precipitated abstinence is meant the production of signs that cannot be attributed to the non-specific interactions of the morphine-like drug and the antagonists.

The 1963 report referred to studies indicating that dogs became physically dependent on morphine after a slow intravenous infusion of morphine (acute technique) and mice became dependent after implantation of morphine pellets (subacute technique). The abstinence syndrome precipitated by an antagonist served as evidence for the development of physical dependence. New acute and subacute techniques have been developed, the advantages of which are: (1) they are economical, (2) they allow for more thorough studies of dose-effect and dose–time relationships, and (3) they consequently make possible the correlation of dependence-producing properties and other pharmacological characteristics of drugs.  

\* Jacob, J. Psychopharmacologia (Berl.), 1975 (in press).
More compounds should be examined with these techniques to establish their full potential.

For purposes of evaluation, the pellet implantation technique does not appear to be such a promising technique in mice as in rats. Single injections or subcutane administration of the several drugs may yield better results. Saelens et al., studying several opioids, reported agreement between results from mice and those obtained from monkeys and man. However, only one overt sign of abstinence (compulsive jumping) has been used in these techniques and it is not possible to reduce withdrawal symptoms readily by giving low doses of narcotic drugs prior to challenge by naloxone. These and other factors may account for the failure of such techniques to discriminate between some oپivine derivatives.

A number of investigators have established that specific abstinence syndromes are much more easily elicited and observed in rats than in mice, using techniques such as implantation of a reservoir, repeated injections or a single injection of a slow-release preparation, or administration of morphine solution (J. Jacob et al., unpublished observations, 1974). Experiments on the dog are ordinarily more time-consuming, but the results, either in the spinal dog preparation or in normal animals, appear to be particularly relevant in assessing physical dependence of the morphine type. For example, very low doses of morphine (0.1 mg per kg of body weight, intravenously) were sufficient to precipitate a clear-cut morphine-type dependence syndrome, which was not simply an "unmasked" direct stimulatory effect of the opioid but a manifestation of a specific underlying state. Further, the acute effects of the opioid (whether respiratory, cardiovascular, behavioural, autonomic, or neurophysiological) and the corresponding abstinence signs can be compared on the basis of the observations made in the same animals.

An acute in vitro technique uses antagonist-induced contractions of the guinea pig ileum as a means of identifying dependence production of the morphine type (J. E. Villarreal, unpublished observations, 1974. For further discussion, see section 5.2.2.2).

These acute and subacute techniques have yielded much new information about the development of chronic dependence and have increased our

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understanding of precipitated and withdrawal abstinence and the role of
neuro-transmitters in the mechanism of action of dependence-producing
drugs. They have also led to the development of important new hypo-
theses.

Martin et al. have described several abstinence signs persisting up to
six or more months after withdrawal in rats and dogs. This protracted
abstinence may play an important role in relapse. Such experiments,
although of great interest, are not considered suitable for purposes of
evaluation. It has been shown by means of radioimmunological assay that
morphine or its closely related metabolites can be detected in mice up to
one month after a single injection of a relatively low dose. On the basis
of this finding, other techniques might be developed for the detection of
protracted abstinence in this species.

5.2.2.2 Use of in vitro models

In vitro models have great predictive value as far as the agonist and
antagonist potencies of narcotic analgesic drugs are concerned. Moreover,
the development of models that demonstrate pharmacological action and
others that give information on the binding of drugs to specific binding
sites has facilitated understanding of the mode of action of narcotic anal-
gesics, and will continue to do so in increasing measure.

No similar progress has been made with the development of in vitro
models for other dependence-producing drugs. Whereas in the case of
narcotic analgesics it has been possible to detect specific binding sites in the
central and peripheral nervous systems and to study the kinetics of binding
of drugs to these sites and also of agonist-antagonist interactions, similar
success has not yet been achieved in the case of the other drugs with depen-
dence potential.

Because of their structural and functional complexity, no in vitro models
based on central nervous systems have been used for studying the pharmaco-
logical effects of narcotic analgesic drugs and for predicting their agonist
and antagonist potencies. On the other hand, stereospecific binding sites
have been identified in brain homogenates. The estimation of relative
agonist and antagonist properties is based on the fact that binding of
agonists, but not of antagonists, is lower in the presence of 100 μmoles
of sodium ions than in the absence of these ions.

Morphine-sensitive neurons are found at certain sites of the peripheral
autonomic nervous system. They are neither species- nor organ-specific,

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with some exceptions. Thus, cholinergic transmission from the myenteric plexus to the longitudinal muscle is morphine-sensitive in the guinea-pig but not in the rabbit. Other morphine-sensitive neurons are those mediating the bradycardia caused by vagal stimulation in the rat and rabbit. Those in the guinea-pig and cat are unaffected by morphine. Two morphine-sensitive adrenergic neurons have been found, specifically in the nictitating membrane of the cat and in the vas deferens of the mouse but not in that of the rat, guinea-pig, or rabbit.

Assessments of the relative agonist and antagonist potencies estimated by the three in vitro techniques are in agreement: the guinea-pig ileum, the mouse vas deferens, and the inhibition of stereospecific binding of naloxone or dihydromorphine in brain homogenates. Moreover, the data obtained from in vitro preparations correlate well with the analgesic potency in man and the ability to precipitate abstinence in monkeys physically dependent on morphine. For the evaluation of agonist and antagonist properties of new drugs, it is important to assess their respective potency by all three techniques. Where new drugs are investigated with these techniques and the data obtained are not in agreement, the pharmacological profile of the drugs probably differs from that of drugs examined so far. Such a possibility has been suggested by the findings in respect of compounds that have recently become available (oxocyclazocines and dimethylfurlurylbenzomorph derivative).

While isolated preparations obtained from dependent animals have been used for the study of tolerance and dependence, in vitro induction of dependence has not been recorded. An interesting observation is the phenomenon that segments of guinea-pig ileum incubated at 5-10°C for 24 h with agonists of the morphine type (e.g., morphine, levorphanol, methadone, and meperidine) respond with a powerful contraction to a challenge with low concentrations of naloxone (J. Villarreal, unpublished data, 1974). Drugs with dual agonist and antagonist actions (e.g., naltorphine, cyclazocine) are almost devoid of this type of activity.

Recently, direct and indirect evidence has been obtained to support the presence of a naturally occurring compound with morphine-like action.

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in the central nervous system and the myenteric plexus of the guinea-pig ileum.\textsuperscript{a, b} Research on the natural interaction of this endogenous compound with morphine binding sites and the modification of this interaction by exogenously administered morphine-like drugs will be important for the study of physical dependence.

