

WORLD HEALTH ORGANIZATION  
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No. 102

**EXPERT COMMITTEE ON DRUGS  
LIABLE TO PRODUCE ADDICTION**

**Sixth Report**

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WORLD HEALTH ORGANIZATION

PALAIS DES NATIONS

GENEVA

MARCH 1956

EXPERT COMMITTEE  
ON DRUGS LIABLE TO PRODUCE ADDICTION

Sixth Session

Geneva, 24-29 October 1955

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Dr H. Halbach, Chief, Addiction-Producing Drugs Section, WHO

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\* Unable to attend the session

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## **EXPERT COMMITTEE ON DRUGS LIABLE TO PRODUCE ADDICTION**

### **Sixth Report \***

The Expert Committee on Drugs Liable to Produce Addiction held its sixth session in Geneva from 24 to 29 October 1955.

On behalf of the Director-General, the session was opened by the Assistant Director-General, Department of Central Technical Services. After welcoming the members, he referred to the agenda, whose items reflected the Committee's responsibility in the concerted international action against drug addiction, and emphasized the appreciation of their valuable assistance to the World Health Organization.

#### **1. Report on the Tenth Session of the Commission on Narcotic Drugs of the United Nations Economic and Social Council**

The Committee took particular note of the discussion of synthetic substances in the report of the tenth session of the Commission on Narcotic Drugs of the United Nations Economic and Social Council,<sup>1</sup> and of resolution No. 588 (XX) D relating thereto which was adopted at the twentieth session of the Council.<sup>2</sup> The Committee was of the opinion that any narcotic substance, whether synthetic or derived from a natural alkaloid, must be considered individually, and that for the purposes of control no distinction should be made between the group of natural alkaloids and their derivatives on the one hand and the group of synthetic substances on the other. Further reference to this point will be made under section 3.2 (see page 5).

The Committee was pleased to note the decision of the Commission on Narcotic Drugs to recommend that governments should limit their imports

\* The Executive Board, at its seventeenth session, adopted the following resolution :  
The Executive Board

1. ADOPTS the sixth report of the Expert Committee on Drugs Liable to Produce Addiction ;
2. THANKS the members of the Committee for their work ;
3. AUTHORIZES publication of the report ; and
4. REQUESTS the Director-General to transmit the report to the Secretary-General of the United Nations.

(Resolution EB17.R3, *Off. Rec. Wld Hlth Org.*, 1956, 68, 2)

<sup>1</sup> United Nations, Economic and Social Council (1955) *Commission on Narcotic Drugs : report... on the tenth session... 18 April to 12 May 1955* (Mimeographed document E/2768—E/CN.7/303)

<sup>2</sup> United Nations, Economic and Social Council (1955) *Economic and Social Council. Official records : twentieth session, 5 July - 5 August 1955. Supplement No. 1. Resolutions*, Geneva, p. 19 (Document E/2795)

of coca leaf and crude cocaine in a manner analogous to that applicable to opium under the Protocol of 1953, and the decision to place cannabis drugs together with diacetylmorphine (heroin) and ketobemidone in the list of prohibited drugs (Schedule IV) to be included in the proposed Single Convention on Narcotic Drugs.

The Committee discussed the seriousness of the placing of drugs in any prohibiting list and expressed the view that it would welcome an opportunity to consider, and give advice on, substances which might be placed in that schedule.

The Committee was pleased to note further that in the provisions of the Single Convention the World Health Organization, as well as governments, should have initiative in notification of new substances and of changes in the position of substances under control regimes.

## 2. Resolutions of the United Nations Economic and Social Council

The Committee was pleased to note in resolution No. 588 (XX) E<sup>1</sup> on abuse of drugs (drug addiction), adopted by the United Nations Economic and Social Council, the recommendations with respect to the continuing effort to collect statistics on the incidence of addiction throughout the world, and with respect to initiation of a study of the best methods for the treatment of addicts.

The Committee took particular note of, and concurred in, the view expressed by the Commission on Narcotic Drugs that in the treatment of drug addiction methods of ambulatory treatment (including the so-called clinic method) are not advisable.

