World Health Organization
Technical Report Series
No. 21

EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION

Report on the Second Session

Geneva, 9-14 January 1950

WORLD HEALTH ORGANIZATION
PALAIS DES NATIONS
GENEVA
MARCH 1950

EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION

Second Session

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Secretary :

Dr P. O. Wolff, Chief, Addiction-producing Drugs Section, WHO

The report on the second session of this committee was originally issued in mimeographed form as document WHO/HFD/20, 16 January 1950.

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* Indicates member unable to attend.

EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION*

Report on the Second Session[1]

1. Resolutions of the Economic and Social Council of 6 July 1949

The committee took note of the resolutions of the Economic and Social Council at its meeting of 6 July 1949 and wished to express its appreciation that the Economic and Social Council requested "the Secretary-General to transmit to all Governments the recommendation of the Expert Committee of the World Health Organization that each Government should endeavour to apply at the earliest possible moment provisions whereby drugs of a particular chemical type, analogues of which have been proved to be habit-forming (for example, analogues of dolantin and amidone), could be placed under control until such time as they have been shown not to be habit-forming."[2]

2. Common Names of Drugs subject to Control

The committee heard a statement by the secretary of the Expert Committee on the Unification of Pharmacopoeias, which included a description of the procedure for the selection of common names and the principles which were being proposed for the guidance of that committee

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* Formerly entitled "Expert Committee on Habit-Forming Drugs"; see page 10 and footnote 15.

[1] The Executive Board, at its fifth session, adopted the following resolutions:

The Executive Board

DECIDES that the following note shall be appended to all expert committee reports examined at the fifth session of the Board:

The Executive Board NOTES the report and AUTHORIZES its publication; taking into account the recommendations of the expert committee in considering relevant items on its agenda, TRANSMITS the present report to the Third World Health Assembly; and POINTS OUT that recommendations of expert committees which concern WHO policy and operations remain recommendations unless and until they are implemented by the Executive Board or the World Health Assembly in adopting and putting into action the annual programme of WHO.

The Executive Board ...

ADOPTS the report of the Expert Committee on Drugs Liable to Produce Addiction; and

AUTHORIZES its publication.

[2] See resolution 246 (IX) G, 6 July 1949, of the Economic and Social Council of the United Nations. *Economic and Social Council. Official Records: Fourth Year, Ninth Session. Supplement No. 1. Resolutions*, page 57.

in this activity. The committee considered these principles and expressed approval of their appropriateness, particularly with respect to the problem of terminology of drugs subject to control.

3. Request from the Swiss Government Regarding "Ipecopan"

The question whether the preparation "ipecopan" should be exempted from the provisions of the 1925 Convention was discussed, special stress being laid on the alkaloidal content of its present composition. It was the committee's opinion that, in as much as this preparation contains a morphine salt equivalent to 37% of anhydrous morphine, the recovery of its morphine content would be possible by simple means in spite of the addition of cephaeline to the extent of 3.1%. Therefore, the following resolution was passed:

> The Expert Committee on Drugs Liable to Produce Addiction
>
> Having considered a request from the Swiss Government to have the preparation "ipecopan" exempted from the provisions of the 1925 Convention by application of its Article 8,
>
> IS OF THE OPINION that such exemption should not be granted in favour of "ipecopan", and
>
> RECOMMENDS that this opinion be notified to the Economic and Social Council of the United Nations for transmission to the Swiss Government.

4. Morphine Derivatives

4.1 *Dihydrocodeine*

4.2 *Acetyldihydrocodeine*

Owing to the fact that the Paris Protocol of 19 November 1948 became effective on 1 December 1949, the committee confirmed its opinion with respect to the addiction-producing properties of acetyldihydrocodeine and dihydrocodeine.[3]

4.3 *Morpholylethylmorphine (notification of the French Government)*

The committee considered a notification received from the French Government requesting the application of the measures laid down in Article 11 of the Convention of 1931 in order to include a new product, morpholylethylmorphine, prepared by a French laboratory, among the drugs mentioned in Group II of Article 1 of the above Convention.

