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Tenth Report

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EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Geneva, 19-24 October 1959

Members :

Dr N. B. Eddy, Chief, Section on Analgesics, Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md., USA

Dr L. Goldberg, Professor of Research on Alcohol and Analgesics, Karolinska Institutet, Stockholm, Sweden (*Chairman*)

Dr H. Isbell, Director, Addiction Research Center, National Institute of Mental Health, United States Public Health Service Hospital, Lexington, Ky., USA (*Vice-Chairman*)

Dr G. Joachimoglu, Professor Emeritus of Pharmacology; formerly Chairman, Superior Health Council, Ministry of Social Welfare, Athens, Greece

Dr J. La Barre, Professor of Pharmacology, Faculty of Medicine and Pharmacy, Université libre de Bruxelles, Brussels, Belgium

Mr J. R. Nicholls, C.B.E., D.Sc., formerly Deputy Government Chemist, London, England (*Rapporteur*)

Dr V. V. Vassilieva, Professor of Pharmacology, Second Moscow Institute of Medicine, Moscow, USSR

Dr V. Zapata Ortiz, Professor of Pharmacology, Faculty of Medicine, National University of San Marcos, Lima, Peru

Representatives of the United Nations :

Mr. A. Lande Dr jur., Chief of Section, Division of Narcotic Drugs, United Nations, Geneva

Mr O. J. Braenden, Ph. D., Division of Narcotic Drugs, United Nations, Geneva

Representative of the Permanent Central Opium Board and the Drug Supervisory Body :

Mr L. Atzenwiler, Secretary of these two bodies, Geneva

Secretariat :

Dr H. Halbach, Chief Medical Officer, Addiction-Producing Drugs, WHO (*Secretary*)

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EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Tenth Report *

The Expert Committee on Addiction-Producing Drugs met in Geneva from 19 to 24 October 1959.

Dr N. I. Grashchenkov, Assistant Director-General, on behalf of the Director-General of the World Health Organization, opened the meeting and welcomed the members of the Committee, the representatives of the Secretary-General of the United Nations, and the representative of the Permanent Central Opium Board and the Drug Supervisory Body. Dr L. Goldberg was elected as Chairman, Dr H. Isbell as Vice-Chairman, and Mr J. R. Nicholls as Rapporteur.

1. Notifications

1.1 *Allylprodine* [1]

Referring to the notification from the Government of the United States of America, the Committee considered that allylprodine (1) produces morphine-like effects, and (2) will suppress abstinence phenomena of a known morphine addiction. Evidence on these points was derived from experiments in monkeys. Previous experience has shown that results obtained in the monkey correlate with those in man, so that, when the former are unequivocal, they may be accepted as evidence for what is to be expected in man. In addition, the chemical structure of allylprodine

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* The Executive Board, at its twenty-fifth session, adopted the following resolution :

The Executive Board

1. NOTES the tenth report of the Expert Committee on Addiction-Producing Drugs ;
2. NOTES the action taken by the Director-General in compliance with resolution WHA7.6 with regard to the notifications forwarded to the Secretary-General of the United Nations ;
3. THANKS the members of the Committee for their work ;
4. AUTHORIZES publication of the report ; and
5. REQUESTS the Director-General to transmit the report to the Secretary-General of the United Nations.

(Resolution EB25.R4, *Off. Rec. Wld Hlth Org.*, 1960, 99)

[1] International non-proprietary name proposed for 3-allyl-1-methyl-4-phenyl-4-propionoxypiperidine

bears an extremely close relationship to those of other drugs known to be addiction-producing (e.g., alphaprodine and alphameprodine). Consequently, the Committee was of the opinion that allylprodine must be considered to be an addiction-producing drug comparable to morphine and that allylprodine and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to allylprodine and its salts be communicated to the Secretary-General of the United Nations.

