

This report contains the collective views of an International group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

WHO Expert Committee on Drug Dependence

Twenty-first Report

World Health Organization
Technical Report Series
618



World Health Organization Geneva 1978

ISBN 92 4 120618 7

© World Health Organization 1978

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. For rights of reproduction or translation of WHO publications, in part or *in toto*, application should be made to the Office of Publications, World Health Organization, Geneva, Switzerland. The World Health Organization welcomes such applications.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

PRINTED IN SWITZERLAND

CONTENTS

	Page
1. Introduction	7
2. General considerations	7
3. Animal studies on psychotropic and dependence-producing drugs	10
3.1 General pharmacology and toxicology	10
3.2 Physical dependence studies	13
3.3 Self-administration studies	15
3.4 Other procedures	19
4. Human pharmacology	21
4.1 General pharmacology	21
4.2 Physical dependence	21
4.3 Subjective effects	22
4.4 Behavioural techniques	23
4.5 Relevance of pharmacological and behavioural data to abuse liability	24
4.6 Decision-making	24
5. Assessment of the public health and social problems	25
5.1 Identification of social problems	25
5.2 Identification of public health problems	26
5.3 Sources of information	27
6. Assessment of therapeutic usefulness	30
6.1 Therapeutic efficacy and safety	31
6.2 Factors modifying the usefulness of a drug	32
6.3 Precautions required in developing countries	33
6.4 Drug utilization studies	34
6.5 Drug combinations	34
6.6 Collection of data	34
7. Decision-making	35
7.1 Drugs that are therapeutically useful but currently abused	35
7.2 New drugs considered for control	35
7.3 Scheduling anomalies	36
7.4 The decision-making process	36
8. Problems of chemically generic extensions to the list of scheduled substances	37
8.1 Salts	37
8.2 Esters and ethers	37
8.3 Isomers	37
8.4 Precursors	38
8.5 Generic descriptions of drugs	38
8.6 Tetrahydrocannabinols	39
9. Recommendations	39
Annex. Salts, esters, ethers, isomers, and precursors of psychotropic substances	41

WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Geneva, 26 September – 1 October 1977

Members *

- Dr E. A. Babayan, Head of the Department of Evaluation of New Drugs and Medical Equipment, and President of the Committee on Narcotic Drugs, Ministry of Health of the USSR, Moscow, USSR
- Dr B. S. Diop, Neuropsychiatry Clinic, University of Dakar, Dakar, Senegal
- Dr L. S. Harris, Professor and Chairman, Department of Pharmacology, Virginia Commonwealth University, Richmond, VA, USA (*Co-Rapporteur*)
- Dr J. Jacob, Head, Pharmacology and Toxicology Service, Pasteur Institute, Paris, France
- Dr P. Kielholz, Professor and Chairman, University Psychiatric Clinic, Basle, Switzerland
- Dr J. Razani, Project Director, Narcotics Addiction Treatment Project, Teheran, Iran (*Co-Rapporteur*)
- Dr C. R. Schuster, Professor and Director, Research Center Studying Drug Dependence and Abuse, University of Chicago, IL, USA (*Chairman*)
- Dr M. I. Soueif, Professor of Psychology, University of Cairo, Egypt (*Vice-Chairman*)
- Dr T. Yanagita, Director, Preclinical Research Laboratories, Central Institute for Experimental Animals, Kawasaki, Japan

Representatives of other organizations

United Nations

- Dr O. J. Braenden, Chief, United Nations Narcotics Laboratory, Division of Narcotic Drugs, United Nations, Geneva, Switzerland
- Mr N. Kandemir, Deputy Director, Division of Narcotic Drugs, United Nations, Geneva, Switzerland
- Dr M. Kilibarda, Chief, Drug Demand and Information, Division of Narcotic Drugs, United Nations, Geneva, Switzerland
- Mr E. Hytten, Chief, European Social Development Programme, Division of Social Affairs, United Nations, Geneva, Switzerland
- Dr G. M. Ling, Director, Division of Narcotic Drugs, United Nations, Geneva, Switzerland
- Mr J. J. Moore, Research Expert, United Nations Social Defence Research Institute, Rome, Italy
- Mr A. Noll, Legal Officer, Division of Narcotic Drugs, United Nations, Geneva, Switzerland

* *Unable to attend*: Dr N. N. Wig, Professor and Head of Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

International Narcotics Control Board

Dr S. Kaymakçalan, Vice-President of the INCB, Professor and Chairman,
Department of Pharmacology, University of Ankara, Turkey
Mr S. Stepczyński, Secretary, INCB, Geneva, Switzerland

International Council on Alcohol and Addictions

Dr P. H. Connell, Director, Drug Dependence Clinical Research and Treatment
Unit, The Maudsley Hospital, London, England
Dr K. Opitz, Professor, University Institute for Pharmacology and Toxicology,
Münster, Federal Republic of Germany

International Criminal Police Organization

Mr J. R. F. Morris, Drugs Subdivision of the Interpol General Secretariat,
Saint-Cloud, France

Secretariat

Dr A. Arif, Senior Medical Officer in Charge of Drug Dependence Projects,
Division of Mental Health, WHO, Geneva, Switzerland (*Co-Secretary*)
Dr H. Halbach, Honorary Professor of Pharmacology, University of Munich,
Federal Republic of Germany (*Consultant*)
Dr D. R. Jasinski, Director, National Institute on Drug Abuse, Addiction
Research Center, Lexington, KY, USA (*Consultant*)
Dr Inayat Khan, Senior Medical Officer, Division of Mental Health, WHO,
Geneva, Switzerland (*Co-Secretary*)
Dr W. H. McGlothlin, Professor in Residence, University of California, Los
Angeles, CA, USA (*Consultant*)
Dr J. Ording, National Board of Health and Welfare, Stockholm, Sweden
(*Consultant*)
Mr G. F. Phillips, Superintendent, Health Services Division, Laboratory of the
Government Chemist, London, England (*Consultant*)
Dr N. Sartorius, Director, Division of Mental Health, WHO, Geneva,
Switzerland
Dr J. Venulet, Medical Department, Ciba-Geigy SA, Basle, Switzerland
(*Consultant*)

Vertical line of text on the left margin, possibly a page number or header.

Main body of text, appearing as a large, faint, and mostly illegible block of characters.

Vertical line of text on the right margin, possibly a page number or footer.

WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Twenty-first Report

1. INTRODUCTION

The WHO Expert Committee on Drug Dependence met in Geneva from 26 September to 1 October 1977.

Dr Ch'en Wen-chieh, Assistant Director-General of the World Health Organization, opening the meeting on behalf of the Director-General, said that the Expert Committee faced a new challenge. It was being asked to make realistic recommendations to the United Nations Commission on Narcotic Drugs regarding substances to be controlled under the Convention on Psychotropic Substances, 1971. Substances falling within the purview of the Convention were of a varied nature and were often used in medical practice. In contrast to the established narcotic control treaties, the 1971 Convention required that the therapeutic value of psychotropic substances be balanced against the risk to public health and social well-being arising from their use. He invited the Committee to review all possible methods of classifying psychotropic substances under the Convention. Drug evaluation was an expensive and cumbersome task but it was nevertheless indispensable for determining, as early as possible, the benefit/risk ratio of therapeutic use and abuse respectively of psychotropic substances.

Dr N. Sartorius, Director of the Division of Mental Health, asked the Committee to recommend operational mechanisms that would improve and hasten the collection of the data necessary for decision-making in the light of the different needs of Member States and of the WHO policy of technical cooperation with and between countries.

2. GENERAL CONSIDERATIONS

According to its preamble, the Convention is intended to prevent and combat the abuse of certain psychotropic substances and the illicit traffic to which it gives rise through rigorous measures to restrict the use of these substances to legitimate purposes while at the same time recognizing that their use for medical and scientific purposes is indispensable and that their availability for such purposes should not be unduly restricted.

In the text of the Convention, the objective of protecting public health is clearly stated in Article 2 on the scope of control. This article stipulates that one of the criteria calling for control is the finding by WHO that "there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control".

To the extent that social problems are inseparably linked to those of public health and in view of the definition of health in the WHO Constitution as "a state of complete physical, mental and social well-being", WHO's functions under the Convention include an appraisal of the overall consequences of drug-taking.

In an attempt to delineate the public health and social problems arising out of drug abuse¹ the Expert Committee, at its sixteenth meeting, stated :

If such a drug abuse or dependence is likely to be, or is known to be, only sporadic or infrequent in the population, if there is little danger of its spread to others, and if its adverse effects are likely to be, or are known to be, limited to the individual user, there is no public health problem . . . On the other hand, if the drug dependence is associated with behavioural or other responses that adversely affect the user's interpersonal relations or cause adverse physical, social, or economic consequences to others as well as to himself, and if the problem is actually widespread in the population or has a significant potential for becoming widespread, then a public health problem does exist.²

The objective of the Convention is not to control *any* substance detrimental to public health and social well-being but only psychotropic substances. As specified in Article 2 of the Convention, a psychotropic substance eligible for control must be capable of producing :

- (1) a state of dependence and
- (2) central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood.

¹ In view of the fact that the use of psychotropic drugs, whether for medically authorized or unauthorized use, has resulted in a wide variety of social phenomena given various labels with overlapping connotations, the term "drug abuse" will be applied here in the sense conveyed by the Convention. Drug abuse would therefore mean the use of psychotropic substances in a way that would "constitute a public health and social problem". Regarding other relevant terminology, the Committee was of the opinion that adherence to the definition or usage of such terminology as given in the Convention should be the rule.

² WHO Technical Report Series, No. 407, 1969, pp. 6-7.

Evidence of the capacity of the substance to produce dependence and psychic or psychomotor effects is, however, not required if the substance can produce similar abuse and similar ill effects as a substance in Schedule I, II, III or IV of the Convention.

These similarities are considered to be indicative of the substance having the capacity to produce the said psychic or psychomotor effects. The requirement of proof of similarity with what is already controlled was carried over from the Single Convention and the treaties preceding it, in which "similarity" was the principal criterion for control. A finding regarding similarity will normally presuppose a detailed finding regarding dependence and psychic or psychomotor effects and provide for the coverage of agents that might not produce dependence, such as several substances included in Schedule I.

As a result of the wording quoted above from Article 2, the scope of substances falling under the terms of the Convention can be expected to widen. The rather broad scope of effects embraced by "central nervous system stimulation or depression" and by the criterion of similarity—not equality—provides room for new types of substances. This distinguishes the Convention from earlier treaties, which were restricted to substances of the morphine, cocaine, and cannabis type.

In addition to the mandatory control of certain substances, other measures to be taken by the parties to the Convention concern :

- the prescribing of controlled substances in accordance with sound medical practice (Article 9.2) ;
- the labelling of controlled substances in conformity with relevant WHO recommendations (Article 10.1) ;
- the identification and treatment of the drug user, including aftercare, social reintegration, and attendant programmes of education and training (Article 20).