5.2.3 Sedatives and hypnotics

Established methods for testing physical dependence liability of sedatives and hypnotics are the substitution test and a direct physical dependence-producing test in the dog or rhesus monkey. In the substitution test, animals are made physically dependent on barbital by means of repeated oral administration prior to the test. Animals are withdrawn for 24 h and when they manifest clearly observable withdrawal signs a single dose or short-term repeated doses of a test drug are given to determine whether suppression of barbital withdrawal is observed. If a drug suppresses the signs, the smallest dose producing complete suppression is determined. A detailed substitution procedure in the dog has been described elsewhere.\textsuperscript{c} A similar procedure has been developed in the monkey.\textsuperscript{d} These tests demonstrated cross-physical dependence on barbital with some other barbiturates, alcohol, and many non-barbiturate sedatives and hypnotics, including meprobamate and several benzodiazepines. In the dog, some drugs of this class suppressed barbital withdrawal but did not produce physical dependence in the direct test, which suggests that the substitution test is relatively non-specific.

The direct procedure for testing for physical dependence consists of administering a test drug to the monkey orally or by some other route once or twice daily for four weeks. The drug is then withdrawn and the monkeys are observed for seven days for signs of withdrawal. The severity of the signs during this period is graded according to criteria previously established on the basis of barbital withdrawal in the monkey.\textsuperscript{e} When the withdrawal manifestation is unclear in the first withdrawal test, a four-week administration and seven-day withdrawal cycle is repeated two or three times until convincing results are obtained. In this test, barbiturates, alcohol, meprobamate, and many benzodiazepines were found to produce physical dependence as observed by clear-cut withdrawal manifestations in

the monkey. The use of dosing schedules that allow the production of continuous overt signs of drug effect in the animal is essential. When the methodological advantages of using the dog and the monkey were compared, the withdrawal signs were found to be more obvious in the monkey,\textsuperscript{a} but dogs are easier to handle. Since the monkey and the dog are not necessarily the most appropriate species in all cases, and since the supply of monkeys is limited, one of the methodological problems in this field is how to develop testing methods in lower species that may be useful at least for the early stages of dependence studies of this class of drugs. Several approaches are being developed in the mouse, the rat,\textsuperscript{b} and the cat.

Subacute techniques have been explored with barbiturate-like drugs and alcohol. Goldstein & Pal\textsuperscript{c} produced withdrawal responses in mice after inhalation of ethanol. Hammond & Schneider\textsuperscript{d} have been successful in eliciting withdrawal symptoms (head twitches) in mice after subacute administration of ethanol. The appearance of this sign was inhibited by the administration of ethanol, pentobarbital sodium, and chlorpromazine and also by other drug groups such as the antagonists of 5-HT.

5.2.4 New developments

In the last decade research with morphine-like analgesics has produced improvements in the established methods for assessing dependence capacity, newer techniques designed for the same purposes that employ different animal species, and the development of many new analgesic compounds with complex pharmacological profiles.

The development of new drugs with complex patterns of action stimulated interest in the thorough pharmacological analysis of the actions of these substances and led to new conceptual developments as well as to a more comprehensive approach to the evaluation of the dependence capacity of these compounds. It became clear that the simple performance of the classical tests for dependence was not sufficient for reliable assessments. Drugs of the most important new group, the analgesics with mixed agonist and antagonist actions, had to be subjected to thorough pharmacological analysis in both monkeys and man in order to obtain a complete picture of their pharmacological properties to allow sound evaluations of their depen-

Precise determination of the basic pharmacological properties of these drugs in isolated preparations has proved to be of significant predictive value.¹

6. CLINICAL METHODS

6.1 Methods of assessing subjective effects of drugs

By subjective effects of drugs in man is meant changes in mental states that are drug-induced and are verbally reported or inferred from observation. Study of such effects is important in order to understand the pathophysiology of dependence upon those drugs, the psychototoxicity associated with their use, and the identification and classification of new agents for the purpose of determining their dependence potential.

The assessment of subjective effects of drugs is one of the frequently used clinical approaches to evaluating dependence potential, even though it does not measure this potential directly. Drug-taking behaviour is determined also by other factors such as, for example, the attitude of subjects to the drug.

A wide variety of approaches have been used to assess these effects of drugs and techniques have been developed to assess the effects of particular classes of drugs. Haertzen has described a major research attempt to quantify the subjective effects of narcotic analgesics, sedatives, hypnotics, amphetamine-like agents, and LSD-like hallucinogens.² Instruments have been developed for assessing the similarities and differences in dependence-producing drugs, so that researchers can estimate the likelihood that a compound will produce psychological effects similar to a reference drug.

A number of narcotic-analgesics, sedatives, hypnotics, amphetamine-

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like agents, and LSD-type compounds have been compared by means of scales specifically designed for the purpose.\textsuperscript{a, b}

Check-lists, structured questionnaires, scales, and other types of instrument have been developed and used in various groups of subjects. The responses of these subjects were statistically analysed to define various syndromes associated with these classes of drugs. A number of sub-scales have been designed to detect the effects of different classes of drugs. These instruments have been found useful for identifying and classifying the subjective effects of analgesic, antitussive, antidiarrhoeal agents and determining their similarity to morphine-type drugs.

The closer the similarity of the effects of the drug being studied to those already known to occur with morphine-type drugs, the greater the likelihood that the new drug will lead to dependence of the morphine type. To a lesser extent, these instruments have been used for classifying agents to determine their capacity to produce dependence of the amphetamine type.\textsuperscript{c} Although there are instruments for assessing agents for sedative and hypnotic,\textsuperscript{d} LSD-hallucinogenic, and possibly cannabis-type effects, more work is needed to refine existing methods and develop new techniques.

6.2 Methods of assessing tolerance and physical dependence of drugs

Certain dependence-producing drugs produce tolerance and physical dependence; however, these phenomena do not in themselves necessarily mean that the drugs act as reinforcers. Tolerance and physical dependence have been shown to develop with cyclazocine and nalorphine, but these drugs have not been abused, and in experimental settings abstinent patients have not sought them. Further, animals will not self-administer these drugs.

In all probability the critical dimensions of tolerance and physical dependence that are related to dependence-producing effects are (1) the emergence of a discomforting abstinence syndrome and (2) a shift in the nature of the action of a drug. The study of phenomena associated with the chronic administration of agents in man such a precipitation of abstinence, tolerance, cross-tolerance, suppression, and direct depen-

\textsuperscript{c} JANKE, W. & BOH, H. \textit{Arzneimittel-Forsch.}, 11: 783 (1961).
dence have been useful in determining profiles for classifying drugs in terms of dependence liability.