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

The committee was of the opinion, first, that there is insufficient evidence to permit a decision on the addiction-producing properties of this substance, secondly, that in the absence of specific evidence to the contrary it is considered probable that the substance is convertible to morphine, and that in any case as an ether of morphine (other than methylmorphine and ethylmorphine) morpholylethylmorphine (β-morpholinoethylmorphine) is by definition in subgroup b of Group I of the 1931 Convention.

The Expert Committee on Drugs Liable to Produce Addiction

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

4.4 *Situation regarding diacetylmorphine* [4]

The committee took note of the changes in the situation which have occurred since its first session.[5] It was gratified to note that a number of countries have submitted smaller estimates for that drug for 1950. In spite of this the committee was informed that the production of diacetylmorphine is still on the increase. The committee expressed grave concern over this situation, particularly as some important countries continue to maintain that their physicians consider this drug indispensable for certain medical uses.

The committee is still of the opinion that further information is urgently needed as to the reasons governing the continuing use of diacetylmorphine, and particularly with regard to its replacement by less dangerous drugs. Therefore the following resolution was adopted:

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that the Executive Board should take steps to secure information on the use or dispensability of diacetylmorphine in the various countries, soliciting the aid of the World Medical Association and any other organ fitted to participate in this effort.

4.5 *6-Methyldihydromorphine*

The committee received information with respect to tests on the addiction-producing properties of 6-methyldihydromorphine. It is of the opinion that the evidence indicated that this substance must be classified as an addiction-producing drug.[6]

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[4] The Executive Board, at its fifth session, adopted the following resolution:

The Executive Board

RECOMMENDS that the Director-General take steps to secure information on the use or dispensability of diacetylmorphine in the various countries through Governments;

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

[6] See Annex 1, page 11.

5. Synthetic Substances

5.1 *Morphinan type*

The committee wished to draw attention to the further development in the effort to synthesize morphine and the work which has been done on the addiction liability of 3-hydroxy-N-methylmorphinan.[7]

5.2 *Pethidine type*

The committee wished to draw attention again to the statement made during its first session by Dr Eddy [8] concerning 4-(meta-hydroxyphenyl)-1-methyl-4-propionylpiperidine ("keto-bemidone"). The details of the work referred to in that statement have since been published in full.[9] The committee wished to emphasize its opinion that keto-bemidone is particularly dangerous from the standpoint of addiction liability. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

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

5.3 *Methadone type*

The committee received additional information with respect to acetylmethadone (6-dimethylamino-4,4-diphenyl-3-acetoxyheptane) in both its racemic and optically active forms. The committee was of the opinion that the new evidence confirmed its previous recommendation with respect to this substance.[10]

6. Requests of the Commission on Narcotic Drugs of the Economic and Social Council

6.1 *Definition of drug addiction*

Having considered the request of the Commission on Narcotic Drugs, the committee drafted the following definition of "drug addiction":

Drug addiction is a state of periodic or chronic intoxication, detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:

(1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;

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[7] See Annex 1, page 11.

[8] *Off. Rec. World Hlth Org.* **19**, 32

[9] Isbell, H. (1949) *J. Pharmacol.* **97**, 182

[10] *Off. Rec. World Hlth Org.* **19**, 30; see also Annex 1, page 11.

(2) a tendency to increase the dose;

(3) a psychic (psychological) and sometimes a physical dependence on the effects of the drug.

6.2 *Definition of addiction-forming drugs*

The committee was of the opinion that the expression "addiction-forming" and its related grammatical forms should be replaced by "addiction-producing", etc. The committee then adopted the following definition:

An addiction-producing drug is one which produces addiction as defined.

The committee wished to emphasize that all available evidence at the present time indicates that any substance which will sustain an established addiction—i.e., will adequately replace the drug which has produced the addiction—must be considered as also capable of producing an addiction.

6.3 *Definition of habit-forming drugs*

A habit-forming drug is one which is or may be taken repeatedly without the production of all of the characteristics outlined in the definition of addiction and which is not generally considered to be detrimental to the individual and to society.

