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Fourth Report

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EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION

Fourth Session

Geneva, 22-27 June 1953

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* Attended part of the session.

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EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION

Fourth Report *

The Expert Committee on Drugs Liable to Produce Addiction held its fourth session in Geneva from 22 to 27 June 1953.

The session was opened by the Director-General, who welcomed the members and expressed the Organization's appreciation of their willingness to devote their time and energy to problems of such worldwide significance.

1. Resolutions of the United Nations Economic and Social Council

The committee noted the resolutions taken by the United Nations Economic and Social Council on 22, 27, and 28 May 1952,[1] particularly the resolution G concerning the control of synthetic narcotic drugs, in which the Council thanked WHO and other bodies concerned for the vigilance they had exercised with regard to these substances and endorsed their recommendations.[2] The committee was glad to learn that the Council had requested the Secretary-General of the United Nations to draw the attention of governments to the desirability of bringing synthetic addiction-producing drugs under national legislation (if this is not already their practice) as soon as such drugs appear.

2. General Views on Experimental and Clinical Work on Addiction-Producing Drugs

The committee referred to the statement made at its second session[3] concerning the inadequacy of medical research on drug-addiction problems. However, the committee drew attention to, and commended the

* The Executive Board, at its thirteenth session, adopted the following resolution:
The Executive Board
1. ADOPTS the fourth report of the Expert Committee on Drugs Liable to Produce Addiction;
2. THANKS the members of the committee for their work; and
3. AUTHORIZES publication of the report.
(Resolution EB13.R9, *Off. Rec. Wld Hlth Org.* **52**, 4)

[1] United Nations, Economic and Social Council (1952) *Economic and Social Council. Official Records: fourteenth session, 20 May - 1 August 1952. Resolutions. Supplement No. 1*, New York, p. 28 (Document E/2332)

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

[3] *Wld Hlth Org. techn. Rep. Ser.* 1950, **21**, 8 (section 6.5)

work done by, the Committee on Drug Addiction and Narcotics of the National Research Council, Washington, D.C., which promotes research, both governmental and private, on many aspects of addiction. At the same time, note was taken of the lack everywhere of any adequate means of ascertaining the incidence of addiction, including that arising from the legitimate medical use of potentially addicting drugs. The committee again recommended that governments be urged to consider the desirability of setting up, or adding to, facilities for investigating the various aspects of drug addiction, particularly because of the rapidly accumulating number of synthetic substances with morphine-like effect.

3. Morphine and its Derivatives

3.1 *The structure of morphine*

The committee considered at length the various proposals for the best means of characterizing the structural configuration of morphine and chemically related substances. The suggestions are essentially of two types, the one basing the structure upon the phenanthrene and the other upon the isoquinoline nucleus. Each of these is scientifically correct and feasible for particular purposes. The committee was of the opinion, however, that the characterization based on phenanthrene is preferable for classification of addiction-producing drugs, since it permits of essential differentiation between (1) morphine and chemically morphine-like alkaloids, such as those described in the 1931 Convention as " the phenanthrene alkaloids of opium ", and (2) the other opium alkaloids, papaverine, etc., which contain an isoquinoline but not a phenanthrene nucleus. Therefore,

> The Expert Committee on Drugs Liable to Produce Addiction
>
> RECOMMENDS that the procedure now in use with respect to morphine and related alkaloids, namely, their description in relation to the phenanthrene nucleus, be continued in documentation on international control of addiction-producing drugs.

3.2 *The conversion of codeine and ethylmorphine into morphine*

The committee, recognizing that some degree of conversion of codeine to morphine had been accomplished, was of the opinion that there should be no relaxation in the control of codeine, and that, in the formulation of any future agreement concerning the control of this substance, the possibility of its conversion into morphine should be taken into account.

Furthermore, it was accepted that conversion of ethylmorphine to morphine should be possible with no greater difficulty than the conversion

of codeine to morphine. Therefore, the statements with respect to control of codeine apply equally to control of ethylmorphine.

3.3 *Morphine retard preparations*

The committee noted the many efforts that have been, and are being, made to prepare morphine for therapeutic use in a form which will prolong its effectiveness. It recognized the desirability of such an objective, if it can be achieved with safety, but was of the opinion that the various means employed to bring about this result in no way affect the essential addiction liability of the morphine component. Therefore, the committee concluded that preparations of this type must be handled and controlled in all respects exactly as are other preparations of morphine.