1.2 *Benzethidine* [1]

Referring to the notification from the Government of the United Kingdom, the Committee considered that benzethidine (1) produces morphine-like effects, and (2) will suppress abstinence phenomena of a known morphine addiction. Evidence on these points was derived from experiments in monkeys. Previous experience has shown that results obtained in the monkey correlate with those in man, so that, when the former are unequivocal, they may be accepted as evidence for what is to be expected in man. In addition, the chemical structure of benzethidine bears an extremely close relationship to those of other drugs known to be addiction-producing (e.g., anileridine). Consequently, the Committee was of the opinion that benzethidine must be considered to be an addiction-producing drug comparable to morphine and that benzethidine and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to benzethidine and its salts be communicated to the Secretary-General of the United Nations.

1.3 *1-Cyclohexyl-2,2-di-diethylaminomethyl-1-phenylethane*

Referring to the notification from the Government of France, it was observed that reference was made therein to a certain similarity in chemical structure between this drug and methadone. The Committee was of the opinion that, in the present instance, it was not possible to infer that this similarity would imply similar pharmacological properties. The other information submitted was insufficient to enable a decision to be made;

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[1] International non-proprietary name proposed for 1-(2-benzyloxyethyl)-4-phenyl-piperidine-4-carboxylic acid ethyl ester

action was therefore deferred until adequate information became available.

1.4 *Furethidine* [1]

Referring to the notification from the Government of the United Kingdom, the Committee considered that furethidine (1) produces morphine-like effects, and (2) will suppress abstinence phenomena of a known morphine addiction. Evidence on these points was derived from experiments in monkeys. Previous experience has shown that results obtained in the monkey correlate with those in man, so that, when the former are unequivocal, they may be accepted as evidence for what is to be expected in man. In addition, the chemical structure of furethidine bears an extremely close relationship to those of other drugs known to be addiction-producing (e.g., anileridine). Consequently, the Committee was of the opinion that furethidine must be considered to be an addiction-producing drug comparable to morphine and that furethidine and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to furethidine and its salts be communicated to the Secretary-General of the United Nations.

1.5 *Levophenacylmorphan* [2]

Referring to the notification from the Government of the United States of America, the Committee was of the opinion that levophenacylmorphan, because it (1) produces morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered to be an addiction-producing drug comparable to morphine, and that levophenacylmorphan and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to levophenacylmorphan and its salts be communicated to the Secretary-General of the United Nations.

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[1] International non-proprietary name proposed for 1-(2-tetrahydrofurfuryloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester

[2] International non-proprietary name proposed for (—)-3-hydroxy-N-phenacylmorphinan

1.6 *Metazocine* [1]

Referring to the notification from the Government of the United States of America, the Committee was of the opinion that metazocine, because it (1) produces morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered to be an addiction-producing drug comparable to morphine, and that metazocine and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addicion-Producing Drugs

RECOMMENDS that its opinion with respect to metazocine and its salts be communicated to the Secretary-General of the United Nations.

1.7 *Norlevorphanol* [2]

Referring to the notification from the Government of the United States of America, the Committee was of the opinion that norlevorphanol, because it (1) produces morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered to be an addiction-producing drug comparable to morphine, and that norlevorphanol and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to norlevorphanol and its salts be communicated to the Secretary-General of the United Nations.

1.8 *Phenazocine* [3]

Referring to the notification from the Government of the United States of America, the Committee was of the opinion that phenazocine, because it (1) produces morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered to be an addiction-producing drug compar-

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[1] International non-proprietary name proposed for 1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocine (also known as 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan)

[2] International non-proprietary name proposed for (—)-3-hydroxymorphinan

[3] International non-proprietary name proposed for 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine (also known as 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan)

able to morphine, and that phenazocine and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to phenazocine and its salts be communicated to the Secretary-General of the United Nations.