## 3. Morphine and its Derivatives

### 3.1 *Situation regarding diacetylmorphine (heroin)*

The Committee noted with satisfaction the resolution of the Commission on Narcotic Drugs of the United Nations Economic and Social Council urging all governments which have not heretofore done so to prohibit the use and manufacture of, and trade in, diacetylmorphine.<sup>2</sup>

<sup>1</sup> United Nations, Economic and Social Council (1955) *Economic and Social Council. Official records: twentieth session, 5 July - 5 August 1955. Supplement No. 1. Resolutions*, Geneva, p. 19 (Document E/2795)

<sup>2</sup> United Nations, Economic and Social Council (1955) *Commission on Narcotic Drugs: report... on the tenth session... 18 April to 12 May 1955, Annex B*, p. 4 (Mimeographed document E/2768—E/CN.7/303)

It was reported to the Committee that, of the 20 States which have supplied estimates for diacetylmorphine for 1956, only 4 are not prepared to suppress the use of the drug; several of the others have announced that they will discontinue its use when present stocks are exhausted. It was emphasized that in general the estimates are significantly smaller than in former years and that over-all licit production has shrunk from 839 kg in 1948 to 132 kg in 1954. The Committee concluded from this information that more and more physicians throughout the world are finding it possible to substitute less dangerous drugs for diacetylmorphine, in accordance with the Committee's repeatedly expressed view on the replaceability of this dangerous addicting agent.

The small number of countries still persisting in the use of diacetylmorphine, the reduction in estimates for the next year, and the marked decrease in production of the drug reflect very gratifying progress in the campaign against diacetylmorphine.

3.2 *Reconsideration of sections 5.1 and 7.3.2 of the fifth report of the Committee on request of the Executive Board at its fifteenth session*

It is now almost universally recognized that diacetylmorphine is a dangerously addicting drug. Such was not always the case. Diacetylmorphine was introduced into medicine little more than fifty years ago as a non-addicting substitute for morphine, and this impression of relative safety was corrected only by accumulated clinical experience.

Pethidine also was introduced with the claim in some quarters of relative safety with respect to addiction liability, and again clinical experience is demonstrating the incorrectness of this claim. The Committee again concluded that pethidine is comparable to morphine in addiction liability; neither pethidine nor morphine is comparable to diacetylmorphine in this respect. The Committee was of the opinion that the rising trend in pethidine addiction<sup>1</sup> can only be combated by recognition of the danger and by as much care in the use of the drug as with morphine.<sup>2</sup>

The Committee wished to emphasize in this connexion its view that synthetic analgesic drugs differ from one another in addiction liability just as do drugs derived from natural substances such as opium; that members of each class must be considered individually with respect to inherent risk and therapeutic advantage; and that the risk of addiction through the use of

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<sup>1</sup> See *Wld Hlth Org. techn. Rep. Ser.*, 1955, **95**, 13. During the period covered in the Lexington report, the total number of addicts treated at the Public Health Service Hospital, Lexington, Kentucky, USA, irrespective of the drug of addiction, was 12 682.

<sup>2</sup> See *Wld Hlth Org. techn. Rep. Ser.*, 1955, **95**, 10 (section 7.3.2).

synthetic drugs is neither greater nor less than the risk encountered through the use of morphine, related opium alkaloids, or substances derived therefrom.

The Committee concluded that morphine, related substances, and synthetic drugs are equally useful for medical needs, and that there is a wide range of potency available among members of each group.

### 3.3 *Myristyl ester of benzylmorphine*

Having noted the report, dated 11 May 1955, of the body of three experts set up under Article 11, paragraph 4, 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, the Committee reconsidered the evidence on the addiction liability of the myristyl ester of benzylmorphine and again found it adequate for the conclusion that the drug possesses no addiction liability.<sup>1</sup> It was nevertheless very clear that the drug is readily convertible into benzylmorphine or morphine to a degree and with an ease sufficient to constitute a hazard to public health. The Committee reiterated its opinion that the degree of control to be applied to this substance should be decided on the basis of its convertibility. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with regard to the addiction liability and the convertibility of the myristyl ester of benzylmorphine be communicated to the Secretary-General of the United Nations.

### 3.4 *Dihydrodesoxymorphine*

The Committee took note of a report on the therapeutic value and the addiction-producing properties of dihydrodesoxymorphine-D (desomorphine).<sup>2</sup>

The Committee noted that in 14 years the drug has not become very widely accepted and that the original producer has now ceased its manufacture, which has resulted in substantial withdrawal of the drug from trade.

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<sup>1</sup> Attention was drawn to the fact that in the addiction-liability tests with myristyl ester of benzylmorphine the oral route only was employed because of the impracticability of parenteral administration of the necessarily large doses. The work of the Addiction Research Center, Public Health Service Hospital, Lexington, Kentucky, USA, had demonstrated repeatedly that similar qualitative results with respect to addiction liability are obtained with either the oral or the parenteral route of administration.

<sup>2</sup> Study prepared, on request of WHO, by Dr P. O. Wolff, formerly Chief, Addiction-Producing Drugs Section, WHO.