Such activities fall clearly within the constitutional objectives of WHO, and from its inception the Organization's programme in this area has included both alcohol and the drugs controlled by international conventions.

The present report deals exclusively with the analysis of the specific functions conferred on WHO by Article 2 of the Convention.

The Committee was advised by the Director of the United Nations Division of Narcotic Drugs on the functions of the United Nations Commission on Narcotic Drugs and their relation to the specific functions entrusted to WHO by the Convention on Psychotropic Substances.

The Committee was advised, in particular, that the assessments made by WHO in any recommendation to the Commission with regard to drugs in the schedules annexed to the Convention "shall be determinative as to medical and scientific matters". However, the Commission, when making its final decision, would also bear in mind "economic, social, legal, administrative and other factors it may consider relevant".

The Committee was informed that the International Narcotics Control Board had implemented progressively the relevant provisions of the Convention. The Committee was pleased to note that the majority of countries had responded favourably to the Board's request by sending the relevant statistics to be published by the Board in the near future. These statistics would thus become available for the assessments that WHO is responsible for carrying out under the terms of the Convention.

3. ANIMAL STUDIES ON PSYCHOTROPIC AND DEPENDENCE-PRODUCING DRUGS

3.1 General pharmacology and toxicology

To be relevant to the problem of abuse the study of a psychotropic substance in animals must be designed to demonstrate a specific profile of effects, including the overall side-effects and toxic effects. The specific effects that are to be searched for correspond, at least in part, to the drug's potential psychic toxicity and potential therapeutic properties; the balance between these two is one of the major bases for the evaluation of the drug. As some relevant effects of known psychotropic drugs are not present or not pronounced in all laboratory animals, it is essential to use the appropriate animal species and strain for studying these effects. Several routes of administration may be used.

3.1.1 Single-dose studies

Numerous techniques are available in single-dose studies, ranging from the simple observation of locomotor disturbances and abnormal movements and postures to examinations of specific sensory or motor systems. Changes in sexual function, appetite, vigilance, arousal, and the performance of learnt activities should be observed and physiological effects should be studied by means of electrocardiography, electroencephalography, and the measurement of heart rate, blood pressure, temperature, respiration, and pupillary changes. Further information

might be obtained from biochemical investigations—in particular, the determination of the levels and turnover of biogenic amines and other brain components and the affinity of some psychotropic drug, such as lysergide, for specific receptors.

The profile determined in the acute studies might permit the drug in question to be assigned to an already well characterized class of drugs. The psychotropic drugs scheduled in the 1971 Convention belong to the following classes :

- (1) hallucinogens of the lysergide, STP, or tetrahydrocannabinol type,
- (2) central nervous system (CNS) stimulants of the amphetamine type, and
- (3) CNS depressants of the barbiturate and other types.¹

Phencyclidine, which is also scheduled, displays a mixed profile. Of course, numerous types of psychoactive drugs are not represented in the four schedules of the Convention, e.g., hallucinogens of the belladonna alkaloid type, stimulants of the MAO-inhibitor type, and depressants of the benzodiazepine type. Furthermore, in the future there will be drugs with differently combined or absolutely new profiles.

The profiles include not only psychotoxic activity but also therapeutically useful activity such as anorexigenic, sleep-inducing, or tranquilizing effects.

The study of general side-effects with conventional methods is also necessary because abuse-liability is affected by their presence or absence. Abuse is less likely to occur, for instance, when the drug in question is irritating or produces diarrhoea.

3.1.2 *Multiple-dose studies*

Many important characteristics of drugs will be disclosed only in studies with repeated administrations. Some of these studies are conventional, such as the short- and long-term toxicity tests that disclose perturbations in food intake, growth, blood cells, clinical chemistry, histology, etc. Other studies are less conventional, referring more specifically to behavioural disturbances that appear only after repeated

¹ Specific profiles of these three classes of drugs are given in an unpublished WHO document No. OMH/76.6. Copies of this document are available on application to the Division of Mental Health, World Health Organization, 1211 Geneva 27, Switzerland.

administration and are subject to factors such as tolerance or sensitization. For instance, it has been shown that repeated administration of amphetamines can lead to profound behavioural alterations in animals accompanied by irreversible neurochemical and neurophysiological manifestations.

Similarly, conventional teratological and fertility studies are prerequisites for a thorough evaluation of any drug to be used in humans, and particular emphasis should be placed on possible disturbances in the behaviour of the offspring.

Although "rebound" phenomena (e.g., depression following stimulation or vice versa) might sometimes be observed after a single administration, they are much more likely to occur after repeated doses.

3.1.3 *Antagonism, cross-tolerance, and interactions*

The use of antagonists is often very helpful in determining the profile of a compound. However, the interpretation must be made with caution because there is no antagonist as yet that can be considered specific to one single class of substances scheduled in the Convention (i.e., that will antagonize a given effect only of these substances and not of any other drug). There is also no antagonist that will suppress all the effects of a single psychotropic substance.

When a class of psychotropic drugs displays the phenomenon of tolerance, evidence of cross-tolerance with a new substance under study may be considered one of the most valid criteria for the existence of a close resemblance between the new product and the prototype. It may be difficult, however, to establish the specificity of a particular instance of cross-tolerance. Nevertheless, the use of antagonism and cross-tolerance may be helpful in characterizing mechanisms of action.

Besides drug antagonism and cross-tolerance, other interactions might be worth studying for both scientific and practical reasons. These include the interactions between psychotropic drugs and ethanol, between barbiturates and amphetamines, and between reserpine and amphetamines.

3.1.4 *Pharmacokinetics*

The determination of the pharmacokinetics of a psychotropic substance given by one or several routes is essential for the design of experiments involving repeated administrations and for predicting the dependence potential. Naturally, the time course of absorption, distribution, and excretion depends not only on the chemical constitution of a given drug but also on its physical characteristics (solubility, polarity, etc.)

and the kind of formulation. Drugs that remain in the body for long periods of time might present special hazards. The drugs most likely to produce dependence are those whose effects have a rapid onset. The choice of the appropriate animal species for dependence studies on particular drugs can be based on such factors as pharmacokinetic and pharmacodynamic similarity to man, susceptibility to the substance, and availability of valid methods. However, when these factors are not well known the use of a variety of animal species is of great importance.

A report by a WHO scientific group on the bioavailability of drugs ¹ provides further information on this subject.

3.1.5 *Environmental factors*

The effects of psychotropic drugs may be influenced by environmental and even social factors. For instance, temperature, temporal rhythm, and the size and nature of the cage have been shown to modify the intensity and duration of various stimulatory or depressant phenomena. The effects of psychotropic drugs on learnt behaviour is, to a great extent, determined by the reward contingencies maintaining the behaviour. Typically, crowding increases the toxicity of amphetamine-like drugs in suitable strains of mice. The administration of a psychotropic drug to one member of a monkey colony may profoundly modify the behaviour of the other animals.

3.2 **Physical dependence studies**

On the basis of many years of study with the opiates, well defined methods have been developed for the assessment of physical dependence in animals. In general the drug under investigation must satisfy two requirements: first, it must have the ability to substitute for a known dependence-producing agent in animals physically dependent on that agent; secondly, it must be capable of inducing primary dependence when administered at the appropriate doses and time intervals for an appropriate period of time. Methods utilizing these principles have been developed for drugs of the sedative-hypnotic class, and these will be discussed in more detail below. A recent symposium ² has summed

¹ WHO Technical Report Series, No. 536, 1974.

² THOMPSON, T. & UNNA, K. R., ed. *Predicting the abuse dependence of stimulant and depressant drugs*. Baltimore, University Park Press, 1977.

up much of the present state of the art. Physical dependence has been definitely established only for central nervous system depressants. The question of physical dependence on drugs of the amphetamine type and on some hallucinogenic substances has still not been completely resolved. The relationship of physical dependence to drug-seeking behaviour has been established for only a few drugs.

3.2.1 *Direct induction studies*

The production of primary dependence on sedative-hypnotic drugs depends on the proper choice of dose, dosing interval, duration of treatment, and route of administration. On termination of drug treatment, withdrawal signs are seen the severity of which depends on the degree of physical dependence. Withdrawal signs for the sedative-hypnotics are characterized by hyperirritability, tremor, "delirium", and convulsions. A variety of rating scales have been used in attempts to quantitate the degree and severity of the dependence. The method of Jones and co-workers¹ is probably the most sophisticated and best validated system. On the other hand, the monkey may offer some advantage in the clarity of withdrawal signs.² Extensive work in this regard has also been carried out in the cat.³

Rodents have not proved to be as useful, although they have the advantage of lower cost. Mention should be made of some newer rodent techniques which, although promising, have not yet been validated. These include schedule-induced polydipsia⁴ and continuous intraperitoneal infusion.^{5, 6}

3.2.2 *Substitution studies*

For several decades attempts have been made to develop methods for determining whether new drugs would substitute for barbiturates in animals. The first practical method was probably that of Deneau &

¹ JONES, B. E. ET AL. *Psychopharmacologia*, **47** : 7 (1976).

² YANAGITA, T. *Journal of pharmacology and experimental therapeutics*, **172** : 163 (1970).

³ OKIMOTO, M. ET AL. *Journal of pharmacology and experimental therapeutics*, **192** : 555 (1975).

⁴ FALK, J. L. Personal communication.

⁵ TEIGER, D. G. *Journal of pharmacology and experimental therapeutics*, **190** : 408 (1974).

⁶ PATRICK, G. A. ET AL. *Proceedings of the Committee on Problems of Drug Dependence*. Washington, DC, National Research Council, National Academy of Sciences, 1976.

Weiss,¹ which involved dogs maintained on barbital sodium. Signs and symptoms of withdrawal were semiquantitated, and the ability of the test drug to substitute for barbital was determined. Similar methods have been developed for the monkey,² and recently quantitative procedures have been developed for the dog.³ Procedures using rodents have not been as well validated, although mention should be made of the methods of Goldstein.⁴

3.3 Self-administration studies

3.3.1 Reinforcing property of drugs

A reinforcing effect on drug-seeking and drug-taking behaviour is an essential property of drugs common to all types of psychotropic substances that produce and/or perpetuate the repeated use of drugs in man. Physical dependence may be regarded as of secondary importance because it does not necessarily develop with all types of dependence-producing psychotropic substances. Laboratory methods of assessing the reinforcing effect of drugs in animals have been developed over the past 15 years and are now being used for the prediction of the dependence potential in man.⁵

In these tests conditions are arranged so that a selected behavioural response is followed by the administration of the drug. If the response increases in frequency, the reinforcing effect is said to be positive and the behaviour can be called drug-seeking and/or drug-taking behaviour.