1.9 *Piminodine* [1]

Referring to the notification from the Government of the United States of America, the Committee was of the opinion that piminodine, because it (1) produces morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered to be an addiction-producing drug comparable to morphine, and that piminodine and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to piminodine and its salts be communicated to the Secretary-General of the United Nations.

2. Work of International Bodies Concerned with Narcotic Drugs

The Secretary summarized the report of the fourteenth session of the Commission on Narcotic Drugs of the Economic and Social Council; [2] the relevant resolutions of the Economic and Social Council; [3] and the latest reports of the Permanent Central Opium Board [4] and the Drug Supervisory Body.[5] Among the items of interest, some of which will be referred to later in this report, note was taken of the difficulties encountered in the international control system as a result of delays by some governments in subjecting new narcotic drugs to national control. The placing of a

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[1] International non-proprietary name proposed for 1-(3-phenylaminopropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester

[2] United Nations, Commission on Narcotic Drugs (1959) *Report of the fourteenth session (27 April - 15 May 1959) — (Economic and Social Council. Official Records: twenty-eighth session. Supplement No. 9)*, Geneva (Document E/3254 - E/CN.7/376)

[3] United Nations, Economic and Social Council (1959) *Official Records: twenty-eighth session, 30 June - 31 July 1959. Supplement No. 1: Resolutions*, Geneva, p. 9 (Document E/3290)

[4] United Nations, Permanent Central Opium Board (1958) *Report to the Economic and Social Council on the Work of the Board in 1958*, Geneva (Document E/OB/14)

[5] United Nations, Drug Supervisory Body (1958) *Estimated world requirements of narcotic drugs in 1959*, Geneva (Document E/DSB/16)

drug under national control may be the first indication to a medical practitioner that it is addiction-producing; and when a drug comes rapidly into favour for medicinal use, as was the case with dextromoramide, any delay in the recognition of its addicting potentialities enormously accentuates the public health dangers.

In connexion with the abuse of drugs, the Committee noted that statistics on addicts in different countries were based on different criteria. It would be desirable for some common basis to be found for compiling such statistics; and it might be helpful if information on addicts who come into conflict with narcotic laws or become known in some other way could be supplemented by statistics on the number of people for whom particular drugs are prescribed on a long-term basis.

The Committee noted that some of the drugs falling under international control had never been placed on the market. In some instances, it was known that producers decided not to proceed with the commercial development of a drug when a decision had been reached that it was addiction-producing. The number of such drugs may increase in the future and the inclusion of drugs of no commercial importance may result in the list of internationally controlled drugs becoming excessively long, which may be an administrative embarrassment. It would be helpful for certain purposes if the lists of controlled drugs [1, 2] could be complemented by an up-to-date list of drugs actually on the market, arranged according to their international non-proprietary or common names, for the practical use of control authorities. The list should also indicate the names under which each substance is sold and the meaning of each name in terms of base, salt or preparation. Such a list would supplement the " Multilingual list of narcotic drugs under international control " [3] until revision is possible.

The Committee noted the increasing interest in mass campaigns against opium addiction and would point out that, for the treatment of such addicts, simple methods of withdrawal are available which have proved to be successful under various circumstances.

3. Addiction Liability, Chemical Structure, and Control

In 1949, the Commission on Narcotic Drugs of the Economic and Social Council,[4] considering that varying degrees of control should be

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[1] Annex to the Permanent Central Opium Board's statistical form

[2] List of drugs under international control, published annually by the United Nations Division of Narcotic Drugs

[3] United Nations (1958) *Multilingual list of narcotic drugs under international control* (Document E/CN.7/341)

[4] United Nations, Commission on Narcotic Drugs (1950) *Report of the fourth session (16 May - 3 June 1949) — (Economic and Social Council, Official Records : ninth session. Supplement No. 9)*, Lake Success, New York, p. 61 (Document E/1361—E/CN.7/186)

applied to different classes of substances, requested the Expert Committee on Habit-Forming Drugs (as it was then named) "to furnish the Commission, at its fifth session, with definitions of the terms 'drug addiction', 'addiction-forming drugs', 'habit-forming drugs' and 'fundamental structure of an addiction-forming drug', and to illustrate such definitions by references to appropriate drugs".