6.2.1 Morphine-like drugs

The ability to produce morphine-like physical dependence can be demonstrated with substitution tests or direct dependence tests. Valid and reliable methods are available. The current standard substitution techniques are 24-h substitution tests, which not only determine whether an agent suppresses the abstinence syndrome but also can be used to assess the relative potency of the substituted drug.\textsuperscript{a, b} In addition, these tests are conducted at various levels of dependence to assess agents having partial morphine agonist activity.\textsuperscript{a, b}

In direct dependence studies, physical dependence is demonstrated by the occurrence of a characteristic withdrawal syndrome produced by the administration of antagonists or by abrupt withdrawal.\textsuperscript{a, b} However, more recently, it has been shown that the abstinence syndrome produced by the abrupt withdrawal of agents of the naltorphine and cyclazocine type is different from that produced by the withdrawal of morphine-like agents.\textsuperscript{a, d, e}

6.2.2 Barbiturate-like drugs

The abstinence syndrome produced with barbiturate-like agents is quite different from that seen with the morphine-like drugs or the cyclazocine-nalorphine-type drugs. Both direct addiction and substitution studies have been conducted.\textsuperscript{a, g}

6.2.3 LSD-like drugs

Studies showing tolerance to and cross-tolerance between drugs of this type have been conducted in both animals and in man. Measures of both physiological and subjective states have been used in studies by various investigators.\textsuperscript{a} Physical dependence does not seem to be an important factor in the non-therapeutic use of the hallucinogen type of drug.

\textsuperscript{f} ISSELI, H. \& CHEPUSZIEL, T. L. \textit{Bull. Wild Hlth Org.}, 43 (suppl.) (1970).
\textsuperscript{g} FRASER, H. F. \& ISSELI, H. \textit{J. Pharmacol. exp. Ther.}, 112 : 261 (1954).
6.2.4 Amphetamine-like drugs

Clinical studies have demonstrated that abrupt cessation of chronically administered \( \alpha \)-amphetamine is associated with psychological and physiological effects; however, there is no clear evidence of the relationship of these phenomena to the reinforcing properties of amphetamine. Similarly, tolerance and possibly cross-tolerance within the amphetamine class have also been recognized.\(^a\)

6.2.5 Cannabis

Clinical experience and some experimentation have indicated that abrupt cessation of cannabis use after chronic ingestion is associated with psychological and physiological changes but no clear relationship has been demonstrated between these changes and the reinforcing properties of cannabis.

7. EPIDEMIOLOGICAL METHODS CONCERNING USE OF AND DEPENDENCE ON DRUGS

In a previous report\(^b\) a WHO Expert Committee discussed the potential value of epidemiological methods for the study of drug use. These methods can serve many research purposes unrelated to the dependence liability of drugs, but only their value in this respect is discussed here.

Epidemiology can contribute to the study of dependence liability as follows:

1. It may identify new substances being used non-medically, or an increase in use of already available substances, and thus suggest that these substances need testing for dependence potential.

2. It may validate the pharmacological classification of a drug as having dependence potential by determining the extent and nature of use. The fact that such use is not observed will not invalidate the pharmacological classification; it suggests only that non-pharmacological factors are also necessary for dependence liability to be reflected in social use.

3. It may identify, and perhaps even measure, some of the non-pharmacological factors associated with the dependence liability of drugs.

\(^a\) See section 5.2.3.
7.1 Prospective, retrospective, and other studies

Prospective studies could be used to detect the emergence of new forms of non-medical drug use, but they may be much more costly than retrospective studies in terms of the finance, time, and effort needed.

(a) Surveys

Techniques for the study of a population or a defined subgroup of it are highly developed epidemiological methods. Surveys to determine the incidence and prevalence of drug use pose special problems in relation to validation of the data they obtain, requiring large samples or repeated study of smaller samples to provide reasonably precise estimates of behaviour that occurs infrequently. Such approaches are limited in the amount of detail they can produce because of the need to restrict interview time to what the research subjects will tolerate. Despite this and other limitations, the survey approach is the preferred manner for investigating questions of drug use in the general population.

Large numbers of drug use surveys have been conducted in recent years but their contribution to our knowledge has often been disappointing. Among the reasons for this are:

1. Methodological inadequacies. Questions of the reliability and validity (or even credibility) of the data are often ignored. Established procedures of item formulation and questionnaire or interview construction are sometimes not followed. Statistical analysis is often weak or inappropriate and control variables are not employed as widely as they should be.

2. Non-comparability of measures. Aggregation of the findings from separate surveys has been almost impossible because of lack of comparability of data. “Current use” of the drug, for example, may be undefined or have a completely different meaning in different studies; for instance it may mean that the drug has been used within a day, a few days, a few weeks, or a few months of the time when the information is obtained.

3. Heterogeneity of samples. Most surveys have been conducted on school populations, employees, or military units, and it is impossible to combine the results to extrapolate from them to the general population.

Survey studies of large populations are often expensive and time-consuming, and delays in publication may mean that the findings are out of date before they are available. Such problems are not insoluble, how-

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ever. The series of surveys in San Mateo County, California, for example, have avoided them by setting limited, but important, goals.

There is a need for experimentation with approaches other than traditional interview or questionnaire techniques with an individual. It is conceivable that families, juvenile gangs, or other groups could be used as sampling units. Timely information that is only approximately accurate may be more valuable than precise data at a later time. However, appropriate methods of statistical analysis can provide the research worker with an assessment of the degree of error in his results.

(b) Retrospective studies

Studies of patients as they enter treatment and of arrested persons as they are identified by law enforcement officers often provide valuable data for retrospective studies. Studies of these samples will not, in general, reveal new patterns of non-medical use (with one exception noted in section 7.2, below), but examination of the characteristics of users may identify subgroups in the population especially likely to use drugs and may also indicate some of the non-pharmacological factors that determine the extent of psychological dependence on drugs.

Retrospective studies might improve knowledge of how historical factors influenced drug use in the past. In most societies, drug use of one kind or another is endemic, occasionally assuming epidemic proportions. The ability to predict such changes in the future probably depends upon increasing understanding of how they have occurred in the past.

The usefulness of retrospective studies depends primarily on the credibility of the responses given by the subjects and of the source documents. Among methods available to investigators to carry out at least a partial check on the validity and reliability of such data are:

1. correlating urine test results with self-reporting of drug use;
2. including in the sample subjects known to the investigator to be drug users, without giving the interviewers information concerning their past drug use;
3. including in the list of drugs plausible-sounding but non-existent drugs, and asking the subject to indicate whether or not he has used these fictitious compounds;
4. providing for a consistency check with data obtained in different ways;
5. interviewing other informants, especially family members and physicians, where appropriate and feasible, so as not to risk harm to research subjects;
(6) checking against existing records, such as those relating to arrests, hospitals, or clinics;
(7) determining the agreement between verbal statements and the presence of drugs in the medicine cabinet in the home; and
(8) examining the contents of pockets and handbags to determine consistency with verbal statements.

Each of these methods has been successfully used in at least one study, and others may be developed. Not all would be appropriate in any single study, but an investigator should consider these or similar procedures whenever questions of validity or reliability arise.

7.2 Monitoring and surveillance

Just as the survey can reveal present and past patterns of drug use, repeated surveys of the same population can reveal trends in patterns of use over time. The San Mateo studies mentioned above are an example of surveillance, in the sense that annual data are collected on junior and senior high-school students in that California County.