Self-administration techniques have been developed using rats,⁶ cats,⁷ dogs,⁸ and monkeys.^{9, 10} In most cases the pressing of a lever by

¹ DENEAU, G. A. & WEISS, S. *Pharmakopsychiatrie, neuro-psychopharmakologie*, **1** : 270 (1968).

² YANAGITA, T. *Journal of pharmacology and experimental therapeutics*, **185** : 307 (1973).

³ JONES, B. E. ET AL. *Psychopharmacologia*, **47** : 7 (1976).

⁴ GOLDSTEIN, D. B. *Journal of pharmacology and experimental therapeutics*, **183** : 14 (1972).

⁵ JOHANSON, C. E. & SCHUSTER, C. R. In : Thompson, T. & Unna, K. R., ed. *Predicting the abuse dependence of stimulant and depressant drugs*. Baltimore, University Park Press, 1977.

⁶ WEEKS, J. R. *Science*, **138** : 143 (1962).

⁷ BALSTER, R. L. ET AL. *Psychopharmacologia*, **46** : 229 (1976).

⁸ JONES, B. E. & PRADA, J. *Psychopharmacologia*, **30** : 1 (1973).

⁹ YANAGITA, T. ET AL. *Excerpta medica International Congress Series*, **87** : 453 (1965).

¹⁰ THOMPSON, T. & SCHUSTER, C. R. *Psychopharmacologia*, **5** : 87 (1964).

the animal activates an infusion pump, and a preset amount of drug solution is delivered to the animal through a permanently implanted catheter. The most widely used route of self-administration is the intravenous route, but other routes such as intragastric¹ and intranasal² are also in use for water-insoluble and inhalant forms of drugs.

The use of these techniques has shown that substances abused by man—such as opiates, some synthetic analgesics, cocaine, sedative-hypnotics, alcohol, stimulants, nicotine, and organic solvents—have a reinforcing effect in animals.^{2, 3, 4} No animal studies have demonstrated reinforcing effects with lysergide,⁵ and problems exist for Δ^9 -tetrahydrocannabinol⁶ and methaqualone.⁷

Thus, within the above limitation, the assessment of the reinforcing effect in laboratory animals is believed to be a useful approach for predicting the dependence potential of psychotropic substances in man.

3.3.2 Cross self-administration—"substitution"

Animals are trained to self-administer a prototypic drug intravenously at a dose previously determined to be effective in producing lever-pressing at a significantly higher rate than that for the vehicle. Typically, daily experimental sessions last for several hours, during which the drug is delivered once for every fixed number of responses (e.g., 1, 5, or 10). After establishment of a stable rate and pattern of drug-reinforced responding, a test drug may be substituted for the standard drug. The rate and pattern of response maintained by the test drug are compared with the rate and pattern observed with the standard drug and the vehicle. If the response rate for the test drug is higher than that for the vehicle, the test drug is considered to have a positive reinforcing effect. Tests must be made of a broad range of unit doses (i.e., the dose contained in each infusion) in order to determine whether a drug has positive reinforcing properties.

¹ YANAGITA, T. & TAKAHASHI, S. *Journal of pharmacology and experimental therapeutics*, **185**: 307 (1973).

² YANAGITA, T. *Japanese journal of clinical pharmacology*, **1**: 13 (1973).

³ THOMPSON, T. & UNNA, K. R., ed. *Predicting the abuse dependence of stimulant and depressant drugs*. Baltimore, University Park Press, 1977.

⁴ DENEAU, G. A. & INOKI, R. *Annals of the New York Academy of Sciences*, **142**: 277 (1967).

⁵ YANAGITA, T. *Bulletin on narcotics*, **25** (4): 57 (1973).

⁶ KAYMAKÇALAN, S. *Bulletin on narcotics*, **25** (4): 39 (1973).

⁷ YANAGITA, T. Personal communication.

3.3.3 *Continuous self-administration*

In this procedure animals are allowed to self-administer drugs, intravenously or by some other route, without dose or time limitation. The experiment is usually started with self-administration of the vehicle for 1–2 weeks to observe the baseline response rate for each animal. The test drug is then substituted. The initial unit dose used is based on results obtained in preliminary tests or in the above-mentioned cross self-administration experiment.

If a significant increase in response rate is generated by the test drug, the experiment is continued for several weeks and the daily dose levels, the drug-taking patterns, and the overt physical and behavioural manifestations of the effects of the drug are observed.¹ If no increase in response rate is seen with the test drug, shifts of unit dose and/or forced programmed administration of the drug for a certain period (e.g., 2 weeks) should be attempted to determine whether the animal will then initiate and maintain self-administration. Withdrawal signs and changes of the response rate may be observed by depriving the animal of the drug for 24–48 hours or longer. The use of experimentally naive animals is regarded as an essential part of this experiment for demonstration of the primary reinforcing property of drugs. This procedure permits assessment not only of the reinforcing effect but also of some other properties of drugs, such as behavioural effects and toxicity at the self-regulated dose regimen.

3.3.4 *Procedures designed to assess reinforcing efficacy*

The mere fact that a drug has a reinforcing effect is not sufficient evidence to predict its abuse liability in man. For that purpose the reinforcing efficacy of the drug must be determined. Several attempts have been made to establish procedures to quantitate the reinforcing effects.

Progressive-ratio procedure. Responding is first established with a standard drug, then the test drug is substituted and the number of responses required for drug reinforcement is systematically increased. The response requirement that the animal fails to meet is called the breaking-point. Results obtained from this procedure have a good predictive value for certain classes of psychotropic drugs.^{2, 3}

¹ JOHANSON, C. E. ET AL. *Pharmacology, biochemistry and behaviour*, **4**: 45 (1976).

² GRIFFITHS, J. D. ET AL. *Psychopharmacologia*, **43**: 81 (1975).

³ YANAGITA, T. *Bulletin on narcotics*, **25** (4): 57 (1973).

Choice procedure. This procedure permits the experimental animal to choose between two drug solutions. Animals are trained to choose between a prototypic drug and saline. After initial training, the test drug may be substituted at various doses. Two measures can be derived—the percentage choice of one solution compared with the other and rate of response maintained by the two solutions. This procedure appears to have considerable promise in the rank-ordering of drugs for reinforcement efficacy.^{1, 2}

Second-order schedule procedure. Animals are trained to respond on a simple reinforcement schedule in which a brief stimulus (e.g., a light or tone) is presented concurrently with a drug. It is found that the stimulus is able to sustain behaviour even when only intermittently coupled with drug delivery. This procedure has not been applied to the prediction of relative abuse liability of drugs although it has the advantage that extended samples of behaviour leading to drug reinforcement can be maintained with little or no confounding effect of previous drug administration (e.g., earlier the same day).³

3.3.5 Importance of other observations during self-administration studies

The possible information obtainable in continuous self-administration experiments concerns the animals' drug-taking patterns, the self-regulated dose levels that are specific to each drug, and the ability of the drug to produce physical and behavioural effects and toxicities at the self-regulated dose regimen. The development of tolerance and physical dependence to a drug can also be observed in continuous self-administration procedures.^{4, 5}

Although physical dependence is of only secondary importance for prediction of the abuse liability of psychotropic substances, its development is relevant to the prediction of abuse liability when some aversive withdrawal signs (due to physical dependence) intensify drug-seeking behaviour. This has been shown by comparing the reinforcing efficacy in physically dependent and non-dependent monkeys.^{6, 7}

¹ JOHANSON, C. E. & SCHUSTER, C. R. *Journal of pharmacology and experimental therapeutics*, **193** : 676 (1975).

² BALSTER, R. L. & SCHUSTER, C. R. *Cocaine and other stimulants*, New York, Plenum, 1977, p. 571.

³ GOLDBERG, S. R. ET AL. *Federation proceedings*, **34** : 1771 (1975).

⁴ DENEAU, G. A. ET AL. *Psychopharmacologia*, **16** : 30 (1969).

⁵ JOHANSON, C. E. ET AL. *Pharmacology, biochemistry and behavior*, **4** : 45 (1976).

⁶ YANAGITA, T. *Pharmacological reviews*, **27** (4) : 503 (1976).

⁷ SCHUSTER, C. R. *Federation proceedings*, **29** : 2 (1970).

3.4 Other procedures

3.4.1 Discriminative stimulus techniques

The dependence potential of psychotropic drugs is largely related to their subjective effects, which are qualitative. Drug discrimination studies are based on the hypothesis that the property of psychoactive drugs that enables them to function as discriminative stimuli in animals is analogous to the property responsible for producing subjective effects in man. For the evaluation of the discriminative stimulus properties of drugs, rats or monkeys are trained to make one response following the administration of a prototypic drug in order to obtain a reinforcement (presentation of food or water or termination of shock) and to make a different response following the administration of the drug vehicle. A test drug is judged to produce discriminative stimuli similar to those produced by the training drug if the animals emit the drug-appropriate response following administration of appropriate doses of the test compound.¹ The procedure has been validated for narcotic analgesics as well as analgesics with mixed agonist and narcotic antagonist properties.²⁻⁷

Discrimination procedures for evaluating psychomotor stimulants have also been developed.^{8,9} They permit differentiation between dexamphetamine and levamfetamine as well as between amphetamine-like and other stimulants.

These procedures may be of particular importance when considering hallucinogenic drugs that are not self-administered by animals. Unfor-

¹ SCHUSTER, C. R. & BALSTER, R. L. *Advances in behavioural pharmacology*, 1 : 85 (1977).

² SHANNON, H. E. & HOLTZMAN, S. G. *Journal of pharmacology and experimental therapeutics*, 198 : 54 (1976).

³ KUHN, D. M. ET AL. *Journal of pharmacology and experimental therapeutics*, 196 : 121 (1976).

⁴ COLPAERT, F. C. ET AL. *Journal of pharmacology and experimental therapeutics*, 197 : 180 (1976).

⁵ HOLTZMAN, S. G. ET AL. Discriminative properties of narcotic antagonists. In : Lal, H., ed. *Discriminative stimulus properties of drugs*. New York, Plenum Press, 1977, p. 47.

⁶ COLPAERT, F. C. ET AL. *Life sciences*, 16 : 705 (1975).

⁷ HIRSCHHORN, I. D. & ROSECRANS, J. A. *Psychopharmacologia*, 47 : 65 (1975).

⁸ SILVERMAN, P. B. & HO, B. T. Characterization of discriminative response control by psychomotor stimulants. In : Lal, H., ed. *Discriminative stimulus properties of drugs*. New York, Plenum Press, 1977, p. 107.