The committee was of the opinion that the expression " habit-forming " in the sense of addiction-producing should be eliminated from all texts.

6.4 *Fundamental structure of an addiction-producing drug*

The committee was of the opinion that the fundamental structure of an addiction-producing drug is that particular arrangement of atoms within the molecule which is responsible for the addiction properties of the drug. In the present state of our knowledge it is not possible to say what part of the molecule of a drug is responsible for its addiction properties. Nevertheless, it is known that certain drugs having, in the main, a common structure produce in some degree a similar addiction. Therefore other substances which have a similar structure must be liable to suspicion as being addiction-producing. It is such analogues which are referred to under section 1 of this report. Examples of common structure with relation to addicting-production include the groups of which morphine, pethidine, methadone and cocaine are members. The committee would emphasize that this list is not complete and that probably new compounds of different structure will be developed which are also addiction-producing. Therefore the question of the relation of chemical structure to addiction-producing properties must remain open.

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that the above definitions and opinions should be communicated to the Secretary-General of the United Nations for transmission to the Commission on Narcotic Drugs of the Economic and Social Council.

6.5 *Request of the Commission for consultation with " the World Health Organization with a view to ascertaining the present state of medical research on drug addiction "*

Having considered the request of the Commission on Narcotic Drugs, the committee concluded that the only medical researches on drug addiction (other than ad hoc or sporadic) of which it had knowledge were being carried out by the US Public Health Service through the Research Division of its Hospital at Lexington, Kentucky, and by groups of investigators in parts of South America. The committee wished to emphasize the meagreness of medical research on drug-addiction problems and noted particularly the lack of any adequate means of ascertaining the incidence of addiction production in connexion with the legitimate medical use of potentially addicting drugs. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that Governments be urged to consider the feasibility of initiating or amplifying medical research on drug addiction.

7. Consultations with the Expert Committee on Mental Health

The committee heard a statement concerning a proposal to convene meetings of experts on drug addiction and on alcoholism. It would be the aim of these meetings to study drug addiction and alcoholism particularly with respect to their etiological, epidemiological, sociological and anthropological aspects, bridging the gap between previous purely pharmacological investigations on the one hand and purely clinical studies on the other hand.

The committee was of the opinion that the holding of such meetings would be of great importance and concurred in the pertinent recommendations of the Expert Committee on Mental Health.[11] The committee was further of the opinion that, because of the many points of mutual interest in its own work and in the proceedings of such meetings, it would be most desirable that the Expert Committee on Drugs Liable to Produce Addiction should be represented at the proposed meetings by one of its members. Therefore,

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[11] See *World Hlth Org. techn. Rep. Ser.* 1950, **9**.

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that the Executive Board should approve the convening of the meetings on drug addiction and alcoholism recommended by the Expert Committee on Mental Health; and further

RECOMMENDS that the Director-General should arrange for the Expert Committee on Drugs Liable to Produce Addiction to be represented at these meetings.

8. Chronic Barbiturate Intoxication

The committee viewed a film on "Chronic Barbiturate Intoxication" produced by the Research Department of the United States Public Health Service Hospital, Lexington, Kentucky, and accepted for inclusion as an annex to this report a statement of the scope of the experiment which the film portrayed.[12]

Each of the experts drew attention to the existence of a similar barbiturate problem in varying degree in his country.

9. 2-(1'-naphthylmethyl)-imidazoline

The committee noted a statement by Dr Carratalá with respect to abuse of 2-(1'-naphthylmethyl)-imidazoline (also known as naphazoline, the hydrochloride of which is registered under the names of "privine", "diazolin", etc.) in Argentina. The committee was of the opinion that this problem is similar to that referred to by Dr Wolff in his statement to the committee at its first session with respect to abuse of amphetamine [13] and that it did not consider it necessary to modify its previous recommendation.

10. Present Status of Drug Addiction in India

The committee received a report by Sir Ram Nath Chopra concerning the present status of drug addiction in India. It was of the opinion that this subject falls within the scope of the meetings on drug addiction proposed by the Expert Committee on Mental Health.[14] Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that if such meetings are held this statement be forwarded for appropriate attention.

