WORLD HEALTH ORGANIZATION

TECHNICAL REPORT SERIES

No. 142

EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Eighth Report

WORLD HEALTH ORGANIZATION

PALAIS DES NATIONS

GENEVA

1958

EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Geneva, 14-19 October 1957

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This report was originally issued in mimeographed form as document WHO/APD/101, 19 October 1957.

PRINTED IN SWITZERLAND

EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Eighth Report *

The Expert Committee on Addiction-Producing Drugs met in Geneva from 14 to 19 October 1957.

The Deputy Director-General on behalf of the Director-General of the World Health Organization opened the session 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 Drug Supervisory Body. Dr N. B. Eddy was elected as Chairman, Dr L. Goldberg as Vice-Chairman and Mr J. R. Nicholls as Rapporteur.

1. Report on the Twelfth Session of the Commission on Narcotic Drugs of the United Nations Economic and Social Council [1]

The Committee had its attention drawn to many points of particular interest, some of which relate directly to items in its agenda.

A valuable report on the present position with regard to narcotic drugs has been prepared by the United Nations Secretariat.[2] It is to be noted that the comparisons between different drugs are based on usual therapeutic doses rather than on gross amounts. This gives a more precise judgement of the extent to which they are being used and hence the relative importance of their usage as one of the factors in the production of addiction.

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

The Executive Board

1. NOTES the eighth report of the Expert Committee on Addiction-Producing Drugs;
2. NOTES the action taken by the Director-General in compliance with resolution WHA7.6, as reported in document EB21/4, 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 full report to the Secretary-General of the United Nations for his information.

(Resolution EB21.R4, *Off. Rec. Wld Hlth Org.*, 1958, **83**)

[1] United Nations, Commission on Narcotic Drugs (1957) *Report to the Economic and Social Council on the twelfth session* ... (Mimeographed document E/3010—E/CN.7/333)

[2] United Nations (1957) *Survey of available information on synthetic and other new narcotic drugs* (Mimeographed document E/CN.7/319)

The Committee felt that it was pertinent to point out in this connexion, that the present practice with respect to the introduction of new drugs does not always adequately inform the medical profession on all points of advantages and disadvantages, including addiction liability. It should be the responsibility of all concerned in such introduction to avoid over-enthusiastic or possibly premature claims and to take every precaution to see that physicians are fully aware not only of effectiveness but also of any potential dangers. Only thus can be minimized incidents of medically-produced addiction which, for example, were observed particularly initially with heroin and oxycodone, and again with pethidine and ketobemidone, and seem possible to occur with *d*-3-methyl-2,2-diphenyl-4-morpholino-butyrylpyrrolidine (R 875) or other new drugs, unless necessary precautions are taken.

The Committee was fully in accord with the continuation of the search for improved narcotic drugs but thought that any subsequent introduction of a drug of this class into general medical use should be accompanied by full information on both disadvantages and advantages.

2. Resolutions of the United Nations Economic and Social Council

The Committee noted the increasing interest in the Technical Assistance Programme with respect to the drug addiction problem, as expressed in resolutions 667 (XXIV) F and G,[1] which placed emphasis on the treatment of drug addicts. Regional seminars, in the opinion of the Committee, would materially contribute to improving the present position.

3. Reports of the Permanent Central Opium Board [2] and the Drug Supervisory Body [3]

The Committee noted that the consumption of certain narcotic drugs continues to increase. In part this may be accounted for by such medical uses as are not liable to be factors in the production of addiction ; for example, supplementation of anaesthesia, obstetrical analgesia, endoscopic examinations.

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[1] United Nations, Economic and Social Council (1957) *Official records : twenty-fourth session, 2 July - 2 August 1957. Supplement No. 1 : Resolutions, Geneva*, p. 15 (Document E/3048)

[2] United Nations, Permanent Central Opium Board (1956) *Report to the Economic and Social Council on the work of the Board in 1956*, Geneva (Document E/OB/12)

[3] United Nations, Drug Supervisory Body (1956) *Estimated world requirements of narcotic drugs in 1957*, Geneva (Document E/DSB/14)

4. Morphine and its Derivatives

4.1 *Diacetylmorphine (heroin)*

The Committee noted that the relatively small residuum of licit use of diacetylmorphine was tending to be further reduced, indicating that the goal of the Economic and Social Council, the Commission on Narcotic Drugs, the Permanent Central Opium Board, the Drug Supervisory Body, and the World Health Organization, with respect to the cessation of the medical use of diacetylmorphine, was being more nearly approached.

