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EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION

Third Report

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EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION

Third Session

Geneva, 7-12 January 1952

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Secretary :

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The report on the third session of this committee was originally issued in mimeographed form as document WHO/APD/33, 12 January 1952.

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* Indicates member who attended part of the session.

EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION

Third Report [1]

The Expert Committee on Drugs Liable to Produce Addiction held its third session in Geneva from 7 to 12 January 1952.

The Director-General, in opening the third session, referred to the results already achieved by the committee and the important work remaining to be done by it. He underlined the worldwide scope of this task and the decisive role the experts play in this respect.

The Director of the Division of Therapeutic Substances stressed the importance of the committee's deliberations from the point of view of the clinical and public-health aspects of the drug-addiction problem.

1. Commission on Narcotic Drugs of the Economic and Social Council

The committee received with appreciation the commendatory statement of the Commission on Narcotic Drugs at its fifth session [2] concerning the work done on drug addiction at its request, which the Economic and Social Council of the United Nations had noted on 27 February 1951 at its twelfth session.[3]

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[1] The Executive Board, at its ninth session, adopted the following resolution:

The Executive Board

1. ADOPTS the report of the Expert Committee on Drugs Liable to Produce Addiction on its third session;
2. THANKS the members of the committee for their work;
3. AUTHORIZES publication of the report, and
4. REQUESTS the Director-General again to ask those States which have not yet answered his first inquiry regarding diacetylmorphine, and those which do not yet consider it possible to discontinue its medical use, whether or not they can do without the drug in the interest of international public health and safety, particularly in view of the fact that the physicians of so many countries consider that there are other substances which are satisfactory substitutes for diacetylmorphine.

(Resolution EB9.R96, *Off. Rec. World Hlth Org.* **40**, 34)

[2] United Nations, Economic and Social Council (1950) *Economic and Social Council. Official Records: twelfth session. Supplement No. 2. Commission on Narcotic Drugs: report of the fifth session (1-15 December 1950)*, New York, p. 21 (Document E/1889/Rev.1—E/CN.7/216/Rev.1)

[3] United Nations, Economic and Social Council (1951) *Economic and Social Council. Official Records: twelfth session. 20 February - 21 March 1951. Supplement No. 1. Resolutions*, New York, p. 12 (Resolution 355 (XII) A) (Document E/1987)

2. Request from the Swiss Government regarding Ipecopan Preparations

The committee noted the request of the Swiss Government of 2 October 1951 to reconsider the opinion expressed at the second session of the committee [4] regarding the position of Ipecopan and its commercial preparations under the provisions of the 1925 Convention. It was understood that the new request from the Swiss Government referred specifically to the following preparations: Ipecopan malted tablets, Ipecopan solution, Ipecopan malted syrup, Ipesandrine sugar-coated tablets, Ipesandrine solution, Ipesandrine syrup.

These preparations contain less than 0.2% anhydrous morphine compounded with other medicaments; furthermore, evidence was presented that separation of morphine from these preparations is not practicable.

The committee reaffirmed its opinion that Ipecopan powder should not be exempted from the provisions of the 1925 Convention for the reason stated in the report on its second session, but expressed the opinion that such exemption should be granted for the preparations mentioned which contained not more than 0.2% anhydrous morphine compounded with other medicaments. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinions with respect to Ipecopan and its commercial preparations be notified to the Economic and Social Council of the United Nations.

3. Morphine Derivatives

3.1 *6-Methyldihydromorphine*

The committee received additional information with respect to this substance which confirmed its previously expressed opinion [5] that it must be classified as an addiction-producing drug.