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[12] See Annex 2, page 13.

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

[14] See section 7, page 8.

11. Name of the Committee

The committee was of the opinion that the expression " habit-forming " in the designation of the committee is no longer appropriate, having regard to the opinion in section 6.3 of the present report and that the designation should be changed.[15]

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[15] The Executive Board, at its fifth session, adopted the following resolution:

The Executive Board ...

DECIDES to change the denomination of the Expert Committee on Habit-Forming Drugs to "Expert Committee on Drugs Liable to Produce Addiction";

Annex 1

EVIDENCE ON ADDICTION POTENTIALITY [1]

1. 6-Methyldihydromorphine

Single doses of 30 to 60 mg., administered at the height of abstinence from an established morphine addiction, caused no appreciable diminution in the intensity of the abstinence syndrome. Doses of 90 to 120 mg., similarly administered, decreased the intensity of abstinence. Reduction in point scores was about equal to that seen after administration of 10 to 15 mg. of morphine. Relief of abstinence with 6-methyldihydromorphine was transient, point scores rising again to the preinjection level in four to six hours after administration of the drug.

Five former addicts, free of drugs for six months or more, were given 6-methyldihydromorphine in increasing amount to a total dosage of 60 mg. three times a day and a total administration of 32 days. The behaviour of the patients throughout the experimental addiction was similar to that observed during morphine addiction. Only partial tolerance to the sedative action occurred. The drug did not cause consistent elevation of the pain thresholds as determined by a modified Hardy-Wolff technique but did decrease the amplitude of the psychogalvanic response to thermal stimuli.

Following abrupt withdrawal only mild signs of abstinence were observed in four patients, but moderate signs in the fifth patient who, however, had been ill with a fever of obscure origin throughout the latter half of the experiment. The results suggest that the physical dependence liability of 6-methyldihydromorphine is considerably lower than that of morphine although its potency and length of analgesic action are just as great as and perhaps even greater than that of morphine.

2. 3-Hydroxy-N-Methylmorphinan

Single doses administered subcutaneously or intravenously produce very marked euphoria, but the effect is not obtained nearly as rapidly as following intravenous injection of morphine or methadone. Single doses administered at the height of abstinence from morphine afforded relief of the abstinence syndrome. Five men received the drug daily, the dose increasing to 15 mg. four times daily on the 17th day and continuing at that level for 21 days. In the beginning the patients were exhilarated and showed

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[1] Note submitted by Dr N. B. Eddy, based upon unpublished reports of the Research Department, US Public Health Service Hospital, Lexington, Ky., USA.

increased psychomotor activity. Later they were more sedated. Other morphine-like effects have been seen. Complete tolerance to the sedative action did not develop. Following abrupt withdrawal very definite signs of abstinence appeared at about the rate of signs of abstinence from morphine. The overall severity of abstinence appeared to be quite similar to abstinence in individuals who had received about 240 mg. of morphine per day for 30 days. The drug has addiction liability which is approximately equal to that of morphine.

3. Acetylmethadone

Comparison of *dl*-α-acetylmethadone with its *d*- and *l*- isomers. The *l*-form and the racemate are effective analgesics in rats; the *d*-form has about one-third the analgesic potency of the racemate, but its effect is delayed for 30 to 90 minutes after the drug is injected. In man 20 to 30 mg. of *dl*-α-acetylmethadone or 15 to 20 mg. of *l*-α-acetylmethadone caused intense euphoria beginning in about 30 minutes and lasting at least 24 hours. Nausea and vomiting occurred with either drug early after administration. After 30 mg. of *d*-α-acetylmethadone no changes were observed for six to eight hours. Thereafter euphoria appeared and gradually increased. All patients liked the effect of this isomer. The results were strikingly different from those with *d*-methadone which seemed to be totally inactive in man.