⁹ SCHECHTER, M. D. & ROSECRANS, J. A. *European journal of pharmacology*, 21 : 212 (1972).

tunately, the evaluation of discriminative properties is not as complete for the hallucinogenic drugs as it is for the opiate and stimulant classes of drugs.¹⁻³

3.4.2 *Techniques for evaluating lysergide-like hallucinogens*

No positive reinforcing properties have been demonstrated for lysergide-like hallucinogens, but these drugs can nevertheless be identified through the analysis of pharmacological syndromes. For instance, these agents produce head twitching in mice, bizarre behaviour in several animal species, and hyperthermia in rabbits.⁴ Furthermore, in monkeys they act as negative reinforcers. The "chronic spinal dog" has also proved to be of value for the study of lysergide-like hallucinogens.⁵ As in man, lysergide produces in the "chronic spinal dog" pupillary dilation, tachycardia, increased respiratory rate, increased body temperature, facilitation of the hind limb flexor reflex, and evocation of the stepping reflex. When lysergide is administered repeatedly, tolerance develops to some of these effects, and cross-tolerance has been shown to other lysergide-like hallucinogens. Conversely other lysergide-like hallucinogens can induce tolerance as well as cross-tolerance to lysergide. Serotonin and tryptamine antagonists selectively antagonize certain actions of lysergide-like agents.⁶ Thus serotonin and tryptamine antagonism may be of value in identifying lysergide-like activity. By means of these procedures, the actions of lysergide and amphetamine can be separated.⁷ Validation of some of these procedures for hallucinogens has been made by testing mescaline, psilocin, and STP. These psychotomimetic drugs produce pharmacological profiles predominantly similar to those of lysergide. In addition, several other substituted amphetamine derivatives have been evaluated.^{8,9} The

¹ SCHECHTER, M. D. & ROSECRANS, J. A. *Psychopharmacologia*, **26** : 313 (1972).

² WINTER, J. C. *Federation proceedings*, **33** : 1825 (1974).

³ KUHN, D. M. ET AL. Discriminative stimulus properties of hallucinogens : behavioural assay of drug action. In : Lal, H., ed. *Discriminative stimulus properties of drugs*. New York, Plenum Press, 1977, p. 137.

⁴ JACOB, J. *Proceedings of the European Society for the Study of Drug Toxicity*, **8** : 59 (1967).

⁵ MARTIN, W. R. ET AL. *Drug and alcohol dependence*, in press.

⁶ JACOB, J. & GIRAULT, J. M. Serotonin. In : Lomax, P. & Schönbaum, E., ed. *Body temperature : regulation, drug effects and therapeutic indication*. New York, Dekker, in press.

⁷ VAUPEL, D. B. ET AL. *Pharmacologist*, **18** : 128 (1976).

⁸ VAUPEL, D. B. ET AL. *Drug and alcohol dependence*, **2** : 45 (1977).

⁹ NOZAKI, M. ET AL. *European journal of pharmacology*, in press.

problem of classifying these compounds is complex since some have mixed lysergide- and amphetamine-like effects, some have predominantly amphetamine-like effects, and some have effects that resemble neither those of lysergide nor those of dexamphetamine. Despite these problems, the evaluation techniques (including the use of antagonists) show promise of being able to differentiate the various hallucinogenic substances.

4. HUMAN PHARMACOLOGY

4.1 General pharmacology

Prior to any specific evaluation, a careful study to determine the possible range of drug doses—from minimally effective doses to those producing undesirable side-effects—must be carried out in man. Such a study should include complete monitoring of both physiological characteristics (e.g., blood pressure readings, EGG, neurological examination) and behavioural characteristics (e.g., overt signs and symptoms, assessment according to behavioural rating scales). The study must include clinical chemistry and haematology examinations and urinalysis. When possible, both single-dose and multiple-dose studies should be carried out, and both a placebo and a positively acting substance should be included. In the ideal situation, pharmacokinetic data (e.g., half life) may also be obtained.

Information from such studies is invaluable in planning the more complex abuse liability studies described below. In addition, real and potential drug toxicity might be discovered in such studies.

As with all human studies, such experiments should be subject to peer review and the customary constraints and safeguards, based both on common sense and on ethical considerations. Initiation and continuation of subject participation in a study should be voluntary. All subjects should be informed of the purpose of the study and the associated risks and that they are free to withdraw from the study at any time.

4.2 Physical dependence

Long-term administration studies show that certain sedative-hypnotics in large doses produce physical dependence with abstinence syndromes characterized by convulsions and toxic psychosis. The morbidity and possible mortality associated with drug withdrawal preclude the use of this method for the testing of new drugs ; however,

there is a possibility that some manifestations of withdrawal could be detected after the experimental long-term administration of therapeutic doses.

It was demonstrated many years ago that secobarbital could prevent the toxic psychosis and convulsions associated with the pentobarbital withdrawal syndrome. These results demonstrate that substitution studies with sedative hypnotics can be conducted under experimental conditions. Again the ethical issues associated with high-dose dependence on sedative-hypnotics preclude the use of this method.

In general, the amphetamine-like stimulants and hallucinogens do not produce a significant degree of physical dependence. There is, however, evidence that abrupt withdrawal after long-term administration of a high dose of amphetamine¹ and Δ^9 -tetrahydrocannabinol² leads to the production of withdrawal signs and symptoms.

4.3 Subjective effects

In doses that may be used therapeutically, dexamphetamine sulfate produces in nontolerant drug abusers a characteristic set of alterations in mood, feeling states, perception, physiological characteristics, and behaviour. One evaluated effect is "euphoria" or feelings of elation, well-being and contentment that are considered by many to be indicative of the ability of dexamphetamine to induce drug-seeking behaviour. A series of experimental studies indicate that a number of other agents produce this characteristic profile of subjective behavioural and physiological effects—e.g., methamphetamine, phenmetrazine, methylphenidate, ephedrine, diethylpropion and phentermine. On the other hand, fenfluramine and chlorphentermine are clearly distinguishable from dexamphetamine. This methodology allows the early identification of agents with amphetamine-like activity.³

In near therapeutic doses, pentobarbital also produces a characteristic profile of alterations in mood, perception, feeling states and behaviour in nontolerant drug abusers, as well as a type of euphoria. In addition, pentobarbital facilitates postrotatory nystagmus, a physiological effect useful for bioassay of sedative hypnotics. Limited exper-

¹ JAFFE, J. H. In: Goodman, L. S. & Gilman, A., ed. *The pharmacological basis of therapeutics*. New York, Macmillan, 1975.

² JONES, R. T. & BENOWITZ, N. In: Braude, M. C. & Szara, S., ed. *Pharmacology of marihuana*. New York, Raven Press, 1976, vol. 2.

³ MARTIN, W. R. ET AL. *Clinical pharmacology and experimental therapeutics*, 12: 245 (1971).

imental studies indicate that other agents can produce these pentobarbital-like effects (secobarbital, phenobarbital, and methaqualone) and suggest that this methodology will allow the early identification of agents with pentobarbital-like activity.¹

Among the hallucinogens, lysergide produces a characteristic syndrome of subjective and physiological effects, to which tolerance develops. Other agents produce a similar syndrome of lysergide-like subjective and physiological effects and show cross-tolerance in lysergide-tolerant individuals. These agents may also produce a type of euphoria. Other hallucinogens probably produce other distinct syndromes in man. However, there are no experimental studies to demonstrate the utility of the method in classifying these agents for abuse potential. With perhaps the exception of nonpsychotogenic doses of the tetrahydrocannabinols, it is likely that ethical considerations will prevent the experimental study of hallucinogenic drugs in man.

4.4 Behavioural techniques

There have been several investigations of the reinforcing effects of psychotropic drugs in human volunteers allowed to engage in an operant procedure that is reinforced with the delivery of a drug. Alcohol,² cannabis,³ heroin, and pentobarbital⁴ function as positive reinforcers. In addition, the behavioural toxicity produced by these self-administered drugs may be evaluated.³ These operant procedures could assist also in estimating the dependence potential of psychotropic drugs in man.

More recently an attempt has been made to measure the relative reinforcing efficacy of stimulant drugs using a choice procedure.⁵ Subjects experience two different drugs; later, they each choose the one they prefer. This procedure shows promise for estimating the relative dependence potential of stimulant drugs. It may be applicable to other classes of psychotropic drugs and may serve as a means of validating

¹ JASINSKI, D. R. ET AL. *Progress report on studies from the clinical pharmacological section of the Addiction Research Center*. Presented at the meeting of the Committee on Problems of Drug Dependence, Cambridge, Massachusetts, July 1977.

² BIGELOW, G. ET AL. *Federation proceedings*, **34**: 1785 (1975).

³ MENDELSON, J. ET AL. *Journal of pharmacology and experimental therapeutics*, **198**: 42 (1976).

⁴ GRIFFITHS, R. R. ET AL. *Journal of pharmacology and experimental therapeutics*, **197**: 488 (1976).

⁵ JOHANSON, C. E. & UHLENUTH, E. Presented at the meeting of the American Psychological Association, 1977.

prediction based on studies of the reinforcing properties of drugs in animals.

4.5 Relevance of pharmacological and behavioural data to abuse liability

Prediction of the likelihood of abuse and the risks attendant on abuse of psychotropic substances involves four steps. The first step is the accumulation of pharmacological and toxicological data, mostly obtained from animals but some from man. The extent of the studies in man might vary considerably, depending on the properties of the drug in question. The second step is the use of these data to form a judgement on the dependence potential in man. The third step is the prediction of the likelihood that the substances will be abused by certain individuals within a society or culture. This prediction is based not only on the dependence potential of the substances but also on other factors such as the socioeconomic conditions, the availability of the substances, their therapeutic use, and the record of previous drug abuse in the society concerned. However, it is obvious that the pharmacological properties of the substances play a primary role in initiating and/or maintaining drug abuse. In this regard the relative efficacy of the reinforcing effects and the identification of the substances with a particular class of drugs may be of special importance. The fourth step is the prediction of the risk to both the individual and society when the substances are abused. Again this involves factors other than drug properties, but consideration of the following drug properties may be the most logical approach to prediction of the risk of abuse.

(1) A possible reinforcing effect, which would lead to compulsive drug-seeking behaviour.

(2) Possible pharmacological effects, which would produce behavioural disorders at a dose level consistent with a self-administered regimen.

(3) Possible toxic effects, which would produce pathological changes at a dose level consistent with a self-administered regimen.

(4) Severity of the withdrawal manifestations including risk to life.