3.2 N-*Allylnormorphine*

The committee received information on the antagonistic action of *N*-allylnormorphine to the analgesic, respiratory, and other effects of morphine and pharmacologically morphine-like substances, and on the possibility of its clinical employment for such antagonistic action against overdosage of morphine or morphine-like substances and against foetal

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[4] *World Hlth Org. techn. Rep. Ser.* 1950, **21**, 4

[5] *World Hlth Org. techn. Rep. Ser.* 1950, **21**, 5

respiratory depression which may occur with the use of morphine or morphine-like substances in obstetrics. Information on its action in addicted and previously addicted individuals was also received, leading to the conclusion that liability to its use by addicts is very slight.[6]

3.3 *Dihydrocodeine and acetyldihydrocodeine*

The committee stated that its previously expressed opinion [7] with respect to the addiction liability of these substances is equally applicable to all their salts. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

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

3.4 *Morpholinylethylmorphine* [8]

The committee noted the request of the French Government for re-examination of morpholinylethylmorphine, in the light of fresh information on its addiction liability and its convertibility into an addiction-producing drug.

The committee expressed the opinion that morpholinylethylmorphine is not more liable than codeine to produce addiction and is therefore not assimilable to the drugs mentioned in Article 1, paragraph 2, Subgroup (a) of Group I of the 1931 Convention, and that it is less readily convertible than codeine to an addiction-producing drug and is, in consequence, assimilable to the drugs mentioned in Group II of that Convention. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

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

3.5 *Situation regarding diacetylmorphine*

The committee reiterated its opinion as expressed in its previous reports [9] with respect to the continuing gravity of the diacetylmorphine situation.

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[6] See Annex 1, page 13.

[7] *World Hlth Org. techn. Rep. Ser.* 1950, **21**, 4

[8] Previously described as morpholylethylmorphine; chemically β-4-morpholinyl-ethylmorphine or β-morpholinoethylmorphine. See also *World Hlth Org. techn. Rep. Ser.* 1950, **21**, 4.

[9] *Off. Rec. World Hlth Org*, **19**, 31; *World Hlth Org. techn. Rep. Ser.* 1950, **21**, 5

Concerning the request for information circulated to governments by the Director-General of WHO, it is now possible to state that there are 50 Member States of WHO who have discontinued, or are willing to discontinue, the medical use of diacetylmorphine. The committee was gratified by this evidence of changing attitude on the part of the medical profession of many countries in favour of the dispensability of diacetylmorphine inasmuch as at the time of its first session, held in January 1949, so far as was known there were only 24 countries which had discontinued the medical use of the drug.

The committee was of the opinion that the complete abolition of legally produced diacetylmorphine in the world would greatly facilitate the struggle against illicit use of this substance. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that the Executive Board of the World Health Organization should take steps to approach again those states which have not yet answered the first inquiry of the Director-General, or who do not yet consider it possible to discontinue the medical use of diacetylmorphine, asking them whether or not they could do without the drug in the interest of international public health and safety, particularly in view of the fact that the physicians of so many countries find other agents equally satisfactory for symptomatic relief.

4. Synthetic Substances

4.1 *Synthetic derivatives of morphinan type*

4.1.1 *3-Hydroxy-*N*-methylmorphinan.* The committee was of the opinion that 3-hydroxy-*N*-methylmorphinan, because it (1) produces morphine-like euphoria, (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 3-hydroxy-*N*-methylmorphinan 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.[10] Therefore,

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[10] The committee noted the fact that the racemic form of 3-hydroxy-*N*-methylmorphinan has been marketed in one country, and the laevo-rotatory form in another, under the same trade name Dromoran. The dosage of these two substances being in the proportion of 5 to 2, the committee would draw attention to the confusion that must arise from this situation and to the great danger for therapeutic use should both substances become available under the same name in the same country.

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with respect to 3-hydroxy-*N*-methylmorphinan and its salts be communicated to the Secretary-General of the United Nations.

4.1.2 *3-Methoxy*-N-*methylmorphinan*. The committee was of the opinion that 3-methoxy-*N*-methylmorphinan, because it (1) produces morphine-like euphoria, (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 3-methoxy-*N*-methylmorphinan 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 Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with respect to 3-methoxy-*N*-methylmorphinan and its salts be communicated to the Secretary-General of the United Nations.