In view of the wide range of potency (analgesic, antitussive and otherwise) represented by the large number of substances with morphine-like effect (whether chemically derived from morphine or of completely synthetic origin),[1] diacetylmorphine can be replaced by more than one drug with less risk to public health and the choice of a particular drug should be left to the discretion of the physician according to the circumstances in any individual case.

4.2 *Nalorphine*

4.2.1 *Analgesic properties*

With reference to the goal of development of a strong but non-addicting analgesic, the Committee considered recent observations on nalorphine of great interest and importance. The antagonism of nalorphine to various effects of morphine and substances with morphine-like effect is well established. The non-addicting character of nalorphine has also been recognized. Now it is reported that nalorphine is as effective as morphine for the relief of some types of clinical pain. Unfortunately, its general use as an analgesic is impractical because of the likelihood of the occurrence of disturbing side-effects, especially if the patient has been receiving other opiates. However, many compounds related to nalorphine (or to levallorphan) are known or could be developed, which exhibit wide differences in antagonistic and analgesic actions in experimental animals. It is possible that one of these may possess such a balance of properties as to constitute a practical non-addicting analgesic.

4.2.2 *Use for testing addiction*

With suitable conditions as to dose and time of administration it has been demonstrated repeatedly that nalorphine (and levallorphan) will precipitate a typical abstinence syndrome when physical dependence (addiction) on morphine or other substances with morphine-like effect is

[1] See: Eddy, N. B., Halbach, H. & Braenden, O. J. (1958) Synthetic substances with morphine-like effect. Clinical experience: potency, side-effects, addiction liability. *Bull. Wld Hlth Org.*, **17**, 569.

present. Hence such administration might be used as a tool for the diagnosis of addiction.

The Committee was of the opinion that such use of nalorphine or other antagonist could be of practical value as an aid in detecting addiction if proper safeguards are employed. Reliance should not be placed solely upon the appearance of one element of the abstinence syndrome and results should always be checked by placebo controls.

5. Synthetic Substances with Morphine-like Effect

5.1 *Synthetic substances of methadone type*

5.1.1 d-*6-Dimethylamino-4,4-diphenyl-3-heptanone* (d-*methadone*)

In its seventh report the Committee stated the conditions under which exemption could be recommended of an optical isomer whose antipode had been shown to have strong addiction-producing properties.[1] Such conditions required specific evidence on the absence of addiction liability and specific or strong presumptive evidence on the impracticability of racemization or conversion to the optical form having addiction liability. To this should be added the impracticability of conversion into any addiction-producing drug. Referring to the request of the Government of Sweden for exemption of *d*-methadone, the Committee was of the opinion that no satisfactory evidence had been produced of non-addicting properties of *d*-methadone and that some evidence was now available presumptive of its having addiction-producing properties. In addition it has been shown that the not too difficult chemical operations of reduction and acetylation could convert the drug into acetylmethadols, drugs of known addiction-producing properties already under international control. The Committee was of the opinion that exemption of *d*-methadone should not be granted. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to *d*-methadone be communicated to the Secretary-General of the United Nations.

5.1.2 *Preparation containing 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone *)*

The Committee considered a request from the Government of Italy to have the preparation " Ticarda " [2] exempted from international control

* Proposed international non-proprietary name

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1957, **116**, 6 (section 5.1)

[2] The solution for oral application contains 1% normethadone and 2% *p*-oxyphenylmethylaminopropanol; one tablet contains 7.5 mg of normethadone and 10 mg of *p*-oxyphenylmethylaminopropanol.

by application of Article 8 of the 1925 Convention. The preparation contains normethadone, a substance which has been placed in Group I of Article 1, paragraph 2, of the 1931 Convention, and in the opinion of the Committee it would be possible by simple means to recover the normethadone in spite of the other medicament present. Furthermore, cases of addiction to " Ticarda " have been reported. The Committee was of the opinion that exemption should not be granted in favour of " Ticarda ". Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to the preparation " Ticarda " be communicated to the Secretary-General of the United Nations.