A. *Definitions*

The Committee put forward draft definitions of drug addiction and habituation in its second report[1] and attempted to clarify them in its third report.[2] The definitions were revised in its seventh report.[3]

These definitions have had some acceptance and have served a useful purpose. However, in order to make them applicable to the various substances under international control, they had to include heterogeneous criteria and these criteria are difficult to interpret. Even if the definitions were re-written to be specifically descriptive of the various qualitative types of addiction, all of which involve drug-induced behavioural disturbances, some difficulties would still remain regarding their applicability to control. The fundamental criterion for control is the extent to which these drug-induced behavioural disturbances are a risk to the community.

B. *Chemical structure*

In response further to the Commission's request, the Expert Committee stated *inter alia* in its second report[4] that, in the present state of knowledge, it was not possible to say what part of the molecule of a drug was responsible for its addiction properties, but that it was known that certain drugs, having, in the main, a common structure, produced in some degree a similar addiction. At that time, examples of common structure with relation to addiction-production included the groups of which morphine, pethidine, and methadone were members. The Committee emphasized that this list was not complete and that probably new compounds of different structure would be developed, still possessing addiction-producing properties. This has since been realized, for example in dimenoxadol and certain benzimidazole derivatives.

In this connexion, it was said only a few years ago[5] that certain chemical characteristics are common to morphine-like analgesic and addiction-producing drugs. Since then, structures have become known which are

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1950, **21**, 6 (section 6)

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1952, **57**, 9 (section 6.1)

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1957, **116**, 9 (section 8)

[4] *Wld Hlth Org. techn. Rep. Ser.*, 1950, **21**, 7 (section 6.4)

[5] Eddy, N. B., Halbach, H. & Braenden, O. J. (1956) *Bull. Wld Hlth Org.*, **14**, 353

potent in both respects, but which lack one or other of the common chemical characteristics.[1]

There is, in addition, some evidence that analgesic effect and addiction liability can be modified in one substance in opposite directions, i.e., substances have been synthesized which combine strong morphine-like analgesia with a lowered addiction liability. Substances are known which are more potent than morphine in analgesic effect, in the production of morphine-like subjective effects, in the suppression of abstinence phenomena, and in the prevention of such phenomena by substitution in morphine-addicted individuals. On these accounts alone, these substances would be rated more likely to abuse and hence perhaps more dangerous than morphine. On the other hand, the abrupt withdrawal of these same substances (after substitution or direct addiction) results in a relatively mild abstinence syndrome, the only available measure of physical dependence. This evidence would indicate less liability to the development of physical dependence under conditions of prolonged administration (see Annex).

C. *Control*

It should be clear from the foregoing that the primary criterion for the establishment and degree of control is liability to abuse, resulting in risk to the community.

No definition, however descriptive, can be a complete guide to what should be controlled. Similarly, in the light of present knowledge chemical structure *per se* cannot be the sole criterion. There are certain chemical groups of drugs—e.g., the morphine, pethidine and methadone groups—one or more members of which have been shown to be addicting. Within such groups, closely similar structures must be suspect, unless and until there is convincing evidence that they are not addiction-producing. In the meantime, control measures of a provisional nature are justified.

Diverse structures are being developed which have a morphine-like action with varying degrees of addiction liability. In every case, it is necessary to assess the degree of risk to the community, based on liability to abuse, and to consider the therapeutic advantages. Then, the degree of control commensurate with the risk to the community can be established by the World Health Organization.