4.6 Decision-making

It is important to recognize that pharmacological techniques necessarily play a predominant role in the scheduling of new psychotropic

substances that are being introduced into therapeutics. In the case of an agent that has a pharmacological profile similar to that of a prototypic drug of abuse (e.g., pentobarbital, dexamphetamine, lysergide), a decision to control it can be made with a relative certainty that it has the capacity to be abused. Two provisos must be emphasized, however. First, there is evidence of inherent species differences in reactivity to individual drugs within given classes. Thus some knowledge of the human pharmacology of the drug must be available to validate the techniques used in animals. Secondly, the actual incidence of abuse of an agent is influenced by factors other than its pharmacological properties. Many of these factors are unknown, but it is generally felt that the customs and passing fashions of the particular culture, the availability of the drug, the physicochemical properties of the drug, the type of pharmaceutical preparation, and the abuser's knowledge of the effects of the drug all contribute to the actual incidence of abuse. Thus, certain drugs may have the pharmacological profile of a prototypic drug of high abuse potential, but at any given time or in a particular society their incidence of abuse may be low or nil.

New psychotropic agents developed for their unique therapeutic value will not usually produce pharmacological profiles similar to those of prototypic drugs. This fact constitutes a major problem for the prediction of a new drug's dependence-producing potential. Complications already arise with agents that only partially resemble the prototypic agent or have a mixed profile of effects.

5. ASSESSMENT OF THE PUBLIC HEALTH AND SOCIAL PROBLEMS

5.1 Identification of social problems

The identification of social problems arising from the unauthorized and excessive use of psychotropic substances calls for a prior recognition that not all the social problems that may be encountered by drug abusers are caused by their drug consumption. At times, indeed, the non-medical use of these drugs is symptomatic of pre-existing functional difficulties faced by these individuals. The nature of this relationship, and the attendant need for caution in understanding it, have been discussed elsewhere.¹

¹ *The aetiology of psychoactive substance use.* Paris, United Nations Educational, Scientific and Cultural Organization, 1977.

Drug abuse characteristically gives rise to two main problems : first, the interpersonal relationships of the user are adversely affected ; secondly, the adverse social effects impinge on many individuals. Whether a certain kind of behaviour is a problem in the society in which it occurs depends on the views of both the official agencies and the community itself. If there is no general agreement between the various perceptions involved, closer inspection is called for.

It is possible to identify certain specific social problems associated with drug abuse. Among them are the following.

(1) Drug abuse may result in economic losses that have an impact on the user's immediate social circle (family or other dependents) and ultimately on society as a whole.

(2) There may be a deterioration in family relations resulting from (1) or from the user's incapacity to function as a partner or parent.

(3) Drug users might be involved in various forms of criminal behaviour beyond the illicit possession of drugs for their own consumption. Such behaviour could include crimes committed in order to acquire drugs, offences in vehicular traffic or at work, trafficking in drugs in order to ensure the users' own supplies, and crimes of violence committed under the influence of certain drugs.

(4) Drug abuse leads to demands on social services and medical resources, the cost of which is borne not only by drug users but by the general public.

(5) Drug users are potential agents in the spread of drug abuse both in their immediate social milieu and, when they travel, in other national or international settings.

5.2 Identification of public health problems

Non-medical drug use does not of itself, or necessarily, constitute a public health problem. What is important is the degree of harm that may ensue from such drug use. Hence strategies devised to investigate drug use must seek to determine not only the existence of the phenomenon but also its extent, patterns of use, populations involved, and possible harmful consequences.

Among the public health problems that have been associated with drugs of abuse are : serum hepatitis, infections, and septicaemia from the use of nonsterile injection methods ; physical disabilities resulting

from vehicular and other accidents ; death due to overdose and mixing of psychotropic drugs with other substances ; nonspecific health disorders resulting from neglect of personal hygiene and inadequate nutrition ; mental disorders and toxic psychoses precipitated by certain psychotropic drugs ; damage to tissue, the central nervous system, and the fetus.

5.3 Sources of information

Information collected for purposes other than epidemiology can prove extremely valuable, particularly since it can be obtained quickly and fairly cheaply.

5.3.1 *International sources*

Sources of information that might be employed by WHO in meeting its obligations under the Convention exist in various international organizations. The data are of varying quality and relevance but should not be ignored. In the future it will be necessary to determine precisely which elements of these sources are specific to the needs of WHO. These sources include the following.

(1) The annual reports of the International Narcotics Control Board on the licit manufacture, export, and import of drugs controlled by the Convention.

(2) Reports from governments received by the Secretary-General and analysed by the United Nations Division of Narcotic Drugs regarding illicit cultivation, manufacture, drug trafficking seizures, and drug abuse.

(3) The WHO programme on the international monitoring of adverse reactions to drugs, which collates reports on this matter.¹

(4) Reports prepared by the General Secretariat of the International Criminal Police Organization (Interpol—ICPO) from information furnished by the national central bureaux of ICPO Member countries. Such reports provide statistical and other information about the scale of the illicit traffic, trends in the distribution of particular substances,

¹ The programme receives information about all types of drugs (not just psychotropic) used for approved indications (therapeutic, diagnostic, and prophylactic).

the appearance of new substances in the illicit traffic, the extent and nature of manufacture in clandestine laboratories, and the areas of the world affected by the movement of these substances.

(5) The WHO international network of collaborating centres for the study of psychotropic drugs.

(6) Nongovernmental organizations involved in drug-related programmes.

Reference should be made here to the WHO research and reporting project on the epidemiology of drug dependence, which is developing methods of helping planners to obtain case reports on drug users, the results of youth surveys, and information on treatment evaluation.

5.3.2 *National sources*

No single national source can provide all the information necessary on drug abuse at the national level, but the following national sources may provide parts of the total picture.

(1) National alerting or early warning reporting systems, which collect data systematically from a number of reporting points strategically located throughout a country or region.

(2) Centres for narcotic maintenance detoxification or treatment of drug dependent persons, where interviews and urinalysis can reveal the various drugs in current use.

(3) Forensic or public health chemical laboratories, where drugs illicitly in circulation can be analysed.

(4) The reports of coroners when autopsies have been performed in cases of deaths suspected of being related to drugs.

(5) Public health reports regarding conditions that may be related to the nonmedical use of drugs (e.g., serum hepatitis).

(6) Case registers that record contacts of drug users with treatment and other institutions.

(7) Police and other law enforcement services in close contact with the milieu of the illicit distribution and use of drugs.

(8) Emergency treatment centres and “ street ” clinics, which are in contact with persons suffering from the adverse effects of drugs or combinations of drugs.

(9) Youth and student counselling services, where information may be provided about drug use.

(10) Reports and references appearing in youth-oriented publications and broadcast by youth-oriented radio stations.

When applied in national reporting systems, the foregoing sources should provide useful information for assessment of the public health and social problems associated with the use of psychotropic drugs.

An additional potential source of important information is the pharmaceutical industry, which has data on the production and distribution of drugs as well as data relating to similar substances that did not reach the stage of marketing. At present, these are rarely made available to government authorities. Efforts should continue to be made to obtain useful monitoring data from this source.

5.3.3 *Systematic epidemiological studies*

While the use of existing data sources can provide valuable insights into potential hazards associated with drug abuse, a more reliable assessment of possible problems may require a more systematic approach. However, differences in culture, the structure of society, resources and available expertise in the communities to be studied make it impracticable to apply a single set of standards or procedures for research. Therefore, when a systematic approach is contemplated, a broad range of existing investigative techniques and strategies must be considered either by WHO or by other teams of investigators.

However, this does not rule out the evident need for WHO to develop a coherent and comprehensive investigative strategy that it can apply when called on to do so. In essence the prime goal of this strategy should be to determine the extent of abuse of the drugs in question, the pattern of such abuse, and the nature of any associated public health and social problems.

WHO should advise the signatories to the Convention on the step-by-step development that should be undertaken for data collection. In the broadest sense, this should take account of :

(1) the drug, the prevalence and incidence of its abuse, and its patterns of use (including dose, frequency, duration of use, and route of administration) ;

- (2) the characteristics of the user population ; and
- (3) the incidence and nature of public health and social problems associated with abuse of the drug.

Data should be gathered by countries in a format that ensures a minimum level of uniform reporting. If such national data collection programmes are to be considered components of a WHO international data gathering and monitoring system, WHO should cooperate with countries in the training of personnel and in the development of methodology.

The WHO data collection system should be planned with a view to ensuring a continuous flow of current information about the abuse of psychotropic drugs in all parts of the world and about the related social problems. Its operational function could be to receive, compile, and classify the data provided by countries and to initiate and/or integrate programmes of data collection in order to respond to specific requests for information about existing or potential public health or related social problems associated with the abuse of psychotropic substances.

As a matter of priority, WHO should encourage and facilitate the development of relevant components of national health information systems, particularly in developing countries, since it is obvious that national systems must be introduced before an international system can function effectively. It would also be advisable for WHO to test the system on a pilot basis, in selected countries where data collection activities are at various stages of development.

6. ASSESSMENT OF THERAPEUTIC USEFULNESS

In contrast to earlier treaties on the international control of drugs, the Convention on Psychotropic Substances requires from WHO an assessment of the therapeutic usefulness of a substance or preparation notified for control. This requirement responds to the view expressed in the sixteenth report of the WHO Expert Committee on Drug Dependence¹ that "the need, type and degree of international control must be based on two considerations : (a) the degree of risk to public health and (b) the usefulness of the drug in medical therapy". The drug's

¹ WHO Technical Report Series, No. 407, 1969, p. 18.

usefulness must be weighed against the potential or established risks from its abuse, and the resulting ratio determines both the need for control and the degree of control.

Because of the established therapeutic usefulness and the necessary and legitimate use of many of the drugs included in the schedules of the Convention (and of other drugs that may become candidates for inclusion), the impact of the Convention on medical practice may be greater than that of other international Conventions concerned with drug control. The responsibility of WHO in implementing the Convention is amplified by considerations concerning individual and public health. Thus WHO must make every effort to ensure that the inclusion of drugs in the schedules is justified by the appropriate assessment of the balance between risk and benefit.

In the absence of precise evidence on the criterion for therapeutic usefulness, recourse must be had to reputed usefulness, which reflects the general opinion of practitioners or expert panels. This opinion may change with time or even vary between countries.

With the passage of time therapeutic usefulness itself may be subject to change. For instance, new effects (desired or undesired) may be discovered, and the need for a drug may increase or the drug may become obsolete.

During the past two decades new avenues to the drug treatment of mental disorders have been opened through the introduction of highly active and very specific psychotropic agents. Thus, the assessment of the therapeutic usefulness of these agents is of paramount importance for the progress of psychopharmacotherapy.

6.1 Therapeutic efficacy and safety

The proof of efficacy and the demonstration of safety should be basic conditions for obtaining permission to launch a drug on to the market. The scientific approach to the evaluation of both efficacy and safety is of recent date. It involves many disciplines, including toxicology, pathology, pharmacology, clinical pharmacology, behavioural science, biopharmacy, biochemistry, and biometrics. General principles for the evaluation of the efficacy and safety of drugs have been formulated by a number of WHO expert groups.¹

¹ WHO Technical Report Series, No. 341, 1966; No. 364, 1967; No. 403, 1968; No. 425, 1969; No. 426, 1969; No. 482, 1971; No. 536, 1974; No. 563, 1975.