5.1.3 *4-Dimethylamino-3-methyl-1,2-diphenyl-2-propionoxybutane (propoxyphene *)*

The Committee examined the request of the Government of the United States of America for reconsideration of its finding with respect to 4-dimethylamino-3-methyl-1,2-diphenyl-2-propionoxybutane (propoxyphene).[1]

Whereas it has not been shown that propoxyphene is devoid of addiction-sustaining or addiction-producing properties, although its potentiality in these respects is substantially less than that of codeine,

Whereas it is desirable to keep close watch on and to restrict carefully to medical and scientific needs the manufacture of a new substance with some narcotic properties, but strict control of such a substance at all levels may not be necessary, and

Inasmuch as the control provided in the 1931 Convention for drugs in Group II is designed for recording and supervision of manufacture and wholesale trade without restriction on retail trade,

The Committee concluded that its opinion with respect to classification and control of propoxyphene and its salts as a codeine-like substance, assimilable to the substances in Group II of Article 1, paragraph 2, of the 1931 Convention, is valid and should be maintained. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to 4-dimethylamino-3-methyl-1,2-diphenyl-2-propionoxybutane (propoxyphene) and its salts be communicated to the Secretary-General of the United Nations.

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* Proposed international non-proprietary name

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1956, **102**, 9 (section 5.2.2)

5.1.4 *3-Methyl-2,2-diphenyl-4-morpholinobutyrylpyrrolidine* [1]

Referring to the notifications from the Governments of Belgium, France and the Netherlands, the Committee was of the opinion that *d*-3-methyl-2,2-diphenyl-4-morpholinobutyrylpyrrolidine (dextromoramide,* also known as R 875), 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 an addiction-producing substance comparable to morphine, and that *d*-3-methyl-2,2-diphenyl-4-morpholinobutyrylpyrrolidine (dextromoramide) 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.

Further, the Committee was of the opinion that the principle regarding control of isomeric forms stated in its seventh report [2] should apply in the present instance. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to *d*-3-methyl-2,2-diphenyl-4-morpholinobutyrylpyrrolidine (dextromoramide) and its salts and with respect to the other isomeric forms of this substance (levomoramide and racemoramide) and their salts be communicated to the Secretary-General of the United Nations.

5.2 *Synthetic substances of pethidine type*

5.2.1 *1-(2-Morpholinoethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester (morpheridine *)*

Referring to the notification from the Government of the United Kingdom, the Committee was of the opinion that morpheridine, 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 an addiction-producing substance comparable to morphine, and that morpheridine 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 1-(2-morpholinoethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester (morpheridine) and its salts be communicated to the Secretary-General of the United Nations.

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* Proposed international non-proprietary name

[1] Proposed international non-proprietary names of the isomeric forms: racemoramide, dextromoramide and levomoramide

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1957, **116**, 6 (section 5.1)

5.2.2 *1,2,5-Trimethyl-4-phenyl-4-propionoxypiperidine (trimeperidine*)*

Referring to the notification of the Government of the Union of Soviet Socialist Republics, the Committee examined the evidence submitted and was of the opinion that trimeperidine (also known as Promedol), because it produces morphine-like effects and its use has been shown to result in a significant number of cases of addiction, must be considered an addiction-producing substance comparable to morphine and that trimeperidine 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 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine (trimeperidine) and its salts be communicated to the Secretary-General of the United Nations.

5.2.3 *1-[2-(2-Hydroxyethoxy)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester (etoxeridine*)*

Referring to the notification of the Government of France, the Committee considered that the evidence submitted indicated that etoxeridine has morphine-like properties and that supplementary tests dealing with the question of addiction were to be made. The Committee observed the chemical and pharmacological relationship between etoxeridine and pethidine and regarded these drugs as analogues such as were referred to in its first [1] and second [2] reports. In accord with the recommendation in its first report, the Committee was of the opinion that etoxeridine and its salts should be subject to the same control as pethidine (1931 Convention, Article 1, paragraph 2, Group I). Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to 1-[2-(2-hydroxyethoxy)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester (etoxeridine) and its salts be communicated to the Secretary-General of the United Nations.