Any population on which data are periodically acquired can furnish some useful information on drug use, but the obvious population to be closely monitored consists of those users of drugs who appear in treatment agencies and those who are identified by law enforcement agencies. If a new drug begins to be used non-medically, it is more likely to be used by those who have already experimented with a variety of drugs than by naive subjects. Changes in patterns of use—for example, age at onset, the sex ratio of users, the use of a combination of drugs—will necessarily be seen among users.

Users who receive treatment are not necessarily representative of all users. The extent to which they are representative varies with the drug and other factors. Thus, among heroin users, the physically dependent person, using large quantities, is more likely to be in need of treatment than the experimental or casual user. In the case of LSD and other hallucinogens, however, it may well be that the neophyte who has not yet learned to handle the effects of the drug is most likely to ask for help.

Systems already exist for the monitoring of patients in treatment agencies—for example, the Client Oriented Data Acquisition Process (CODAP) in the USA. In so far as descriptive data on patients are acquired, changes in their characteristics over time can easily be determined and subsequently checked by other methods.

Prescription of drugs for medical purposes can also induce dependence, and one form of monitoring is a system of automated processing of medical
prescriptions, such as already operates in several districts of Prague.a,b,c
This can serve as a warning system to detect increases in the frequency
of prescriptions for a drug. Changes in the frequency of prescriptions
should be studied to determine whether the increase or decrease has a
therapeutic explanation.

7.3 Comprehensive monitoring of adverse effects of drugs as an
epidemiological tool

The WHO Drug Monitoring Centre is responsible for the development
of the international system of collecting and disseminating information on
suspected adverse reactions to drugs.4 Numerous national centres already
exist. Their present purpose is to monitor unintended noxious reactions
to doses normally used in man, a very much wider goal than identifying
dependence liability. The system does elicit some reports in which drug
dependence is listed as the suspected reaction, but their number is small.
The system could be expanded to accommodate such information, but the
feasibility of such a change is not presently known. Administrative con-
siderations permitting, the monitoring of adverse effects could be an effec-
tive epidemiological tool for assessing dependence liability of those drugs
obtained from medical sources. The systems developed in Sweden and
the United Kingdom are examples of endeavours that could possibly meet
these objectives.

8. RESEARCH AND METHODOLOGICAL ISSUES CONCERNING
EVALUATION OF DEPENDENCE LIABILITY AND DEPENDENCE
POTENTIAL OF VARIOUS CATEGORIES
OF PSYCHOACTIVE DRUGS

8.1 Morphine and morphine-like analgesics

Characteristic profiles of the pharmacological properties of drugs of
this type have been described for several species (man, monkey, mouse,
dog, etc.). These profiles include: (a) psychomotor and autonomic effects
that are typical for each species; (b) effects antagonized by specific antag-
onists (e.g., naloxone); (c) tolerance and cross-tolerance; (d) capacity to

initiate and sustain morphine-like physical dependence; (e) capacity to suppress most signs of morphine abstinence, in contrast to drugs that modify only some aspects of the syndrome in a non-specific manner; and (f) reinforcement of self-administration behaviour. In addition, specific morphine-like action can be demonstrated in certain isolated organs.

The above properties are highly correlated. With respect to these properties, drugs differ mainly over a wide range in their mg per mg potency. The same characteristic profile is found in substances from widely diverse chemical families. Many non-specific side effects are not correlated with specific morphine-like effects.

8.2 Drugs with morphine agonist and antagonist properties

Following the introduction of nalorphine as a morphine antagonist and the demonstration of its usefulness as an antidote for morphine poisoning, it was discovered that nalorphine itself was capable of producing certain morphine-like effects, most importantly analgesia. Evaluation of the effects of nalorphine indicated a dissociation of analgesia from the ability to produce reinforcement of drug-seeking behaviour and the ability to produce physical dependence of the morphine type.

Subsequently large numbers of compounds were synthesized in an attempt to develop agents having analgesic or other therapeutically desirable actions without dependence potential. The underlying assumption was that the presence of morphine antagonist properties in these compounds would result in a dissociation of actions similar to that observed for nalorphine. In several animal species studies of a number of such agents have demonstrated that there are wide variations in their relative agonist and antagonist properties.

These new agents possess the following three types of properties in different proportions: (a) morphine-like agonist properties, (b) cyclazocine-like agonist properties, and (c) specific antagonist properties. Drugs in which morphine-like agonist properties are predominant will produce morphine-like physical dependence with abstinence syndromes accompanied by increased motivation for drug taking. Drugs in which cyclazocine-like agonist properties are predominant will produce a low-grade physical dependence qualitatively different from that of morphine, with abstinence syndromes not accompanied by motivation to self-administer the drug. Chronic administration of drugs with pure antagonist properties does not seem to produce physical dependence.

8.3 Sedatives and hypnotics

The dependence-producing properties of sedatives and hypnotics may be estimated by demonstration of their reinforcing effects and a charac-
teristic physical dependence. Techniques have been developed in man and a number of animals (primarily the monkey and dog) to measure these properties. The tests are applicable to a broad class of drugs acting upon the central nervous system, commonly termed "depressants".

8.3.1 Animal testing

Physical dependence. The methods used to test physical dependence in animals with regard to this class of drugs have been discussed in section 5.2.3.

Reinforcing properties. The reinforcing properties of this class of drugs can be demonstrated by self-administration techniques in laboratory animals. The testing procedures presently available are those of continuous self-administration in subhuman primates, dogs, and rats.

The cross-self-administration procedure, widely used for opiates, synthetic analgesics, psychomotor stimulants, and some other drugs, is not used for some drugs in this class since many cannot be administered by the intravenous route because of their low water-solubility. The intragastric route poses more difficulties because of delayed onset of drug effects. Only sodium pentobarbital and diazepam have been tested with intravenous administration; the reinforcing effects of these drugs were demonstrated. In the continuous self-administration procedure, using the intravenous or intragastric routes, many drugs such as sodium or calcium pentobarbital, alcohol, and several benzodiazepines were self-administered. Monkeys self-administered pentobarbital and alcohol both intravenously and intragastrically to the point that they were anaesthetized. However, the dose of diazepam, chlordiazepoxide, and some other benzodiazepines self-administered per day was relatively low. Ataxia, but not anaesthesia, was observed.

With the intragastric route of self-administration in the monkey, a substantial reinforcing effect is demonstrable; the final ratio of 6400 lever-pressing responses per unit injection dose was achieved for calcium pentobarbital in the progressive ratio procedure described in Section 5.1.

8.3.2 Clinical testing

The development of clinical methods for assessing the dependence-producing properties of sedative and hypnotic drugs has been limited. This discussion, therefore, will be confined to the feasibility and practicability of such methods as are available.

The classical studies of Isbell et al. demonstrated that chronic administration of intoxicating doses of pentobarbital, amobarbital, and seco-
barbital produced tolerance and physical dependence with an abstinence syndrome upon abrupt withdrawal, the major manifestations of this abstinence syndrome being convulsions and a delirium state. Fraser et al. substituted pentobarbital in seccobarbital-dependent individuals and suppressed abstinence symptoms.  