Many governments have accepted the responsibility of ensuring that the drugs made available to doctors and patients comply with established standards of efficacy and safety. To the extent that these responsibilities are discharged appropriately, the basic requirements for the determination of the usefulness of a drug can be presumed to have been fulfilled. In these circumstances WHO would not have to scrutinize the relevant preclinical and clinical data.

The situation is quite different with substances, like some of those in Schedule I of the Convention, which have not been introduced into medical practice (or which have been introduced only in a limited way). In such cases WHO would itself have to engage in studying or possibly generating the documentation needed for the assessment of efficacy and safety and the resultant therapeutic value.

The consideration of efficacy and safety should not be limited to the study of information available at the time of official approval (registration) and marketing of the drug but should extend to post-registration information such as that resulting from long-term application.

As required by the Convention, a comparison must be made with existing drugs. Differences must be expected in the pharmacological profiles of drugs of similar chemical structure—except those with very minor modifications known not to entail differences in respect of pharmacokinetics or mechanism of action. Even slight structural changes might lead to differences in effects, which again would make it difficult to equate substances of similar chemical structure with regard to their usefulness.

Cases are known where new therapeutic properties and uses were detected in a drug after it had been used in medical practice for some time. For example, methaqualone was developed as an antimalarial drug; later on its value in relieving arthritic pain was discovered. Today methaqualone is used as a hypnotic only. It is conceivable that events might occur in the reverse order—i.e., the initial use of a psychoactive substance might be followed by the discovery of other possibly more valuable therapeutic properties. Such discoveries might be forestalled by too rigid control at an early stage of drug development.

6.2 Factors modifying the usefulness of a drug

Among the factors determining the usefulness of a drug are its availability and cost and the knowledge and experience of those prescribing and administering it.

The more serious the illness against which the drug in question is used, the greater its usefulness in absolute terms. The fewer the other drugs available of comparable effectiveness and safety for treating an illness, the greater the usefulness of the drug in relative terms.

Superior efficacy and/or safety when making comparisons between drugs will increase the usefulness. The comparison must take into account the need for any precautionary measures in administering the drug. For instance, a drug requiring the monitoring of levels in the blood (e.g., lithium) is less useful than a drug not requiring such monitoring.

6.3 Precautions required in developing countries

Many developing countries do not manufacture psychotropic drugs themselves but import them from industrialized countries. Their need for psychotropic drugs is probably equal to that in industrialized countries. There is often a tendency to overemphasize therapeutic usefulness and minimize risk, and in developing countries there are special considerations to be taken into account. With the experience of industrialized countries in mind, it may be found that psychotropic drugs act differently on the populations of some developing countries owing to environmental, cultural, and genetic factors. Therapeutic efficacy and safety may be influenced by nutritional status and the presence of infectious and parasitic diseases, which may produce lesions of the central nervous system and digestive tract.

Transcultural studies, particularly those of clinical evaluation and in the field of epidemiology, would be of great value in promoting better knowledge of the mode of action of psychotropic drugs and the understanding of drug dependence in different areas of the world.

A developing country is particularly at risk of developing drug abuse problems in the absence of drug control. A case could be made for recommending that some Member States introduce controls more stringent than those required by the Convention on Psychotropic Substances. Such a course might well prevent the development of problems of drug dependence and allow health personnel to deal with existing health problems.

Developing countries need the assistance of WHO and of other international organizations to protect their populations and especially to fulfil their obligations with regard to the international control treaties to which they are parties.

6.4 Drug utilization studies

Drug utilization studies investigate the actual consumption of a drug or drugs in a given population.¹⁻⁷ This method is more accurate than those that merely examine the number of doses sold since drugs dispensed are not necessarily used. Experience suggests that data derived from such studies could contribute to the assessment of therapeutic usefulness.

6.5 Drug combinations

The Committee learned that WHO was shortly convening a group of consultants to examine the question of preparations in relation to the principles that might be used in exempting preparations from controls under Article 3 of the Convention.

The Committee wished to draw attention to the fact that mixtures of different substances may have either a more potent effect or a less potent effect than either substance taken alone. Thus, there seems to be a strong case for the evaluation of preparations as entities rather than as a predicted sum total of the separate effects of their constituents.

6.6 Collection of data

The Committee recognized that in this complex field great reliance would need to be placed on the collection of data on therapeutic usefulness from many sources, if sound evaluation and advice were to be forthcoming.

The Committee therefore considered that there was a need to expand existing services, such as the reference centres and the epidemiological

¹ KIELHOLZ, P. *Schweizerische Ärztezeitung*, 49 : 1077 (1968).

² BALTER, M. B. ET AL. *New England journal of medicine*, 290 : 769 (1974).

³ *Clinical pharmacology and therapeutics*, 19 : 644-662 (1976).

⁴ LUNDE, P. K. M. Differences in national drug prescribing patterns. In : *Clinical pharmacological evaluation in drug control*. Copenhagen, WHO Regional Office for Europe, 1975 (document ICP/SQP 004) Annex III, p. 19.

⁵ WESTERHOLM, B. Epidemiological studies on drug consumption. In : *Clinical pharmacy*. Amsterdam, Elsevier, 1977, p. 209.

⁶ BOETHIUS, G. & WESTERHOLM, B. *Acta psychiatrica et neurologica Scandinavica*, 56 : 147 (1977).

⁷ GRISSON, A. ET AL. *Nordisk Medicin*, 92 : 49 (1977).

facilities of international and national bodies, and to create new ones, so that data become available as early as possible in the development of drug problems.

7. DECISION-MAKING

The decision whether or not to include a drug under the terms of the Convention rests on a comparison of the expected benefits of control versus the economic and other costs of control. While this is the basic consideration, the decision also depends on the existing prevalence of drug use and the therapeutic usefulness.

7.1 Drugs that are therapeutically useful but currently abused

In addition to assessing the public health and social costs arising from the abuse of a certain drug, it is necessary to estimate the costs of placing the drug under control. Where large numbers of persons throughout the world require the drug for medical reasons, these costs can be considerable. It should be possible to obtain rough estimates of these costs but it may be difficult to weigh them against deaths and other consequences of drug abuse. It is important to realize that by no means all the cost of the abuse can be attributed to the drug under consideration. The appropriate question is the reduction in social and public health costs that would result from the control of the specific drug. If it is controlled, there is still the possibility of its being obtained through illicit sources or the probability that another drug will be substituted for it.

7.2 New drugs considered for control

New drugs require a somewhat different evaluative approach from that used for older drugs whose medical value and liability to non-medical use have been established. Where the drug is a generic extension of one already controlled, it should be considered for inclusion even though there has been no opportunity for abuse. Where the pharmacological profile of a new drug is sufficiently similar to that of one already included in Schedules I and II *and* where laboratory tests indicate significant abuse potential, it may also be advisable to place it under control in the absence of actual evidence of abuse. Such decisions should be reviewed at a later date to determine if subsequent epidemiological evidence warrants continuing the control. Where a new drug is found to be subject to abuse prior to its being controlled, it is important to

establish the *rate* of abuse among those exposed. Thus, one hundred cases of abuse under conditions of limited exposure would be of considerably greater significance than the same number of cases under conditions of wide availability.

7.3 Scheduling anomalies

The scheduling approach adopted by the Convention considers both abuse liability and medical usefulness. Since Schedules I and II require stricter control than do Schedules III and IV, it would be preferable if nonmedical abuse varied inversely with medical usefulness—i.e., those with low medical usefulness and high abuse liability would be placed in Schedules I and II, and those with high medical usefulness and lower (but still significant) abuse liability in Schedules III and IV. Since not all drugs considered will have this kind of inverse relationship, scheduling anomalies may result. In particular, this approach may lead to inappropriate control of drugs with low medical usefulness and low abuse liability. Drug control entails some cost even when there is little known medical value. Since it is not the aim of the Convention to impose unnecessary controls, this type of drug should be examined for appropriateness of scheduling primarily in terms of abuse liability.

7.4 The decision-making process

While it is very likely that the final decision on scheduling will depend on expert opinion, better decisions would result if the individual components to be considered were identified and separately evaluated. For instance, it has been suggested that drugs might be evaluated according to medical benefits, dependence liability, individual and public health hazards, public safety, and risks to the dominant social order and traditional culture. While some of these criteria, such as those based on laboratory tests for dependence liability, might be expressed in quantitative or semiquantitative terms, the appreciation of other criteria is hampered by the lack of adequate means of measurement.

The Convention provides for scheduling new drugs in terms of their similarity to those already under control, and even where similarities do not exist expert opinion will still probably utilize experience with controlled drugs as a baseline. A decision can be reached by simply determining whether or not the new drug under consideration rates higher or lower than a roughly similar drug already under control. Methods also exist for the development of rating scales that permit

more precise comparisons. Of course, where the new drug is rated higher than the reference drug in some ways and lower in others, there will still be a need for scientific weighting of the different variables.

8. PROBLEMS OF CHEMICALLY GENERIC EXTENSIONS TO THE LIST OF SCHEDULED SUBSTANCES

The Expert Committee was asked to consider the problems that might arise if the description of substances in the 1971 Convention was extended to include salts, esters, ethers, isomers and precursors and to examine the meaning of the expression, in Schedule I, "all isomers" of the tetrahydrocannabinols. The detailed assessment is set out in the annex to this report. The conclusions of the Expert Committee are as follows.

8.1 Salts

Regarding the absence of reference to salts in the 1971 Convention the Committee noted that, following a recommendation by WHO, the United Nations Commission on Narcotic Drugs had added the salts to each of the schedules. The Committee confined itself to tabulating those substances that may form salts (see annex).

8.2 Esters and ethers

Of the presently scheduled substances, six have a structure that includes hydroxyl groups and are thus capable of forming esters and possibly ethers. Four of them—DMHP, parahexyl, psilocine, and the tetrahydrocannabinols—are listed in Schedule I, and consideration should be given to the need for individual control of all their esters provided they can be shown to have similar effects to those of the parent compound. The other two substances—ethchlorvynol and pipradrol—, which are cited in Schedule IV, are in therapeutic use and it would be necessary to evaluate evidence of prospect of abuse of any particular ester. The Committee had no evidence of abuse or medical utility regarding the ethers of these six substances and made no recommendations.

8.3 Isomers

The concept of "isomers" covers a broad range of modifications of chemical structure. The term should be qualified in such a way as to indicate whether structural, positional, geometrical, optical or con-

formational isomerism is intended. These types of isomerism may, and usually do, profoundly affect the chemical and pharmacological properties of the parent substance. For this reason, the Committee believe that potential isomers of each scheduled substance should be considered on their merits. The geometrical and optical isomers that are theoretically possible within the specific chemical designation of all scheduled substances are indicated in the annex. Apart from the special case of isomers of the tetrahydrocannabinols which are dealt with in section 8.6, the Committee noted that there are at present 15 scheduled substances capable of existing as optical isomers; for none of these substances is a particular stereoisomer specified in the Convention. The 15 substances are listed in section 3.3 of the annex.