4.2 *Synthetic derivatives of pethidine type*

4.2.1 *β-1-Methyl-3-ethyl-4-phenyl-4-propionoxypiperidine (otherwise known by the symbol NU-1932)*. The committee was of the opinion that this substance, and its salts, must be considered as liable to produce addiction and 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 β-1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine and its salts be communicated to the Secretary-General of the United Nations.

4.2.2 The committee stated that its previously expressed opinion [11] with respect to the addiction liability of the following substances is equally applicable to all their salts (chemical names used at the first session of the committee are given in square brackets):

1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester (pethidine)

1-methyl-4-(3-hydroxyphenyl)-piperidine-4-carboxylic acid ethyl ester [1-methyl-4-metahydroxyphenyl-piperidine-4-carboxylic acid ethyl ester] (bemidone)

α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine

β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine

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[11] *Off. Rec. World Hlth Org.* **19**, 30

4-(3-hydroxyphenyl)-1-methyl-4-piperidyl ethyl ketone [1-methyl-4-metahydroxyphenyl-4-propionyl-piperidine] (keto-bemidone).

Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinion be communicated to the Secretary-General of the United Nations.

4.3 *Synthetic derivatives of methadone type*

4.3.1 The committee stated that its previously expressed opinion [12] with respect to the addiction liability of the following substances is equally applicable to all their salts (chemical names used at the first session of the committee are given in square brackets):

4,4-diphenyl-6-dimethylaminoheptanone-3 [6-dimethylamino-4,4-diphenyl-3-heptanone] (methadone)

4,4-diphenyl-5-methyl-6-dimethylaminohexanone-3 [6-dimethylamino-5-methyl-4,4-diphenyl-3-hexanone] (*iso*-methadone)

4,4-diphenyl-6-dimethylaminoheptanol-3 [6-dimethylamino-4,4-diphenyl-3-heptanol]

4,4-diphenyl-6-dimethylamino-3-acetoxyheptane [6-dimethylamino-4,4-diphenyl-3-acetoxyheptane]

4,4-diphenyl-6-morpholinoheptanone-3 [6-morpholino-4,4-diphenyl-3-heptanone] (phenadoxone).

Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinion be communicated to the Secretary-General of the United Nations.

4.3.2 *Methadols and acetylmethadols.* The committee noted a report on the methadols and acetylmethadols which can be derived from methadone and its isomers. Sharp differences in the intensity and duration of action of these various derivatives were noted, particularly with respect to oral and parenteral administration. There is evidence that some members of the group are liable to produce addiction. The committee concluded, therefore, that because of their close similarity of structure and action probably all these methadols and acetylmethadols have to be considered as drugs liable to produce addiction.

4.3.3 *Combination of addiction-producing drugs with atropine.* The committee noted a statement that the inclusion of an atropine-like substance in methadone preparations decreases the liability of addiction to methadone.

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[12] *Off. Rec. World Hlth Org.* **19**, 30

There is no clear evidence that the addition of an atropine-like substance to morphine and related drugs has such an effect. The committee, therefore, was of the opinion that preparations containing methadone and atropine or an atropine-like substance are liable to produce addiction like preparations of methadone itself and must be similarly controlled.

4.4 *Dithienylbutylamines*

The committee received information with respect to compounds of this type (a new synthetic group of potential analgesics of which 3-diethylamino-1,1-di-(2'-thienyl)-but-1-ene is an example) indicating that such compounds produce some morphine-like effects. Experiments with this group are continuing and a definite opinion as to their addiction liability cannot be expressed at this time.

5. Morphine Assay in Opium

The proposal had been made that the search for a better assay method should be taken up by WHO, in continuance of the studies undertaken on this subject by the Health Organization of the League of Nations. However, some work along these lines is already being done by the Division of Narcotic Drugs of the United Nations, and the committee was of the opinion that duplication of effort should be avoided.