Annex 2

CHRONIC BARBITURATE INTOXICATION[1]

Chronic barbiturate intoxication is becoming a matter of increasing concern to physicians, lay groups, law enforcement officers and legislators in the USA but it is not a problem exclusively of that country. Production of barbiturates has steadily increased and now appears to exceed greatly the amount needed for therapeutic purposes. In 1948 total production in the USA amounted to 336 tons (about 300,000 kg.), or approximately 24 therapeutic doses for each person in the USA. Acute intoxication with barbiturates has been steadily increasing and is probably parallelled by increasing chronic intoxication, though the exact extent of the latter is not known. Since 1940 an increasing number of morphine addicts, who were also taking large amounts of barbiturates, have been admitted to the US Public Health Service Hospital at Lexington, Ky. Morphinists prefer pentobarbital, seconal or amytal and will ordinarily take 15 or 16 capsules a day. Following abrupt withdrawal of barbiturates from such persons or even following abrupt reduction of this dosage to less than 50% of the amount to which they are accustomed, convulsions and/or psychotic symptoms frequently ensued. As far back as 1913, German authors described convulsions during barbiturate withdrawal, and there have been similar references occasionally in the English literature. Neither, however, has given much attention to the occurrence of psychoses. It is impossible to tell with regard to the cases in the literature or the addicts at Lexington whether or not there was a previously existing epileptic or psychotic diathesis. Besides, the patients at Lexington were cases of mixed addiction and were often on admission in very poor nutritive condition, so that direct relation of the barbiturates to the withdrawal phenomena was not clear. Therefore, an experiment under controlled conditions was undertaken in which individuals, whose neurological and psychological status was known, ingested large amounts of barbiturates for a long period and then were abruptly withdrawn.

The subjects of the experiment were five former morphine addict volunteers. Administration began with therapeutic doses and increased rapidly during the first 21 days to as great an extent as possible without producing an unmanageable state of intoxication. The total period of administration varied from 92 to 144 days. The symptoms of chronic barbiturate intoxication resembled those of alcoholism and included

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[1] Note submitted by Dr N. B. Eddy, based upon the work of Dr H. Isbell, Research Director, US Public Health Service Hospital, Lexington, Ky., USA.

impairment of mental ability, confusion, regression, increased emotional instability, nystagmus, dysarthria, ataxia in gait and station, and depression of the superficial abdominal reflexes. The intensity of the intoxication with the same dose varied from individual to individual and in the same individual from day to day, partly associated with the amount of food taken before the morning dose. This variation made it difficult to determine the extent of tolerance, but about three months after withdrawal four of the individuals were started abruptly on the maximum dose which they had attained in the experiment. The first two doses caused such intense intoxication that administration was discontinued. Undoubtedly significant tolerance had developed during the prolonged administration and disappeared during withdrawal.

Following abrupt withdrawal of the barbiturates a definite abstinence syndrome developed in each of the five subjects. It was characterized by disappearance of the signs of intoxication, weakness, tremor, anxiety, anorexia, nausea and vomiting, rapid weight-loss, elevation of pulses and respiratory rates, fever, increase in blood-pressure, difficulty in making cardiovascular adjustments on standing, convulsions of grand mal type and the development of a psychosis. The barbiturate withdrawal psychosis resembled alcoholic delirium tremens and was characterized by anxiety, agitation, insomnia, confusion, disorientation, chiefly in time and place but not in person, delusions, and auditory and visual hallucinations. Convulsions occurred in all but one of the subjects always within the first five days; psychosis occurred in all but one patient (not the same one) beginning about the third day. Recovery in all respects appeared to be complete. No clinical evidence of permanent damage was detected 60 days or more after withdrawal began.

During chronic barbiturate intoxication the amplitude of electroencephalographic waves of all types increased and the percentage of waves of frequencies of 15 to 30 cycles per second increased. During withdrawal paroxysmal bursts of high amplitude waves of frequencies of four to six cycles per second appeared in the first 12 to 48 hours. Records obtained during and after a convulsion were similar to records of grand mal seizures due to idiopathic epilepsy. The electroencephalographic pattern returned within 30 days after withdrawal to that seen before barbiturate administration was started.

Since chronic barbiturate intoxication resulted in the development of tolerance and dependence, as manifested by a characteristic abstinence syndrome, it must be concluded that the barbiturates are capable of producing addiction.

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