4. Research in the Field of Drug Addiction

The Committee has repeatedly stressed the need for research along various lines in the field of drug addiction. In order to contribute adequately to the World Health Organization's functions under the various

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[1] Eddy, N. B., (1959) *Chem. & Ind.*, **47**, 1462

international conventions controlling narcotic drugs, the Committee must have at its disposal the results of basic and applied research in this field. The Committee has had to deal repeatedly with notifications without adequate information, so that decisions have had to be deferred. At present the Committee's work depends in large measure upon the receipt of information respecting work carried out at the Addiction Research Center (United States of America) and the Department of Pharmacology of the University of Michigan (United States of America), and on the results of controlled clinical investigation, many of which are funnelled through the Committee on Drug Addiction and Narcotics of the National Research Council (United States of America). Because of their heavy workloads, these institutions, even though they have endeavoured to give priority to specific requests from the Expert Committee, have not always been in a position to furnish the Committee with the necessary information in time for it to take action as early as desirable. Thus, the preventive character of the international control measures has been hampered. In order to ameliorate this situation, means should be found to expand research activities, as outlined above, and to extend them to other parts of the world.

Moreover, the Committee emphasized again that drug addiction affects large numbers of people in many areas of the world and is, therefore, an international public health problem of great magnitude. Research in this field has not had the degree of support commensurate with its importance. The Committee therefore strongly urged that research on narcotic action and other aspects of drug addiction should be strengthened and expanded. A few of the topics on which work could profitably be enhanced or initiated include :

Basic investigations of the mechanisms of action of addicting drugs and of drug addiction, utilizing techniques from all pertinent fields, such as pharmacology, experimental psychology, biochemistry, neurophysiology ;

Epidemiology of drug addiction [1] (almost nothing has been done on this subject) ;

Controlled evaluations of programmes for treatment of drug addiction ;

Development and calibration of methods for assessing addiction liability in animals ;

Clinical evaluations of new drugs with respect to analgesic action, liability to cause side actions, and development of tolerance and physical dependence under conditions of clinical use ;

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[1] World Health Organization, Study Group on the Treatment and Care of Drug Addicts (1957) *Wld Hlth Org. techn. Rep. Ser.*, **131**

Cumulation, codification, and making available information on all aspects of drug addiction. An initial effort towards this end is represented by the work on " Coded information on narcotics ".[1]

5. Carriage of Narcotic Drugs in First-Aid Kits of Aircraft engaged in International Flight

The Committee's attention was drawn to a report[2] on the principles under which opiates or similar drugs might be used and carried in first-aid kits on board aircraft engaged in international flight and on the application of efficient safeguards against abuse. The Committee concurred with all the conclusions and suggestions except that it was of the opinion that morphine should not be given orally and that the dose to be used might be reconsidered with a view to its reduction to 10 mg per ampoule. The Committee was also of the opinion that a morphine antagonist (e.g., nalorphine) should be carried and that instruction on the indications which would warrant its use should be included in the training of authorized personnel.

6. Proposed Single Convention on Narcotic Drugs

6.1 *Schedules and scope of control*

The Committee was pleased to note that in drafting the Single Convention on Narcotic Drugs[3] attention had been given to the principle referred to in section 3 of this report, i.e., that the essential criterion for the establishment and degree of control is risk to the community. This consideration appears to be reflected in the implementation of Schedules I to IV, where variations in the degree of the control measures applied are related to differences in the risk involved with various substances.

6.2 *Schedule II*

In this connexion, the Committee wished to state that, in view of its previous conclusions and of the corresponding recommendations of the

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[1] Referred to as "Classified information on narcotics" in the ninth report of the Expert Committee on Addiction-Producing Drugs: *Wld Hlth Org. techn. Rep. Ser.*, 1959, **160**, 14

[2] Unpublished working document WHO/Av. Med./1

[3] United Nations, Commission on Narcotic Drugs. *The Single Convention on Narcotic Drugs (third draft)* (Mimeographed document E/CN.7/AC.3/9)

Director-General of the World Health Organization, the drugs norcodeine [1] and propoxyphene [2] should be listed under Schedule II.