6. Definitions Formulated during the Second Session of the Committee [13]

6.1 *General discussion of the definitions*

After two years' experience with the definitions propounded at its second session, the committee reiterated its opinion that a distinction can and must be made between drug addiction and habituation (habit), and between addiction-producing and habit-forming drugs, that the terms are not interchangeable, and that only the expressions drug addiction and addiction-producing drugs should be used in documentation with respect to substances brought under, or to be brought under, international control. The committee decided, further, to clarify the distinction between addiction and habituation (habit) by the following statement:

The cycle of administration leading to addiction may begin in legitimate medical use but becomes established as a serious problem through self-administration beyond medical need. In the development of addiction there is an interplay between pharmacological action and the psychological make-up of the individual.

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[13] See *World Hlth Org. techn. Rep. Ser.* 1950, **21**, 6.

There are some drugs, notably morphine and pharmacologically morphine-like substances, whose specific pharmacological action, under individual conditions of time and dose, will always produce compulsive craving, dependence, and addiction in any individual. Addiction will develop sooner in those individuals whose psychological make-up leads them to seek and find escape in the pharmacological action of drugs. Sooner or later there must come a time when the use of the drug cannot be interrupted without significant disturbance, always psychic (psychological) and sometimes physical. With these drugs pharmacological action is paramount, psychological make-up adjuvant. Such drugs cause individual and sociological damage and must be rigidly controlled.

There are other drugs which never produce compulsive craving, yet their pharmacological action is found desirable to some individuals to the point that they readily form a habit of administration, an habituation. Administration of such drugs can be interrupted without significant disturbances. With them psychological make-up is paramount, pharmacological action adjuvant. They cause no sociological damage and do not need rigid control.

There are some drugs whose pharmacological action is intermediate in kind and degree between the two groups already delineated so that compulsive craving, dependence, and addiction can develop in those individuals whose psychological make-up leads them to seek and find an escape in drugs. With these substances psychological make-up is the determining factor but pharmacological action plays a significant role. In some instances individual and sociological damage may develop, but since the incidence of the damage is not general, the type and degree of control of drugs of this group are better left at present to national consideration.

6.2 *Consideration of the use of the definitions in the Report of the Commission of Enquiry on the Coca Leaf*[14]

The Report of the Commission of Enquiry on the Coca Leaf clearly shows that coca chewing is detrimental to the individual and to society. The committee, therefore, was of the opinion that coca chewing comes so closely to the characteristics of addiction as defined at its second session that it must be defined and treated as an addiction, in spite of the occasional absence of some of those characteristics.

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[14] United Nations, Economic and Social Council (1950) *Economic and Social Council. Official Records. Fifth year : twelfth session. Special supplement No. 1. Report of the Commission of Enquiry on the Coca Leaf, May 1950*, Lake Success, N.Y., p. 31 (Document E/1666—E/CN.7/AC.2/1)

7. Cannabis sativa L.

The question of justification of the use of cannabis preparations for medical purposes was discussed by the committee. It was of the opinion that cannabis preparations are practically obsolete. So far as it can see, there is no justification for the medical use of cannabis preparations.

8. Barbiturates

The committee reviewed the situation with respect to the use and abuse of barbiturates throughout the world and the effects of chronic intoxication from these substances.[15] In consequence, the committee was of the opinion that the barbiturates must be considered drugs liable to produce addiction, dangerous to public health, although differentiation among them with respect to the intensity of this liability cannot be made at this time. 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 these substances on the national level. Such measures might include:

(1) barbiturates 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. Amphetamine and Derivatives

The committee would again draw attention to the abuse of amphetamine [16] and its methyl derivative (known under names such as desoxyephedrine and pervitin). It appears that these substances are commonly abused by addicts when morphine or morphine-like substances are not available to them. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

IS OF THE OPINION that a close watch should be kept on the use of the amphetamine group of compounds so that appropriate measures for their control may be taken if such become necessary.