3.4 *Situation regarding diacetylmorphine (heroin)*

The committee was gratified to learn of the action taken by the Sixth World Health Assembly in passing without dissent a resolution concerning the medical use of diacetylmorphine (heroin).[4] The committee was in complete accord with the principles set forth in this resolution, since they bring to a focus the recommendations made by the committee at its previous sessions concerning the abolition of diacetylmorphine from medical practice. The committee therefore expressed the hope that means would be found to implement this resolution speedily.

3.5 N-*Allylnormorphine and analogous compounds*

The committee considered the notification of the Government of the USA with respect to *N*-allylnormorphine (nalorphine) and again reviewed the information available with respect to the activity and addiction liability of this drug.[5] When administered alone, nalorphine produces dysphoria rather than euphoria and has not caused the appearance of tolerance or physical dependence. It will not relieve the abstinence syndrome nor sustain a morphine addiction, but will precipitate abstinence phenomena if physical dependence on morphine or a morphine-like drug has been established. When administered with morphine, nalorphine seems to attenuate the development of physical dependence.

The committee also considered the conversion of nalorphine into a drug capable of producing addiction. Such a conversion, although possible, is so difficult, and the yield is so small, that it is impracticable and constitutes no risk to public health.

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[4] *Off. Rec. Wld Hlth Org.* **48**, 22, Resolution WHA6.14

[5] *Wld Hlth Org. techn. Rep. Ser.* 1952, **57**, 4 (section 3.2), 13

The committee was of the opinion that nalorphine cannot be considered either to be an addiction-producing drug or to be capable of conversion into an addiction-producing drug for the purposes of the Convention of 13 July 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, as amended by the Protocol signed on 11 December 1946. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with respect to *N*-allylnormorphine (nalorphine) be communicated to the Secretary-General of the United Nations.

The committee considered further the notification of the Government of the USA with respect to diacetyl-*N*-allylnormorphine. On the basis of the information available, the committee concluded that the position of this substance was analogous to that of *N*-allylnormorphine.

3.6 *6-Methyl-Δ^6-desoxymorphine*

Referring to the notification of the Government of the USA, the committee was of the opinion that 6-methyl-Δ^6-desoxymorphine, because it (1) produces morphine-like effects, (2) will suppress the abstinence phenomena of a known morphine addiction, and (3) will sustain a morphine addiction, must be considered an addiction-producing drug comparable to morphine, and that 6-methyl-Δ^6-desoxymorphine 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, Sub-group (*a*). Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with respect to 6-methyl-Δ^6-desoxymorphine and its salts be communicated to the Secretary-General of the United Nations.

4. Synthetic Substances with Morphine-like Effect

4.1 *General aspects*

The committee referred to the point of view expressed in the report of its first session [6] that compounds having a similar chemical configuration and belonging to the same chemical group as others whose addiction liability is already known must be suspected of having addiction-producing properties until the contrary be proved.

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

The committee confirmed this view and considered that governments should watch these compounds with extreme care and take appropriate action immediately on the discovery of addiction-producing properties in any one of them, as requested by resolution 436 (XIV) G of 27 May 1952 of the Economic and Social Council.[7]

4.2 *Synthetic substances of methadone type*

Referring to the notification of the Government of the USA, the committee was of the opinion that

α-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane (alpha-acetylmethadol),

α-6-dimethylamino-4,4-diphenyl-3-heptanol (alpha-methadol), and

β-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane (beta-acetylmethadol),

because of the evidence, submitted with the notification, that they (1) produce morphine-like effects, (2) suppress abstinence phenomena of a known morphine addiction, and (3) sustain a morphine addiction, must be considered addiction-producing drugs comparable to morphine. These substances and their salts should accordingly 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 Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with respect to α-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane (alpha-acetylmethadol), α-6-dimethylamino-4,4-diphenyl-3-heptanol (alpha-methadol), and β-6-dimethylamino-4,4-diphenyl-3-acetoxyheptane (beta-acetylmethadol), and their salts, be communicated to the Secretary-General of the United Nations.

Furthermore, the committee referred to the notification of 15 February 1952 from the Director-General of WHO to the Secretary-General of the United Nations, in which it was stated that

4,4-diphenyl-6-dimethylaminoheptanol-3 (otherwise known as 6-dimethylamino-4,4-diphenyl-3-heptanol) and

4,4-diphenyl-6-dimethylamino-3-acetoxyheptane (otherwise known as 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane)

are capable of producing addiction and should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, para-

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[7] United Nations, Economic and Social Council (1952) *Economic and Social Council. Official Records : fourteenth session, 20 May - 1 August 1952. Resolutions. Supplement No. 1*, New York, p. 32 (Document E/2332)

graph 2, Group I. The committee reiterated the decision set forth in the Director-General's notification and stated that, in its opinion, the above chemical names in that notification, as well as the respective trivial names, methadol and acetylmethadol, included the optical and other stereoisomers of compounds so designated.