The morbidity and mortality possibly associated with assessing the ability of agents to produce physical dependence of the sedative and hypnotic type precludes the use of routine tests of this kind. Other testing methods are available for measuring the psychological, physiological, and therapeutic effects relevant to the evaluation of dependence of this type. To date, however, clear-cut approaches have not been extensively employed to measure these effects.

**Subjective effects.** It has been shown that the methods developed to assess the subjective effects of narcotic analgesics can be applied to the assessment of those of barbiturate-like drugs and amphetamines.

**Objective effects.** Effects seen in the laboratory (physiological, behavioural, psychophysical, and clinical observations) indicate that certain characteristics of the acute intoxication state produced by these agents may be useful in assigning specific drugs to this general class as well as providing data on comparability with prototype substances (e.g., rapidly-acting barbiturates, certain benzodiazepines, long-acting barbiturates, meprobamate-like substances). Characteristic effects are facilitation of post-rotatory nystagmus, production of anaesthesia, slurred speech, ataxia, and changes in psychomotor performance, EEG, and sleep.

### 8.4 Volatile substances

Abuse of volatile substances is of public and medical concern not only because of reinforcing properties but because of associated psychoactive and organotoxic effects. These effects preclude clinical testing of such substances.

However, a small amount of data is available from studies on monkeys in which voluntary inhalation techniques have been used. Chloroform, ether, and lacquer thinner have been found to be substantially reinforcing.

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Thus, it appears that the reinforcing properties of volatile substances may be assessed by this technique.

8.5 Psychomotor stimulants and related drugs

With currently available methods, physical dependence upon psychomotor stimulant drugs has not been demonstrated. However, their ability to produce psychological dependence in man has been shown. Extensive research has been carried out to develop procedures to evaluate new drugs for their capacity to produce dependence of the "amphetamine type". These methods have included both behavioural and clinical approaches.

8.5.1 Behavioural approaches

Much research has been carried out to characterize the behavioural effects of psychomotor stimulant drugs. Individual drugs belonging to this class may be identified by their effects: anorexia, increased spontaneous motor activity, stereotyped patterns of behaviour, as well as a wide variety of characteristic changes in conditioned behaviour. Following chronic administration of psychomotor stimulant drugs, tolerance to a variety of the behavioural and physiological effects occurs. Drugs showing this type of behavioural profile should be evaluated further for their dependence potential. The need for further testing is based on the fact that psychomotor stimulant drugs have the ability to reinforce operant behaviour, as is evidenced by their self-administration.

In substitution studies it has been shown that monkeys will self-administer cocaine, dexamphetamine and methamphetamine, pipradrol, phentermine, methylphenidate, SPA (α-phenyl-N,N-dimethylphenethylamine), and diethylpropion. In contrast, fenfluramine and penoline (used in dosages limited by solubility) are not self-administered by monkeys under the same conditions.

When given access to those drugs that are self-administered, monkeys show typical signs of psychomotor toxicity as well as the cyclical pattern of intake previously described for man. A further refinement in methods of assessing dependence of the amphetamine type may be possible by means of the use of more complex behavioural procedures. Current

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research on progressive-ratio procedures as well as choice procedures
suggests that drugs in the class of psychomotor stimulants can be ranked
in terms of their relative reinforcing efficacy. If these efforts are successful
they may result in more precise evaluation of the drug's capacity to produce
dependence of the amphetamine type.

8.5.2 Clinical approaches

It is generally agreed that amphetamines and other psychomotor stimu-
lants produce subjective changes that individuals like. This condition gives
rise to compulsive drug-seeking behaviour, leading in some cases to depend-
ence of the psychological type. It is now well documented by both clinical
experience and experimental intoxication studies that chronic adminis-
tration of large doses of amphetamines will induce a toxic psychosis whose
most common manifestations are auditory and visual hallucinations and
paranoid delusions.

Other less well-documented toxic effects associated with chronic use
that may also have great clinical and social implications include a loss of
motivation and of sustained work habits, fatigue, violent behaviour, com-
pulsive and stereotyped behaviour, unconsciousness, aphasia, paralysis,
anorexia, and insomnia. Finally, chronic administration of the amphet-
amines appears to induce tolerance to some of their effects. Several
techniques have been used to assess the dependence-producing property
of amphetamine and other psychomotor stimulants (see section 6).

8.6 Hallucinogens

As these drugs have been classified with many others as dependence-
producing drugs and yet are not used compulsively in man, it is not sur-
prising that animal models devised to delineate psychic or physical depend-
ence have been wholly unsuccessful. Phencyclidine, indeed, is the only
member of the group that is self-administered by rhesus monkeys after
initiation of lever-pressing by cocaine.

(Maudsley Monograph No. 5).
* Griffith, J. D. et al. In: Costa, A. & Garattini, S., ed. International Sym-
* Angliss, B. & Gershon, S. In: Zarafonetis, C. J. D., ed. Drug abuse, Phila-
delphia, Lea & Febiger, 1972, p. 263.
The number of natural plant and animal products and synthetic chemicals capable of inducing states of altered perception, illusions, feelings of dissociation, or frank hallucinations is sufficiently large that patterns of psychotomimetic effects can now be described. A preliminary classification separates a few major classes: (1) compounds of the type of lysergide (LSD) and STP (DOM); (2) phencyclidine; (3) the agonist-antagonist compounds, e.g., cyclazocine; (4) belladonna alkaloids; and (5) Amanita toxins. These drugs have pharmacological properties or profiles that may help in the prediction of dysleptic actions in man and that can be established by means of behavioural, pharmacological, physiological, and biochemical methods.

Many drugs known to produce hallucinations in man have been found to elicit head-witching in mice and bizarre behaviour in rats. In the monkey, LSD caused bizarre behaviour. Furthermore, LSD, mescaline, tryptamine, and related drugs cause hyperthermia in the rabbit. However, these data alone cannot be used in predicting which hallucinogens are most likely to be abused by man. Nevertheless, drugs with LSD-like activity in animals, for example, would be expected to have greater abuse potential than hallucinogens like nalorphine or cyclazocine, which usually cause dysphoria in man.

8.7 Cannabis and delta-9-trans-tetrahydrocannabinol (THC)

Research on cannabis and THC has expanded rapidly in the last decade, but additional research is needed to identify the active constituents of cannabis and the metabolites of cannabis and THC and to establish the patterns and effects of chronic use.

8.7.1 Self-administration and reinforcement schedules

Self-administration of THC in monkeys and cannabis extract and

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*2,5-Dimethoxy-4-methylamphetamine.


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hashish suspension in rats is established only after forced exposure or priming with other drugs or food.

The effects of, for example, cannabinoids on patterns of behaviour generated by various reinforcement schedules have been reviewed by McMillan, the general conclusion emerging from this and other work being that behaviour is generally depressed in a dose-related fashion.