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[15] See also *World Hlth Org. techn. Rep. Ser.* 1950, **21**, 9.

[16] See *Off. Rec. World Hlth Org.* **19**, 31.

10. International Non-Proprietary Names for Drugs Liable to Produce Addiction

The committee was informed by the Secretary of the Subcommittee on Non-Proprietary Names of the Expert Committee on the International Pharmacopoeia of the mechanism for selection of names on the international level, and it discussed ways in which the process would be most expeditious in regard to drugs liable to produce addiction.[17] The committee was of the opinion that a common name for a drug liable to produce addiction which may be brought under international control should be selected at the earliest possible moment. The committee, therefore, recommended that all agencies concerned be invited to inform WHO as early as possible concerning drugs which may be addiction-producing. The committee was gratified to learn that the Permanent Central Opium Board and the Drug Supervisory Body employ, in all their documents, the non-proprietary names already selected by WHO for drugs liable to produce addiction, and that the Board is urging all governments to employ these names whenever possible.

11. Miscellaneous

11.1 *Acknowledgments*

The committee acknowledged the collaboration of Dr. Harris Isbell, Public Health Service Hospital, Lexington, Kentucky, USA, and Dr. Lyndon Small, National Institutes of Health, Bethesda, Maryland, USA, in the supply of information based on their significant clinical and experimental investigations, which has greatly facilitated the work of this session.

11.2 *Fourth Session of the Expert Committee on Drugs Liable to Produce Addiction*

The committee was of the opinion that its future work would be greatly facilitated if it could inspect the set-up for research on drug addiction at the Public Health Service Hospital, Lexington. It recommends, therefore, that its fourth session be held in the United States of America, and that arrangements be made to visit the above-mentioned hospital.

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[17] See also *Off. Rec. World Hlth Org.* **19**, 32; *World Hlth Org. techn. Rep. Ser.* 1950, **21**, 3.

Annex 1

N-ALLYLNORMORPHINE [1]

On the basis of published work and work in progress *N*-allylnormorphine antagonizes the analgesic, respiratory, and other effects of morphine and morphine derivatives, of methadone and *iso*-methadone, and of pethidine. Its dose for antagonistic action is of the order of one part of *N*-allylnormorphine to ten parts of morphine or morphine-like agent. It has been used successfully to treat overdosage with morphine and methadone in man and to combat respiratory depression in both rabbit and human foetuses due to administration, to the mother, of substances with morphine-like action. It is being proposed as an antagonist to narcotic overdosage in clinical practice and it may have great practical value by increasing the safety (for the foetus) of the use of morphine-like agents in obstetric analgesia.

Administered to humans during stabilization on morphine in an established addiction, *N*-allylnormorphine promptly precipitates a typical abstinence picture. The same is true in animals and this particular effect can be shown after as little as a week's addiction. Practically, the drug may be a very useful tool and greatly shorten the time necessary to obtain a preliminary idea concerning the physical dependence liability of new drugs. Administered during withdrawal of morphine, *N*-allylnormorphine intensifies the abstinence syndrome. Administered repeatedly to post-addicts in an attempt to produce a direct addiction, doses of only 100 to 130 mg per day could be reached. The men showed some evidence of sedation, did not "coast" (the phenomenon of alternating somnolence and wakefulness), and their pupils were constricted. All complained of constipation and stated throughout that the effects of the drug were not those which they desired. Yet they neglected their appearance and ceased most productive activity as in morphine addiction. They complained of visual hallucinations and disturbing, frightening dreams. Upon abrupt withdrawal there were no signs of abstinence over a period of ten days.

There seems to be no likelihood of the use of this compound by addicts, and its addiction liability must be very slight.

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[1] Note submitted by Dr. N. B. Eddy.

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