The committee took note of information presented in regard to a preparation which is stated to be, in fact, a mixture of the hydrochlorides of 6-dimethylamino-4,4-diphenylhexanone-3 (a substance very closely related to methadone and differing from it only in the absence of one methyl group) and *p*-oxyphenylmethylaminopropanol. Tests on the addiction liability of this mixture, as well as of its methadone-like component, are to be undertaken; but the committee wished to point out that this preparation is of the type referred to in section 4.1 of this report. Consequently, it should be suspected of having addiction-producing liability until specific evidence becomes available.

4.3 *Synthetic substances of morphinan type*

The committee considered the evidence on the addiction liability and possible clinical usefulness of the dextrorotatory isomer of 3-hydroxy-*N*-methylmorphinan (dextrorphan), and the dextrorotatory isomer of 3-methoxy-*N*-methylmorphinan (dextromethorphan), which is the methyl ether of the former compound. It was concluded that each of these compounds had been demonstrated (1) to have no morphine-like action, (2) to lack ability to sustain a morphine addiction, and (3) to have exhibited no signs of addiction liability. Further, although some transformation of dextromethorphan (or dextrorphan) into a product with some analgesic activity is possible, this is sufficiently difficult, and the yield is so small, for it to be regarded as impracticable and to constitute no risk to public health. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

Having considered the request of the Swiss Government to have dextrorphan and dextromethorphan exempted from the obligations of the international conventions on narcotic drugs,

IS OF THE OPINION that such exemption should be granted in accordance with Chapter 1, Article 3, of the 1948 Protocol, and

RECOMMENDS that this opinion be notified to the Secretary-General of the United Nations.

The committee confirmed its opinion, formulated in its third report,[8] that racemorphan, racemethorphan, levorphan, and levomethorphan are

[8] *Wld Hlth Org. techn. Rep. Ser.* 1952, **57**, 6, 7 (sections 4.1.1 and 4.1.2)

addiction-producing substances. It emphasized the probable necessity for special precautionary measures, particularly with respect to the laevorotatory isomers, if one or another of the dextrorotatory isomers comes into general use in place of codeine, because the procedure for making the dextrorotatory isomer involves the simultaneous production of an equivalent amount of the laevorotatory isomer.

4.4 *Dithienylbutenylamines*

Referring to the notification of the Government of the USA, the committee was of the opinion that

3-dimethylamino-1,1-di-(2′-thienyl)-1-butene and

3-ethylmethylamino-1,1-di-(2′-thienyl)-1-butene,

because they (1) produce morphine-like effects, (2) will suppress abstinence phenomena of a known morphine addiction, (3) will sustain a morphine addiction, and (4) will cause the development of a morphine-like addiction, must be considered as addiction-producing substances comparable to morphine, and that these substances and their 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 Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with respect to 3-dimethylamino-1,1-di-(2′-thienyl)-1-butene and 3-ethylmethylamino-1,1-di-(2′-thienyl)-1-butene, and their salts, be notified to the Secretary-General of the United Nations.

The attention of the committee was drawn to a third dithienyl derivative, 3-diethylamino-1,1-di-(2′-thienyl)-1-butene, now being marketed for use in veterinary medicine. This compound has been shown to be so closely similar in its pharmacological properties to the dithienyl derivatives referred to above that, in the opinion of the committee, 3-diethylamino-1,1-di-(2′-thienyl)-1-butene must also be considered as having addiction liability. Furthermore, the committee was of the opinion that the closest watch should be kept upon the development of new dialkyl-dithienylamines because those so far examined are so closely similar in their properties as to make the group of dialkyl-dithienylamines as a whole suspect with respect to addiction-producing properties.

5. International Non-Proprietary Names

The committee noted the progress made in the procedure for selection of international non-proprietary names. It desired to emphasize the need

for selecting such names for those substances which will come under international control, if possible, at least as soon as such control is instituted. It suggested that the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations should be requested to consider, in all its aspects, the question of the speedy selection of non-proprietary names for addiction-producing substances.