In man the level of self-administration of cannabis by smoking appears to be related to both the properties of the drug and such non-pharmacological factors as, for instance, the appearance and size of the cigarette. Patterns of self-administration and its correlates have been studied within the last two years; additional research on the comparative reinforcement potential of cannabis is needed.

8.7.2 Psychic dependence

The Group agreed with the opinion stated in the report of a WHO Scientific Group on the Use of Cannabis that "many regular (almost daily) users of cannabis exhibit psychic dependence, as do some less frequent but relatively "heavy" users, whereas the great majority of people who use it a few times on an experimental basis, or casually on a few festive occasions a year, could not be said to exhibit psychic or any other dependence on cannabis".

The role of psychic dependence in the development of methods for determining dependence liability and dependence potential of drugs of the cannabis type has not yet been adequately studied. The Group concluded that although some reports are already available further research is needed to clarify the importance of psychic dependence.

8.7.3 Abstinence and physical dependence

The above-mentioned report of a WHO Scientific Group concluded: "... there is no evidence ... to suggest that the withdrawal of cannabis even from an extremely "heavy" user produces an abstinence syndrome that begins to approach in severity those produced by drugs of the alcohol, barbiturate, and morphine types." In view of the equivocal nature of

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the currently available evidence concerning abstinence and physical depend-
ence, that conclusion remains valid today. Evidence for an abstinence
syndrome comes from different sources. Miras and Deneau & Kaymakçalan
have reported the effects of abrupt withdrawal of hashish and THC in monkeys. Symptoms lasting
several days have been reported by hashish users and some phenomena
may persist for several weeks. Perhaps the most impressive experimental
evidence to date in man comes from Jones & Benowitz, who observed
insomnia, irritability, restlessness, sweating, rhinorrhea, decreased appe-
tite, increased salivation, and sudden weight loss by diuresis after cessation
of THC administration. The onset of these effects occurred after 6-8 h
and lasted up to 96 h.

The picture of abstinence and physical dependence is complicated by the
fact that in other studies with rats, chimpanzees and man no obvious withdrawal syndrome was observed. The finding that high-dose
level and constant blood drug level may be important in establishing the
syndrome (R. Jones, unpublished observations, 1974) is most pertinent; however, further experimentally sound, independent clinical studies are
needed to confirm the status of this syndrome in man. When detailed studies covering the entire range of doses have been carried out to determine
dose-response relationships, the relevance of these high-dose experiments to observations made on subjects with the typical pattern of low-dose use
should be evident.

8.7.4 Tolerance

In some species (fish, pigeons, mice and rats, dogs, and monkeys) pharmacological tolerance to a number of effects of THC has been estab-

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lished. The presence or absence of tolerance and its rate of development depends upon the species, the behaviour or function studied, and the schedule of administration and dosage.

In man, marked tolerance to the effects of cannabis appears to depend upon heavy, regular use. In many countries where individuals do not use cannabis heavily, tolerance is not commonly reported but in experimental studies involving prolonged administration in man some degree of tolerance to certain clinical effect has been noted. In a study in man designed to maximize the development of tolerance and dependence, Jones used high-dose (210 mg per day) around-the-clock administration. He reports tolerance to heart-rate effects and subjective effects (level of perceived intoxication and mood changes).

8.7.5 Analgesia

THC at a dose of 1 mg per kg of body weight induces analgesia in dogs. Tolerance to this effect, however, occurs within one week. Analgesic effects of cannabis in man are well documented in the medical literature. These effects of cannabis and THC may be mediated by blocking the biosynthesis of prostaglandin E2.

9. CORRELATION OF RESULTS OF PRECLINICAL AND CLINICAL ASSESSMENTS WITH PATTERNS OF CHRONIC DRUG-TAKING IN MAN

Most drugs acting on the central nervous system produce similar physiological and pharmacological qualitative effects in both animals and man. Quantitatively, there exist both similarities and disparities between the doses required in man and animals according to the class of drug and the effect being measured. Differences also exist between man and animals...

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in the onset and duration of action and degree of effect of most drugs. However, despite some differences, rank orders of drugs on the basis of pharmacological effects are often similar for man and animals.\textsuperscript{a, b, c}

There is general agreement between the data obtained from observations in animals and man, so that such data can serve as a predictive indicator of a drug's potential to be used compulsively without medical supervision. Any drug whose pharmacological profile in animals places it in a class of drugs that have established epidemiological histories of non-medical use should be suspect.

Apart from the pharmacological properties of a drug, the pharmaceutical formulation in which it is available may influence its self-administration by man. For example, sterile ampoules, aerosol preparations, and easily dissolved tablets have greater potential for non-medical use than insoluble drugs and drugs that have a slow onset of action. Such preferential use can be predicted from animal data. There exists a practical correlation between these kinds of pharmaceutical formulation and the prevalence of self-administration.

It is difficult to study in experimental animals the problem of multi-drug use, and particularly the effects of a single drug on the multi-drug user. Further, for various psychological and pharmacological reasons, the multi-drug user may experience effects that are unpredictable.

Data obtained in experiments on animals can often be used to predict toxic functional and morphological effects of drugs in man. However, care must be exercised in extrapolating behavioural characteristics from animals to man. Prediction of a drug's potential for non-medical use cannot be equated with prediction of its dependence liability. Psychological, cultural, psychosocial, environmental, and economic factors influence the incidence and prevalence of non-medical drug use.

Some drugs may be used by man to his detriment as a result of many variables relevant to human life situations; yet their potential for self-administration could not have been predicted by the laboratory experimenters using currently available procedures. A variety of external factors can be simulated in animal experiments. Nevertheless, a number of environmental factors not yet reproducible in the laboratory may be relevant. Comparisons between effects in animals and effects in man have been most extensive in the class of the analgesics with morphine agonist and anta-

\textsuperscript{a} Villareal, J. E. In: Kosteritz, H. W. et al., ed. \textit{Agonist and antagonist actions of narcotic analgesic drugs}, London, Macmillan, 1972, p. 73.


gonist actions. Analysis of the correspondence of findings in animals to the effects in man \(^a\) \(^b\) \(^c\) has shown a close overall parallelism, with a few outstanding exceptions.

10. SOME IMPORTANT AREAS OF RESEARCH

The Group considered the following areas of research as important in elucidating issues relevant to the understanding of drug dependence.

**Multivariate analysis**

Techniques of multivariate analysis may be valuable in future research on drug dependence although they have not been applied on a large scale to date.\(^a\) \(^b\) \(^c\) For instance, numerical taxonomy is a mathematical method of facilitating the empirical classification of drugs. The assignment of a newly synthesized drug to a class of dependence-producing drugs might be of value in predicting whether that drug has dependence potential. Statistical correlation techniques may also be of use in attempts at predicting dependence liability. The simple Pearson’s product moment correlation may be used for measuring the strength of a relationship between two phenomena. Its multivariate equivalents are methods of multiple correlation and canonical correlation analysis. With these techniques the relationship between a whole set of results of various tests and one other phenomenon can be ascertained.