5.2.4 *1-(2-Hydroxy-2-phenyl-ethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester (oxpheneridine*)*

In its sixth report [3] the Committee decided to defer its opinion with respect to oxpheneridine because the information then available was of a

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* Proposed international non-proprietary name

[1] *Off. Rec. Wld Hlth Org.*, 1949, **19**, 31 (section 8)

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1950, **21**, 3 (section 1)

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1956, **102**, 11 (section 5.4)

preliminary nature. In subsequent tests it was not possible to administer sufficiently large doses of this drug on account of its insolubility and its extremely irritating properties. In the doses applied significant addiction liability was not demonstrated. Therefore the Committee was of the opinion that at this stage oxpheneridine need not be regarded as an addiction-producing substance with morphine-like effect.

6. " Tranquilizing " Drugs

The Committee considered further information which had become available, since its last meeting, on " tranquilizing " drugs, and noted that cases of misuse are being reported with increasing frequency. This confirmed the need for governments to keep a close watch on the position, as the Committee had indicated in its seventh report.[1]

7. Coca Leaf

The Committee received a statement on the situation with respect to coca leaf chewing indicating that some amelioration may be expected. In Peru, for example, measures are being taken to restrict coca plantations and to conduct an educational programme designed to emphasize that coca leaf chewing is harmful and is not indispensable.

8. Animal Experiments for Evaluation of Addiction Liability

The Committee was informed of progress being made in developing procedures for evaluating addiction properties using monkeys (and dogs) as test objects. Satisfactory parallelism between the results with monkeys and with man has been reported on the basis of which a screening procedure is now available. This is likely to afford, at an early stage in the development of a new product, warning of the existence of particularly disadvantageous addiction-producing properties, and to make it possible to select from a group of related compounds those with the least disadvantages in this respect. Such a screening process would conserve human testing facilities for critical evaluation of substances whose entrance into clinical use is being contemplated.

The Committee recognized the progress made in this field and commended the availability of an initial screening procedure for detecting

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1957, **116**, 10 (section 10)

addiction liability. It was of the opinion, however, that tests in man continue to be a requisite for ultimate judgement of safety of new compounds which are to be introduced into general medical use.

9. Addiction Information Centre

With reference to the statement in its seventh report on the compilation and dissemination of information on drug addiction,[1] the Committee was informed that a similar effort in a related field had been initiated by the National Institute of Mental Health, USA. Inasmuch as this effort contemplates an extensive collection of the literature "including pharmacological, clinical, behavioral, and experimental studies of the ataraxic, psychotomimetic, and other centrally acting drugs",[2] some duplication of material which the Committee sought to compile would be liable to occur. Tentative negotiations to establish an Addiction Information Centre have been undertaken and, if the two services could be developed jointly, duplication of effort would be avoided.

The Committee emphasized the need for and the value of an Addiction Information Centre and hoped that the negotiations in progress would be fruitful.

10. International Non-proprietary Names

The Committee noted that the World Health Organization had informed governments of a procedure outlined in its seventh report[3] for speeding up suggestions for and selection of proposed international non-proprietary names for narcotic drugs. No objections were raised in the replies from governments and subsequent notifications indicated that the suggested procedure was being followed. The Committee thought that the limited experience so far was very encouraging.

11. Preparations Exempted from International Narcotics Control

The Committee's attention was drawn to a recapitulatory list of exempted preparations[4] and to certain anomalies therein such as the inclusion of

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1957, **116**, 11 (section 11)

[2] *Science*, 1957, **126**, 443

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1957, **116**, 11 (section 12)

[4] League of Nations, Health Organisation (1932) *Recapitulatory list of preparations exempted from the provisions of the 1925 International Opium Convention by application of Article 8 of that Convention*, Geneva (Document **C. 114. M. 54.** 1932. III)

preparations which are today virtually obsolete. The Committee considered an improvement of the list to be desirable and hoped that a suitable programme to that end could be evolved, in which it would be glad to participate.

12. Proposed Single Convention on Narcotic Drugs

The Committee was informed of the progress that had been made in drafting a single convention. It was understood that the World Health Organization had been participating in the drafting and would be invited formally to comment on a completed draft. An opportunity to make observations on the parts which are pertinent to the activities of the World Health Organization would be welcomed by the Expert Committee on Addiction-Producing Drugs.