A list of proposed international non-proprietary names for addiction-producing drugs is given in Annex 1 (see page 12).

6. Mastication of the Coca Leaf

The committee considered again the problem of coca chewing and had drawn to its attention evidence on the absorption of cocaine during the chewing process. It was pointed out that there is a wide variation from individual to individual in the amount of cocaine ingested by the coca chewers, just as there is among individuals who take the pure alkaloid for non-medical purposes. The term cocainism is applicable to the latter and, in the opinion of the committee, coca chewing (cocaism) must be considered a form of cocainism.

The present statement in no way modifies the opinion expressed in the third report.[9]

7. Cannabis sativa L.

The committee was pleased to note that the elimination of cannabis preparations had already begun by national action, following the opinion expressed in its third report that " there is no justification for the medical use of cannabis preparations ".[10]

The committee expressed its agreement with the action taken by the Commission on Narcotic Drugs at its eighth session to the effect that the term " Indian hemp " should be replaced by the term " cannabis ", as proposed by the representative of the World Health Organization.[11] Furthermore, it was of the opinion that the definitions for cannabis and its preparations should be revised on the basis of the presence of active principles.

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[9] *Wld Hlth Org. techn. Rep. Ser.* 1952, **57**, 10 (section 6.2)

[10] *Wld Hlth Org. techn. Rep. Ser.* 1952, **57**, 11 (section 7)

[11] United Nations, Economic and Social Council (1953) *Economic and Social Council. Official Records : sixteenth session. Supplement No. 4. Commission on Narcotic Drugs : report of the eighth session (30 March to 24 April 1953)*, New York, p. 16, paragraph 181 (document E/2423-E/CN.7/262)

8. Amphetamine and Derivatives

The committee's attention was again drawn to cases of abuse of amphetamine preparations.[12] It was concluded that the situation now warrants a recommendation regarding control of these substances and that this should follow the lines previously suggested for the barbiturates.[13] Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

IS OF THE OPINION that it is advisable to take measures to strengthen the control over amphetamine and its derivatives on the national level. Such measures might include :

(1) preparations of amphetamine and its derivatives should be dispensed only on prescription ;

(2) each prescription should specify the number of times it may be refilled or repeated ;

(3) a careful record should be kept of each prescription.

9. Substances which may create Habituation

The committee took cognizance of a memorandum " Do the synthetic antihistaminics produce habituation ? " [14] It was concluded that at present the committee's attitude should be one of careful watchfulness towards future developments in this field as in many others.

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[12] Joachimoglu, G., unpublished working document WHO/APD/35 ; see also *Wld Hlth Org. techn. Rep. Ser.* 1952, **57**, 11 (section 9).

[13] *Wld Hlth Org. techn. Rep. Ser.* 1952, **57**, 11 (section 8)

[14] Lorenzo-Velázquez, B., unpublished working document WHO/APD/37

Annex 1

NON-PROPRIETARY NAMES FOR INTERNATIONALLY CONTROLLED ADDICTION-PRODUCING DRUGS

The following international non-proprietary names have been proposed for addiction-producing drugs under international control:

Oxycodone	for	dihydro-oxycodeinone (Eucodal, etc.)
Hydrocodone	,,	dihydrocodeinone (Dicodide, etc.)
Hydromorphone	,,	dihydromorphinone (Dilaudid, etc.)
Metopon	,,	7-methyldihydromorphinone
Pethidine	,,	1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester (Demerol, Dolantin, Isonipecaine, etc.)
Ketobemidone	,,	4-(3-hydroxyphenyl)-1-methyl-4-piperidyl ethyl ketone (Cliradon, etc.)
Alphaprodine	,,	α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine (Nisentil, etc.)
Methadone	,,	4,4-diphenyl-6-dimethylaminoheptanone-3 (Physeptone, Polamidon, etc.)
Isomethadone	,,	4,4-diphenyl-5-methyl-6-dimethylaminohexanone-3 (not on the market)
Phenadoxone	,,	4,4-diphenyl-6-morpholinoheptanone-3 (Heptalgin, etc.)
Levorphan	,,	L-3-hydroxy-*N*-methylmorphinan } both known as Methorphinan, Dromoran
Racemorphan	,,	DL-3-hydroxy-*N*-methylmorphinan }
Levomethorphan	,,	L-3-methoxy-*N*-methylmorphinan } neither yet available in trade
Racemethorphan	,,	DL-3-methoxy-*N*-methylmorphinan }