The Committee would also point out that, with respect to substances in Schedule II, it would be better to make the exceptions referred to in paragraph 7 of Article 41 only with regard to paragraphs 1(c), 2, 4, and 5 of the same Article.

6.3 *Schedule III*

The Committee took note of resolution 5 (XIV) [3] of the Commission on Narcotic Drugs, which invited the World Health Organization to prepare a revised list of preparations exempted from international narcotics control to be included in Schedule III of the third draft of the Single Convention. It examined individually the preparations tentatively proposed for inclusion in that Schedule. This list contains all preparations which were expressly exempted under the terms of the 1925 and 1931 Conventions and all those preparations which were exempted by the Health Committee of the League of Nations under Article 8 of the 1925 Convention.

Taking into account the content of these preparations with respect to potentially addicting substances and other therapeutic agents; and taking into account also up-to-date medical knowledge and current therapeutic practice, the Committee was of the opinion that only those preparations should be retained as exempted preparations which constitute no risk to public health and from which the potentially addicting agent is not readily recoverable. With these criteria in mind, the Committee recommends that the following should be retained:

Preparations of drugs listed in Schedule II which are adapted to a normal therapeutic use;

Preparations of cocaine or morphine containing not more than 0.1% of cocaine or 0.2% of morphine and compounded with an active substance;

Dover's Powder—Austrian Pharmacopoeia VIII, 1906;

Pulvis Doveri (Pulvis Opii et Ipecacuanhae Comp.)—Deutsches Arzneibuch 6;

Pulvis Ipecacuanhae compositus (Dover's powder)—British Pharmacopoeia, 1914; British Pharmacopoeia, 1932.

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1959, **160**, 5 (section 2.3)

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1958, **142**, 7 (section 5.1.3)

[3] United Nations, Commission on Narcotic Drugs (1959) *Report of the fourteenth session (27 April - 15 May 1959) — (Economic and Social Council. Official Records: twenty-eighth session. Supplement No. 9)*, Geneva, p. 13 (Document E/3254-E/CN.7/376)

6.4 *Schedule IV*

The Committee would reiterate the opinion expressed in its ninth report [1] on the seriousness of placing a substance in Schedule IV with its absolute prohibition as now drafted. When liability to abuse is great, lack of medical need and obsolescence for other purposes could justify prohibition. In any case, very careful balancing of risks against possible therapeutic advantage should be undertaken, restricting as little as possible the availability of medicaments to physicians. Where a drug appeared to represent a particularly high danger to the community, as in the case of diacetylmorphine (heroin), relevant recommendations to prohibit or restrict legitimate use could continue to be made by the international organs concerned; but decisions thereupon should not be mandatory.

In this connexion, the Committee would refer to the repeated references to diacetylmorphine in its reports.[2, 3, 4] The Committee reaffirmed its stand on the replaceability of this dangerous addicting agent; the marked decrease in production of the drug, together with the small number of countries not prepared to suppress its use, indicates that the recommendation of the Commission on Narcotic Drugs of the United Nations Economic and Social Council [5] urging its prohibition had been very largely followed.

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1959, **160**, 12 (section 10.1)

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1956, **102**, 4 (section 3.1)

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1957, **116**, 5 (section 4.1)

[4] *Wld Hlth Org. techn. Rep. Ser.*, 1958, **142**, 5 (section 4.1)

[5] United Nations, Commission on Narcotic Drugs (1955) *Report on the tenth session (18 April - 12 May 1955) — (Economic and Social Council. Official Records : twentieth session. Supplement No. 8)*, Geneva, p. 42 (Document E/2768/Rev. 1—E/CN.7/303/Rev. 1)

Annex

AN ATTEMPT TO DISSOCIATE ANALGESIC ACTIVITY, OTHER MORPHINE-LIKE PROPERTIES, AND PHYSICAL DEPENDENCE POTENCY

Of the many compounds synthesized with this end in view, phenazocine [1] and levophenacylmorphan [2] represent a partial accomplishment. The former has an analgesic potency ten times that of morphine in mice and three to seven times that of morphine in man, depending on the route of administration and the therapeutic indication. Similarly, the ratios for levophenacylmorphan are about 25 : 1 in mice and at least 5 : 1 in man. Both compounds have a low incidence of side effects.