Consider the following example. The response pattern of 20 drugs has been determined in 5 animal tests \((a, b, c, d, e)\) and presented in quantified scores \(X_a, X_b, X_c, X_d, X_e\), and in comparable scores in 5 human experiments (e.g., on psychomotor performance or subjective effects), \(f, g, h, i, j\). Assuming the existence of a reliable measure of the dependence liability of the drugs, obtained, for example, by the proportion of persons who have become dependent after exposure to the drugs, \((y)\), a prediction of the dependence liability of the new drug \((y^*\) can be made with a defined probability, with the help of a multiple regression equation, if we have data on its action in the tests \(a, b, c, d, e, f, g, h, i, j\). The problem is that

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we very rarely have reliable measures of the dependence liability of the reference drugs. Canonical correlation analysis can be used, and "y" can be represented by another set of data such as the number of people hospitalized on account of psychototoxicity, the number of persons arrested, etc.

**Brain biochemistry**

Since it is known that centrally acting drugs interfere with the neurotransmission of biogenic amines, studies using biochemical techniques in combination with behavioural techniques are contributing and will further contribute to a better understanding of the neurochemical basis for their possible reinforcing properties.

In animal experiments dependence-producing drugs (morphine, amphetamine, and ethanol) have been shown to increase catecholamine turn-over and a causal relationship seems to have been established between the stimulatory effects of these drugs in animals and their effect on central catecholamine mechanism. Such a relationship for the euphoriant and stimulant action of amphetamine and ethanol has also been postulated for man, the suggestion being that the reinforcing effects of these drugs may be mediated by central catecholamines. Furthermore, changes in the turn-over of central monoamines have been observed during the development of tolerance to and withdrawal from dependence-producing drugs. Recent evidence that morphine-like drugs and ethanol interact with brain cyclic nucleotides indicates a useful field for the further study of mechanisms of dependence.

**Specific bindings**

The discovery of opiate specific binding in brain homogenates may be relevant to the classification of different types of analgesics and to the

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testing of several hypotheses concerning the multiplicity of receptor systems involved in the onset and maintenance of dependence.

**Pharmacogenetics**

There is limited evidence that within one species, strains differ in their susceptibility to dependence on some drugs. Selected strains might provide models for studying biochemical and other correlates.

**Detection of drug users**

Radioimmunoassays and other refined analytical methods have been applied for the detection of drug users and the surveillance of their treatment. These methods should be developed and applied to comparing the dependence-inducing drugs with regard to their persistence in the organism, a factor that may be related to their ability to produce long-term biochemical lesions.

**Schedules of drug administration**

Drug self-administration research with subhuman primates has indicated that the behavioural components of drug dependence can be effectively studied by means of schedules of reinforcement to control sequences of drug-taking behaviour. Schedules of reinforcement specify the exact manner in which reinforcing and discriminative stimuli are presented in relation to the subject's behaviour. The discriminative control of behaviour by drug states acting in combination with environmental stimuli merits further consideration. A number of factors, including the pharmacological properties of the self-injected drug, the antecedent behaviour of the animal, temporal relations between these variables, and the history of drug self-administration, determine the capacity of the drug to function as a reinforcer. Drug self-administration behaviour in subhuman primates and man can be analysed and interpreted within the context of established conditioning methods.

**Electroencephalographic studies**

The development of stable quantitative measures of the EEG with digital computer analytical procedures has provided a flexible approach

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to the classification of psychoactive drugs in man.\textsuperscript{a} Dextroamphetamine, cannabis, diacetylmorphine, and lysergamide have been shown to have typical EEG profiles.\textsuperscript{b}

The EEGs from the cortex of rhesus monkeys have been used effectively for differentiating between various groups of depressant drugs—barbiturates, non-barbiturate sedative-hypnotics, and the benzodiazepines.\textsuperscript{c, d}

The resultant corticograms are subjected to power spectral analysis and the drugs are classified on the basis of changes in the characteristics of the spectral envelope and the stability of the electrical activity in the brain.

Correlation of these data with the dependence-producing characteristics of the drugs studied is high, giving rise to optimism that this technique has potential for future use in identifying drugs with dependence-producing properties and in assessing these properties at the physiological rather than the behavioural level.

\textbf{Individual differences}

Individual variation in reactivity to psychoactive drugs is well documented.\textsuperscript{\textendash f, i} The literature contains many studies on drug dependence that gave conflicting results (e.g., compare the results of Waskow et al.\textsuperscript{a} with those of Melges et al.\textsuperscript{b} on the acute effects of cannabis consumption). In many cases, these discrepancies arose from the fact that individual differences in relevant variables were not systematically taken into account during the design stage of the work. In a study on a large group of chronic cannabis-takers it was found that those who were illiterate and came from rural districts did not differ significantly from controls with respect to a number of objective psychological variables. However, in the same study, cannabis-takers from urban areas with high levels of literacy differed significantly from controls with respect to most of the test variables (M. I. Souif, unpublished data, 1974).

\textsuperscript{a} \textsc{finn, m.} \textit{Ann. Rev. Pharmacol.}, \textbf{9} : 241 (1969).
\textsuperscript{b} \textsc{finn, m.} \textit{Psychopharmac. Bull.}, \textbf{10}(2) : 27 (1974).
\textsuperscript{c} \textsc{jor, r. m. et al.} \textit{Neuropharmacol.}, \textbf{10} : 483 (1971).
\textsuperscript{d} \textsc{gehrmann, j. e. & killam, k. f.} in: \textsc{kagan, f. et al.}, ed. \textit{Hypnotics : methods of development and evaluation}, Flushing, NY, Spectrum, 1975.
\textsuperscript{e} \textsc{teasdale, j. d.} in: \textsc{everbeck, h. j.}, ed. \textit{Handbook of abnormal psychology}, London, Pitman, 2nd ed., 1973, p. 97.
\textsuperscript{f} \textsc{haertzen, c. a. & hill, h. e.} \textit{J. clin. Psychol.}, \textbf{15} : 434 (1959).
\textsuperscript{g} \textsc{von fleishberg, j. m. et al.} \textit{J. Amer. med. Ass.}, \textbf{157} : 1113 (1955).
\textsuperscript{h} \textsc{waskow, i. e. et al.} \textit{Arch. gen. Psychiatr.}, \textbf{22} : 97 (1970).
\textsuperscript{i} \textsc{melges, f. t. et al.} \textit{Science}, \textbf{168} : 1118 (1970).
Parameters of individual differences thought to be relevant to research on drug dependence may therefore be established. The existing literature on both drug dependence and personality structure can be a source of useful suggestions.