8.4 Precursors

In the opinion of the Expert Committee, consideration for control of "intermediates" should be strictly limited to substances that are immediate precursors capable of being readily converted into a drug that is, or is capable of being, widely abused. It was recognized that Article 2 (4) of the 1971 Convention would require such substances to be themselves capable of similar abuse. The Committee considered several candidate substances, including those mentioned previously in its seventeenth report,¹ but concluded that there was at this stage no case for international control. It recommended, however, that this matter should continue to be kept under review.

8.5 Generic descriptions of drugs

The Expert Committee noted that in order to combat the situation in which an increasing number of structurally related drugs are becoming abused, certain Member States have found it expedient to introduce a generic chemical description that can subsume substances that are known to be abused and anticipate analogous substances that might become abused. The Committee accepted that such descriptions may have their place in the legislation of individual countries, particularly where a localized problem requires speedy solution, but believed that in an international treaty binding on all signatories it is necessary to name each drug individually, with the exception of salts.

¹ WHO Technical Report Series, No. 437, 1970.

8.6 Tetrahydrocannabinols

The Expert Committee accepted that expediency had prompted reference in Schedule I of the Convention to "all isomers" of the tetrahydrocannabinols but, for the reasons set out in paragraph 8.3, considered that this description was too imprecise because it could include alternative cyclic structures or positional isomerism of functions other than hydrogen. On the assumption that the original intention had been to control the tetrahydro derivatives of cannabinol, the Committee recommended that control should be restricted to seven specific double-bond tetrahydrocannabinol isomers, namely $\Delta^{6a(10a)}$, $\Delta^{6a(7)}$, Δ^7 , Δ^8 , Δ^9 , Δ^{10} , $\Delta^{9(11)}$, and their stereochemical variants. If the recommendation is adopted by the Commission it should no longer be necessary to retain the specific chemical designation of one isomer, Δ^8 -tetrahydrocannabinol, in the schedule.

9. RECOMMENDATIONS

1. In order to fulfil its responsibility, under the Convention on Psychotropic Substances, for assessing the public health and social problems arising from the abuse of psychotropic substances, WHO should establish or strengthen mechanisms that will give it timely access to data relevant to the assessment of drugs likely to be covered by the Convention.
2. On request, WHO should assist all parties to the Convention¹ to develop methods relevant to the task of collecting data covered in recommendation 1.
3. On request, WHO should assist all parties to the Convention in their efforts to carry out the above recommendations by providing expertise as required and ensuring the training of personnel.
4. On request, WHO should advise and assist the parties to the Convention to carry out transcultural studies that will allow information on drug abuse to be collected in a more uniform manner.
5. WHO should facilitate the development of scientific methods to improve the pharmacological and toxicological characterization of existing psychotropic substances and to enable new psychotropic sub-

¹ In addition to the parties to the Convention, other Member States of WHO may collaborate with the Organization in a similar way.

stances to be evaluated rapidly and accurately. The special needs of developing countries for simple or specialized methods should be recognized.

6. With reference to Article 3 of the Convention, preparations should be dealt with as single entities in terms of the evaluation of therapeutic effectiveness and of risk of abuse.

7. Under Article 2 of the Convention, WHO should notify the Secretary-General of the United Nations of the Committee's opinion concerning the control of the isomers of tetrahydrocannabinol listed in Schedule I of the Convention and should transmit to him the recommendation that the schedule be amended as specified in section 8.6 of this report.

ACKNOWLEDGEMENTS

The Committee acknowledges with gratitude the special contributions to its deliberations made by the following :

Professor C. A. Salemink and his colleagues of the University of Utrecht, Netherlands, for the preparation of a working paper entitled "Biological activity of the tetrahydrocannabinols"; Dr I. W. D. Henderson, of the Non-Medical Use of Drugs Directorate, Ottawa, Canada, for the preparation of a working paper entitled "Psychotropic substances: risk/benefit in a social perspective"; and Dr S. S. Gothoskar, of the Directorate General of Health Services, India, for the preparation of a working paper entitled "Cooperation with countries in the implementation of the Convention on Psychotropic Substances". The Committee also wishes to thank Dr P. H. Hughes and Dr F. E. Vartanian, both of the Division of Mental Health, WHO, for their contributions made during the meeting.

SALTS, ESTERS, ETHERS, ISOMERS, AND PRECURSORS OF PSYCHOTROPIC SUBSTANCES

The seventeenth report of the WHO Expert Committee on Drug Dependence ² did not explicitly discuss the control of salts, isomers, esters, and ethers of psychotropic substances, and there was only a brief reference (section 4.7) to three precursors. In the text of the Convention on Psychotropic Substances, 1971, no reference is made to salts, esters, ethers, or precursors. Isomers are referred to only in the particular context of the tetrahydrocannabinols. These topics were considered more fully at the present meeting of the Expert Committee and are discussed in detail in this annex.

1. Salts

In 1977, on the recommendation of WHO, the parties to the 1971 Convention, by a majority vote, included salts wherever appropriate in the schedules to the Convention. Table 1 indicates which of the scheduled substances are capable of forming salts. Although technically neutral, the three cannabinoids DMHP, parahexyl, and the tetrahydrocannabinols can, since they are phenols, form phenates. The five depressants—glutethimide, ethchlorvynol, ethinamate, meprobamate, and methyprylon—are neutral substances. The remaining 24 substances are either acidic or basic and therefore form salts. Under certain conditions the ester psilocybine behaves as if it were a salt, i.e., the mono-ester phosphate serves as an anion for the basic centre near by in the molecule.

2. Esters and ethers

The close relationship of ester and ether derivatives of the opiates led to the listing of such derivatives of particular substances in Article 1 of the 1931 Convention—e.g., “diamorphine and other esters of morphine” and “benzylmorphine and other ethers of morphine except codeine and ethylmorphine”. In Schedule I of the 1961 Single Convention on Narcotic Drugs there were supplementary clauses adding esters and ethers, whenever their existence was possible and unless they

¹ Based on a paper prepared by Mr G. F. Phillips, Superintendent, Health Services Division, Laboratory of the Government Chemist, London, England.

² WHO Technical Report Series, No. 437, 1970.

appeared in another schedule. No similar extension for esters and ethers was given for the somewhat milder and therapeutically important narcotics in Schedule II, several of which were already esters and ethers.

Of the substances scheduled in the 1971 Convention, four are esters, two are simple ethers, and four are cyclic ethers (see Table 1). Altogether six substances (three of which are also cyclic ethers) include hydroxyl groups in their structures (see Table 1); these substances form esters and could be expected to form ethers. The six are: DMHP, parahexyl, the tetrahydrocannabinols (isomers), psilocine, ethchlorvynol, and pipradrol.

It is helpful to compare certain of the esters of these six substances with other scheduled drugs that are already esters. Thus, the phosphate ester of psilocine is the potent hallucinogen psilocybine and is already scheduled. The acetate esters of the tetrahydrocannabinol isomers (and, by analogy, of DMHP and parahexyl) have lower activity¹ but may be converted to the corresponding active hallucinogenic phenol. In the case of ethchlorvynol, the carbamate ester is structurally very similar to ethinamate (already in Schedule IV). No evidence is available for the activity of esters of pipradrol. It is concluded that for the four Schedule I substances DMHP, parahexyl, psilocine, and the tetrahydrocannabinols, consideration should be given to controlling all those esters that can be shown to have similar psychotropic effects. For the two therapeutic substances ethchlorvynol and pipradrol, it would be necessary to evaluate evidence of the prospect of abuse of any particular ester. None of the scheduled drugs has a free carboxylic acid function, and so the prospect of esters formed therefrom does not arise.

Ethers such as the ring alkoxy amphetamines or *O*-methylbufotenine are, in general, more potent hallucinogens than the corresponding ring hydroxy substances; however, the natural methyl ether of Δ^9 -tetrahydrocannabinol appears to be inactive. Of the two Schedule IV drugs containing OH groups, pipradrol has its OH group in a benzylic position while ethchlorvynol is an open-chain alcohol; conversion of ethers to the parent hydroxyl requires conditions chemically more vigorous or enzymatically specific.

3. Isomers

In the 1961 Single Convention, the isomers of scheduled drugs were limited to those possible within the specific chemical designation. Two

¹ NEUMAYER, J. L. & SHAGOURY, R. A. *Journal of pharmaceutical sciences*, 60: 1433 (1971).

Table 1. Salts, esters, ethers, and isomers of scheduled substances

	Salt-forming characteristic ^a	Present nature of substance	Substance contains free hydroxyl group ^b	Potential isomers ^c
<i>Schedule I</i>				
DET	basic	—	—	no
DMHP	phenolic	cyclic ether	OH	***
DMT	basic	—	—	no
(+)-lysergide	basic	—	—	+/ β)
mescaline	basic	open-chain ether	—	no
parahehyl	phenolic	cyclic ether	OH	(\pm)
psilocine	basic	—	OH	no
psilocybine	basic	ester	—	no
STP (DOM)	basic	open-chain ether	—	(\pm)
tetrahydrocannabinols (all isomers)	phenolic	cyclic ether	OH	Δ / β **
<i>Schedule II</i>				
amphetamine	basic	—	—	(\pm)
dexamphetamine	basic	—	—	(+)
methamphetamine	basic	—	—	(+)
methylphenidate	basic	ester	—	**
phencyclidine	basic	—	—	no
phenmetrazine	basic	cyclic ether	—	**
<i>Schedule III</i>				
amobarbital	acidic	—	—	no
cyclobarbital	acidic	—	—	no
glutethimide	—	—	—	(\pm)
pentobarbital	acidic	—	—	(\pm)
secobarbital	acidic	—	—	(\pm)
<i>Schedule IV</i>				
amfepramone	basic	—	—	(\pm)
barbital	acidic	—	—	no
ethchlorvynol	—	—	OH	(\pm)/ct
ethinamate	—	ester	—	no
meprobamate	—	ester	—	no

Table 1. Salts, esters, ethers, and isomers of scheduled substances (cont.)

	Salt-forming characteristic ^a	Present nature of substance	Substance contains free hydroxyl group ^b	Potential isomers ^c
methaqualone	basic	—	—	no
methylphenobarbital	acidic	—	—	(±)
methpyrion	—	—	—	(±)
phenobarbital	acidic	—	—	no
pipradrol	basic	—	OH	(±)
lefetamine (SPA)	basic	—	—	(—)

^a Salts may be formed from acidic or basic substances. Alkali phenates (phenolates) may be formed from phenolic substances.