The addictiveness of phenazocine and levophenacylmorphan were assessed by determining :

(1) the potency of the two compounds relative to morphine in inducing morphine-like effects ;

(2) potency in suppressing symptoms of abstinence when substituted for 24 hours in patients addicted to morphine ;

(3) ability to " maintain addiction " by substituting each compound for morphine for ten days in addicted individuals and observing the nature and intensity of abstinence symptoms during substitution and following abrupt withdrawal of the test drugs ; and

(4) ability to create physical dependence (" direct addiction " experiments) by administering progressively increasing doses of phenazocine and levophenacylmorphan for periods ranging from 19 to 127 days to volunteers who were formerly morphine addicts and observing the nature and intensity of abstinence symptoms following abrupt withdrawal of the test drugs, and, in some instances, by precipitating abstinence symptoms with 2-5 mg of nalorphine.

All drugs were administered subcutaneously. Adequate control measures were taken, including placebo administration, keeping the subjects unaware of the identities of the agents being administered, and providing an environment in which the subjects could obtain no other drugs.

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[1] International non-proprietary name proposed for 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine (also known as 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan), tested as the hydrobromide under the code number NIH-7519

[2] International non-proprietary name proposed for (—)-3-hydroxy-N-phenacylmorphinan, tested as the methane sulfonate under the code number NIH-7525

Both drugs were more potent than morphine in inducing morphine-like subjective effects. One mg of phenazocine was equivalent to 3.25 mg of morphine sulfate, and 1 mg of levophenacylmorphan was equivalent to 6.1 mg of morphine. Potencies in constricting the pupils agreed well with the estimates derived from the subjective effects. Likewise, both drugs were more potent suppressors of abstinence symptoms than morphine in 24-hour substitution experiments, 1 mg of phenazocine being equivalent to 8.15 mg of morphine, and 1 mg of levophenacylmorphan being equivalent to 9.1 mg of morphine. Both drugs effectively " maintained addiction ", since symptoms of abstinence were completely suppressed during 10-day periods of substitution and definite symptoms of abstinence appeared following withdrawal of the substituted compounds. The intensity of such symptoms was, however, milder than would have been expected following withdrawal of morphine.

Both drugs created physical dependence as manifested by precipitation of definite abstinence symptoms on administration of nalorphine during " direct addiction " to either compound and by the appearance of definite symptoms of abstinence following withdrawal. While the symptoms following withdrawal of phenazocine and levophenacylmorphan were qualitatively identical with those following withdrawal of morphine, their intensity was significantly less than that of the symptoms after withdrawal of equivalent amounts of morphine. For example, in one experiment in which the same eight patients received morphine for 19-21 days on one occasion and phenazocine and levophenacylmorphan for the same period of time on two other occasions, the TAS-10 scores (measures of the mean total intensity of symptoms of abstinence over the 10-day period of observation) were 198.1 $\pm$ 16.3 [1] " point days " in the case of morphine, 151.8 $\pm$ 12.9 for phenazocine and 145.9 $\pm$ 10.8 for levophenacylmorphan.

While the aim was to separate analgesic activity from other morphine-like properties [2] and from physical dependence potency, what has been accomplished in the two compounds described is a partial dissociation of both the analgesic activity and other morphine-like properties from physical dependence potency, inasmuch as the first two properties have been increased in comparison with morphine and the third decreased. This trend indicates the possibility of greater safety, especially during prolonged administration.

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[1] Standard error of the mean

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1958, **142**, 5 (section 4.2.1)