**Social and environmental factors**

Important advances have been made over the years in the use of laboratory animals for evaluating the dependence potential of drugs. For ethical reasons, studies of this nature have had limited objectives in man. Extrapolation of results obtained from animals in the laboratory setting to the human situation has often been unjustified because of the artificially simplified nature of the experimental settings in which the animal studies have been carried out compared with the complexity of human life situations. In most cases, the animals have been in solitary confinement and other controlled laboratory conditions. Future studies should aim at the deliberate changing of social and environmental factors so that they represent the relevant dimensions of the environment of the study subjects—man or animal. For example, animal experiments could be designed in such a way that the experimental subject is with its usual group and as close to the “natural habitat” as possible. The same applies to human volunteers, who have often been admitted to laboratories or hospital wards in living conditions (e.g., feeding, drinking, relative isolation from peer groups, noxious family situations) that are very atypical.

**II. INTERNATIONAL COLLABORATION AND EXCHANGE OF INFORMATION**

Efforts to establish international collaborative studies face considerable difficulties. Among these are:

(a) differences in nationally held concepts, terminology, societal attitudes, and legal conditions—i.e., the settings in which studies are carried out;

(b) the financial cost and difficulty of sponsoring and organizing meetings and exchanges of co-workers for planning and implementing studies;

(c) the need to develop standardized methods where they do not exist and to train collaborating researchers in their use;

(d) the difficulties in selecting carefully defined and comparable samples of subjects from different areas; and

(e) the different meaning of results obtained in different sociocultural areas.
Some hypotheses can be tested only in such cooperative international efforts. Research in the drug dependence field has shown that social and other environmental factors play an important role in initiating and perpetuating drug-taking; greater variation in these factors is ordinarily found between countries than within a single country. Hence, comparisons among various countries provide a particularly important source of information shedding light on non-pharmacological factors.

On the other hand, converging lines of evidence obtained in various laboratories employing different methods contribute more to the verification of certain hypotheses than such results obtained in only one country or with only one method. It is probable that methods will differ more if applied in different countries. ISGIDAR* has shown that this kind of collaborative approach contributes significantly to advances in knowledge about refining methods and evaluating the results of studies on the reinforcing properties of drugs. While some of the aims of the group could have been achieved without international cooperation, ISGIDAR has clearly demonstrated that international cooperation among already existing centres in different countries is not only feasible but can lead to an acceleration of scientific progress.

The level of international cooperation in research in individuals and populations needs to be raised. The Group considered that an important role of WHO is stimulation and coordination of the efforts of all workers who might contribute to the solution of problems related to drug dependence. The following objectives were recommended:

1. Fostering the dissemination of relevant information at local, national, and international levels.
2. Organizing epidemiological studies of conditions and events associated with problem-related drug use.
3. Fostering the development of methods of study applicable in different national and sociocultural settings.
4. Comparing the effectiveness of various preventive measures and treatment methods.
5. Comparing in different countries the rates of prescribing and adverse reactions of drugs thought to induce dependence.

* International Study Group Investigating Drugs as Reinforcers.
The International Pilot Study of Schizophrenia and the International Study of Affective Disorders have demonstrated that international effort under WHO’s auspices is feasible in spite of the inherent difficulties.

12. CONCLUSIONS AND RECOMMENDATIONS

The WHO Scientific Group on Evaluation of Addiction-producing Drugs that met in 1963 reviewed the methods of evaluating drug dependence and concluded that procedures then in use were not conclusive in respect of the prediction of physical or psychic dependence. Concerning the experimental study of psychic behaviour, the report stated that: "... experimental approach to the assessment of psychic dependence in both animals and man is just beginning, and no definitive statement regarding techniques or their predictive value can as yet be made."

Since that statement was made, methods for evaluating the dependence potential of narcotic and psychoactive drugs in both animals and man have been further developed and improved. A variety of new methods and approaches have been introduced. Of particular interest are methods using subacute and acute administration, in vitro preparations, and especially self-administration approaches to assess the reinforcing properties of drugs. The most important development has been the emergence of self-administration methods and their widespread application for assessing the reinforcing properties of drugs. In addition to providing important information on such properties of both agonists and antagonists of the morphine type, compounds of the barbiturate, alcohol, and volatile solvents type, and drugs with psychomotor stimulant properties, these powerful methods contribute to our understanding of the basic behavioural processes implicated in drug-taking behaviour in man.

Caution must be exercised, however, in the interpretation of data from self-administration studies, since various factors, including the direct behavioural effects of drugs, pharmacokinetics, bioavailability, and interaction of drugs can influence their outcome. To improve their predictive value further refinement of drug self-administration and other methods is needed, in order to facilitate the detailed quantitative evaluation of the degree of dependence resulting from the specific mode and schedule of administration of dependence-producing drugs in subhuman primates and other species.


To increase understanding of drug dependence, information from selfadministration studies in animals and man (both in the laboratory and in naturalistic settings) should be combined with data obtained from studies based on other methods, including a wide variety of techniques for ascertaining psychic changes (structured clinical observation, psychometric profiles, self- and otherwise administered check-lists, questionnaires, rating scales, projective tests, etc.) and physiological changes (autonomic, biochemical, electrical, etc.).

The most difficult and challenging conceptual problem in this field is how to relate the results of these various methods to each other in a meaningful way so as to draw comparisons and conclusions about the drug that go beyond simple extrapolation of data from one or two different methods. To date, common sense and intuition have been primarily used to draw conclusions from studies employing different methods. Whether formal systems will be found that satisfactorily interrelate the results of various methods remains to be seen. The difficulties in predicting the dependence liability of a specific drug result from conceptual, methodological, and empirical problems, including lack of operational definition of some concepts, insufficient quantification and specificity of behaviour or events to be measured, lack of criteria for validation of methods, and the lack of comparability of studies. This lack of comparability can be seen in studies that use the same instrument in quite different ways, different instruments in the analysis of highly similar behaviour or events, subjects with significant differences who are given the same drug, or different institutions or socio-cultural settings that influence the data obtained. While some of these differences reflect the complexity of the phenomena related to drug taking, scientists who do not take this variety of factors into consideration may commit serious errors of evaluation.

The Group recommended the following priorities for action by WHO:

1. Multidisciplinary research should be encouraged to increase our knowledge of the use of dependence-producing drugs.

2. Appropriate steps should be taken to facilitate the integration of results from preclinical, clinical, and epidemiological studies.

3. Existing methods should be standardized to increase comparability of techniques and results from different parts of the world.

4. Collaborative international research and training centres in selected areas of the world should be established to promote research, exchange information, and make critical comparisons to standardize methods to obtain valuable and valid data.
5. Methods suitable for transcultural comparison should be developed for use in the design and execution of epidemiological studies so that data obtained from them may serve as part of the criteria used for validating predictions of drug dependence potential derived from other methods.

Priorities that should be considered by international and national organizations and research institutions concerned with brain, behaviour, and drug interactions related to dependence include research on (1) basic pharmacological properties of analgesics with morphine agonist and antagonist properties and other psychoactive drugs, (2) the development of new biochemical and neurochemical methods to establish the mode of action of dependence-producing drugs, and (3) individual and social factors influencing the complex behaviour induced by drugs.