^b Esters and ethers may be formed from compounds with free hydroxyl group.

^c Isomers theoretically possible:

*** = 3 chiral centres in structure (giving rise to 4 diastereomeric pairs).

** = 2 chiral centres in structure (giving rise to 2 diastereomeric pairs).

(±) = one chiral centre giving racemic product or two enantiomers.

(+) or (—) = particular enantiomer specified.

(+/ β) = particular diastereomer of lysergide.

ct = *cis/trans* isomeric alternatives possible.

Δ = double-bond position isomers occur.

no = no isomerism possible.

isomers were exempted from control. Recognizing the very broad implication of the term "isomers" when used without further qualification, the Expert Committee considered structural, positional, geometrical, and optical isomerism in respect of the substances scheduled in the 1971 Convention.

3.1 Structural and positional isomers

Except for the tetrahydrocannabinols, isomerism of the ring structures or of the position of functional groups within the specific chemical designations of scheduled substances is not possible. With regard to tetrahydrocannabinol (of which the Δ^8 isomer is explicitly defined in Schedule I, although according to the records¹ of the Vienna Conference the Δ^9 isomer was intended) it is said that "all isomers" are to be controlled. This is undesirably imprecise, in that any degree of struc-

¹ Official Records: United Nations Conference for the Adoption of a Protocol on Psychotropic Substances, Vienna, 1971. New York, United Nations, 1973 (document E/CONF.58/7).

tural isomerism in the tetrahydrocannabinol molecule might be implied. The scope of the phrase is discussed in the first paragraph of section 6 of this annex.

3.2 Geometrical isomers

Ethchlorvynol has an isolated double bond, and *cis/trans* isomerism is possible. It may be necessary to control both geometrical isomers. The commoner *trans* isomers of Δ^8 and Δ^9 -tetrahydrocannabinol have corresponding *cis* isomers, differing in the geometry of the B/C ring junction (see first paragraph of section 6 of this annex).

3.3 Optical isomers

Thirteen of the 32 scheduled substances have no asymmetric centre. Fourteen (mostly amphetamine-like) substances have one chiral centre, which usually results in a racemic product, but for three of these substances one enantiomer—significantly more active than the other—is specified (e.g., dexamphetamine). The remaining five substances have two or more optically active centres, although in the case of (+)-lysergide the particular diastereomer is implicitly defined (the other three diastereomers being (–)-lysergide and the (+) and (–) diethylamides derived from isolysergic acid).

The 15 scheduled substances capable of existing as optical isomers, and for which no particular stereoisomer is explicitly or implicitly specified in the Convention, are: DMHP, parahexyl, STP, the tetrahydrocannabinols, amphetamine (racemic), methamphetamine, methylphenidate, phenmetrazine, pentobarbital, secobarbital, amfepramone, ethchlorvynol, methylphenobarbital, methyprylon, and pipradrol.

4. Precursors

The question of precursors is foreshadowed in Article 11 (4) of the 1931 Convention, which refers to a drug not itself capable of producing dependence but convertible into such a drug. This is maintained in Article 3 (3) of the 1961 Single Convention. Although not listed in the schedules of the initial text of the 1961 Convention, five such precursors were subsequently added. These five were intermediates and direct synthetic precursors of three of the controlled drugs—methadone, moramide intermediate, and pethidine. In 1968 the WHO Expert Committee on Drug Dependence considered the possibility of defining an additional group of controlled substances to comprise “chemical precursors capable of relatively simple transformation into dependence-

producing drugs".¹ Both at that meeting and at the meeting in 1970² the Expert Committee expressed doubt about the practicability of developing a list of precursors and concluded that, in general, each substance required individual evaluation. At the latter meeting the Committee did, however, recommend control of three specific precursors—cannabidiol, lysergic acid amide, and lysergic acid. This recommendation was not adopted in the 1971 Convention and no provision was made in the text specifically for precursors that are not themselves psychotropic substances.

Control of "intermediates", if undertaken, should be strictly limited to substances that are immediate precursors of drugs that are, or are capable of being, widely abused. Such a policy, applied to the 32 scheduled drugs, might direct attention to the three substances considered at the 1970 meeting of the Expert Committee and perhaps also to barbituric acid.

In practice, the designation of such precursors (which are not themselves significant psychoactive substances) in an international control schedule is contrary to Article 2 (4) of the 1971 Convention. In individual States legislation becomes a matter of judgement of the balance between legitimate and sometimes totally unrelated use and evidence indicating that the particular substance has been regularly used as a precursor of a widely abused drug. Of the four precursors under review three are subjects of alternative legitimate interest. Cannabidiol has not been reliably implicated as a hallucinogen and may have other therapeutic prospects; lysergic acid is the key hydrolysis product of the oxytocic ergot alkaloids; and barbituric acid has a significant role in the chemical industry (non-pharmaceutical). Only lysergic acid amide (lysergamide)—a mild, naturally occurring, hallucinogen and an immediate precursor of lysergide—is thought to be worthy of consideration for addition to the schedules. It is already controlled in a number of States at the same level as lysergide. Reference to precursors of the tetrahydrocannabinols, specifically the acetate esters and the readily decarboxylated tetrahydrocannabinolic acids, is made in the second paragraph of section 6 below. One other drug in the schedules, methylphenidate, is itself a simple ester of a modified amphetamine bearing a carboxylic function. Any case for controlling its acid precursor would need to rest on evidence either of abuse *per se* or of ready availability for unauthorized conversion to methylphenidate.

¹ WHO Technical Report Series, No. 407, 1969.

² WHO Technical Report Series, No. 437, 1970.

5. Generic descriptions of drugs

In order to deal with a situation in which an increasing number of structurally related drugs are becoming abused, one course that has been adopted by certain countries is to introduce a generic chemical description that can subsume substances that are being abused and analogous substances that may become so. Such a procedure is open to the objection that forensic practice requires constant vigilance in assessing the chemical applicability of such a generic description to new drugs, whether abused or not. Difficulties may also arise from a too wide (or insufficiently chemically restricted) use in legislation of the term "derivative".¹ To control some 20 CNS stimulant and anorectic drugs, a chemically generic description was employed in the United Kingdom in 1964 but later proved objectionably broad.² Nevertheless, the growing number of hallucinogenic substances known to be abused or clandestinely prepared and the social problems waiting on legislative convenience may force individual States to adopt generic chemical descriptions in which particular categories of chemical substitution are selected with explicit qualifications. Such a step was taken by the United Kingdom in 1977.

6. Tetrahydrocannabinols

The reference in Schedule I of the Convention to "all isomers of tetrahydrocannabinols", without further qualification of type of isomerism, implies that alternative cyclic structures or positional isomerism of functions other than hydrogen are intended. According to a still more extreme view, this description might be held to subsume totally different substances isomeric only in respect of a common molecular formula. It must be assumed that the original intention was to control all tetrahydro derivatives of cannabinol. Of these there are six double-bond isomers in the C-ring and one exocyclic to it; theoretically there are six more in the A-ring if the C-ring is aromatic. Less convincingly, hypothetical tetrahydro isomers exist with the (four) double bonds shared between the A and C rings. In practice, any degree of hydrogenation of the A-ring would result in a series of nonphenolic substances with quite distinct chemical, physical, and (presumably) pharmacological properties. The main evidence of abuse potential is for the

¹ PHILLIPS, G. F. *Medicine, science and the law*, 13 : 216 (1973).

² PHILLIPS, G. F. *Chemistry in Britain*, 8 : 123 (1972).

(-)-*trans*- Δ^8 and (-)-*trans*- Δ^9 isomers of tetrahydrocannabinol. The $\Delta^{6a(10a)}$, Δ^7 , and $\Delta^{9(11)}$ isomers have distinctly lower psychotropic potency. Isomer control should therefore be restricted to the first seven double-bond isomers and their stereochemical variants. Chemical designations of the seven isomers, and an indication of their capacity for stereoisomerism, are set out in Table 2.

An extensive series of natural substances has been extracted from cannabis, and there is a considerable literature on their biological properties.¹ Such substances include: (1) the three natural series of fully aromatic phenols comprising cannabinol and shorter-side-chain analogues; (2) a variety of tetrahydro derivatives for which different double-bond positions and stereoisomers exist; (3) various phenolic acetates and carboxylic acid precursors; (4) open-chain cannabinoids in which the terpene (C) (cannabichromene) rings or pyran (B) (cannabinol) rings or both (B and C) (cannabigerol) rings have been opened; (5) cyclized structures of the so-called *iso* series; and (6) internal condensation products comprising phenolic and carboxylic components. In addition, numerous synthetic analogous structures have been reported. Some psychotropic homologues with a larger 5-alkyl side-chain are already scheduled (DMHP and parahexyl). An increasing number of cannabinoid substances show promise as therapeutic agents but not many of them have yet been shown to possess hallucinogenic activity. It is concluded that, on the basis of present knowledge, it is justifiable to control only the C-ring tetrahydrocannabinols. However, since in some instances only simple chemical changes are sufficient to convert such compounds into known hallucinogens, perhaps simple esters, ethers, and carboxylic acid precursors of isomers of tetrahydrocannabinol, as redefined in Table 2, should be considered for control.

The systematic preparation of as many as possible steric forms of isomers of tetrahydrocannabinol, even though restricted by the new definition to tetrahydrogenation only in the C-ring, would require materials of adequate chemical and optical purity in quantities sufficient for the investigation of their pharmacological properties. On the basis of such evidence it might become possible further to reduce the number of isomers of tetrahydrocannabinol under control. However, such a project would represent a major effort in cost and funds.

¹ KETTENES, J. J. ET AL. *Biological activity of the tetrahydrocannabinols*. Unpublished WHO document MNH/DDC/77.7. Copies of this document are available on request from the Division of Mental Health, World Health Organization, 1211 Geneva 27, Switzerland.

Table 2. Seven isomers of tetrahydrocannabinol (THC) recommended for international control

<i>Names</i>	<i>Number of stereoisomers</i>
$\Delta^{6a(10a)}$ -THC or 7,8,9,10-THC	2 (one chiral centre)
$\Delta^{8a(7)}$ -THC or 8,9,10,10a-THC	4 (two chiral centres)
Δ^7 -THC or 6a,9,10,10a-THC	8 (ring fusion and one other centre)
Δ^8 -THC or 6a,7,10,10a-THC	4 (ring fusion, i.e., \pm , <i>cis</i> & <i>trans</i>)
Δ^9 -THC or 6a,7,8,10a-THC	4 (ring fusion)
Δ^{10} -THC or 6a,7,8,9-THC	4 (two chiral centres)
$\Delta^9(11)$ derivative of THC The exocyclic (9-methylene) isomer of THC is systematically defined as: 6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[<i>b,d</i>]pyran-1-ol	4 (ring fusion)