### 3.5 Preparation containing dihydrocodeinone (hydrocodone<sup>1</sup>)

Having considered the request of the Government of the United Kingdom of Great Britain and Northern Ireland for the exemption from the provisions of the 1931 Convention of a troche preparation of the following composition :

Hydrocodone bitartrate . . . . .	0.0014 g
Pentobarbital sodium . . . . .	0.00325 g
Ephedrine hydrochloride . . . . .	0.00325 g
Calcium iodide, anhydrous . . . . .	0.06 g
Apricot-flavoured candy . . . . .	3.7011 g

the Committee concluded that there was no evidence to show that the preparation could give rise to addiction. On the other hand, the fact that the preparation is a candy suggested the possibility of its consumption in an amount many times the intended dose with the result that it might thereby become a factor in addiction.

For these reasons the Committee was of the opinion that this preparation of hydrocodone should not be exempted from the provisions of the 1931 Convention. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

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

## 4. Papaverine

The Committee took note of a report prepared by the Addiction Research Center, Public Health Service Hospital, Lexington, Kentucky, USA, with respect to the testing of papaverine for addiction liability. The Committee accepted the evidence in this report and agreed with the conclusion that papaverine has no addiction liability.

## 5. Synthetic Substances with Morphine-like Effect

### 5.1 Synthetic substances of morphinan type

#### 5.1.1 (–)-3-Hydroxy-N-allylmorphinan, designated also 1-3-hydroxy-N-allylmorphinan (levallorphan<sup>2</sup>)

Referring to the notifications of the Government of Switzerland and of the Government of the United States of America, the Committee reviewed

<sup>1</sup> Recommended international non-proprietary name

<sup>2</sup> Proposed international non-proprietary name

the evidence on levallorphan and found that, like nalorphine, when administered alone it produced dysphoria rather than euphoria and that it had not caused the appearance of tolerance or physical dependence. It would not relieve the abstinence syndrome nor sustain a morphine addiction, but would precipitate abstinence phenomena if physical dependence on morphine or a morphine-like drug had been established.

The Committee also considered the conversion of levallorphan to levorphan. Such conversion, although possible, is so difficult that it is considered to be impracticable and to constitute no risk to public health.

The Committee was of the opinion that levallorphan 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 (–)-3-hydroxy-N-allylmorphinan, designated also *l*-3-hydroxy-N-allylmorphinan (proposed international non-proprietary name “levallorphan”), be communicated to the Secretary-General of the United Nations.

5.1.2 (–)-3-Methoxy-N-allylmorphinan

(–)-3-Acetoxy-N-allylmorphinan

Referring to the notification of the Government of Switzerland, the Committee concluded that the position of these substances is analogous to that of levallorphan and that they cannot be considered either to be addiction-producing drugs or to be capable of conversion into addiction-producing drugs for the purposes of the 1931 Convention. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with respect to (–)-3-methoxy-N-allylmorphinan and (–)-3-acetoxy-N-allylmorphinan be communicated to the Secretary-General of the United Nations.

5.1.3 (–)-3-Hydroxy-N-propargylmorphinan

Referring to the notification of the Government of Switzerland, the Committee decided to reserve judgment with respect to the addiction liability of this substance until information is available on the results of its repeated administration.

5.1.4 3-Hydroxy-N-phenethylmorphinan

Referring to the notification of the Government of the United States of America, the Committee was of the opinion that 3-hydroxy-N-phenethylmorphinan, 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 drug comparable to morphine, and that 3-hydroxy-N-phenethylmorphinan 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-hydroxy-N-phenethylmorphinan and its salts be communicated to the Secretary-General of the United Nations.

The Committee noted further that the very great potency of 3-hydroxy-N-phenethylmorphinan with respect to the production of morphine-like effects and to the suppression of morphine abstinence phenomena indicates that the substance possesses particularly dangerous addiction-producing properties. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

RECOMMENDS that its opinion with regard to the dangerousness of 3-hydroxy-N-phenethylmorphinan and its salts be transmitted to the Secretary-General of the United Nations, emphasizing the desirability of avoiding the manufacture, import, and export of these substances, unless a definite therapeutic advantage can be shown.

## 5.2 *Synthetic substances of methadone type*

### 5.2.1 *4-Morpholino-2,2-diphenyl ethyl butyrate, designated also ethyl-2,2-diphenyl-4-morpholinobutyrate*

Referring to the notifications of the Government of Italy and of the Government of the United States of America, the Committee was of the opinion that 4-morpholino-2,2-diphenyl ethyl butyrate, because it produces marked and prolonged morphine-like effects comparable to those of other addiction-producing substances related to methadone, must be considered an addiction-producing drug comparable to morphine and that 4-morpholino-2,2-diphenyl ethyl butyrate 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 4-morpholino-2,2-diphenyl ethyl butyrate and its salts be communicated to the Secretary-General of the United Nations.

### 5.2.2 *4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane*

Referring to the notification of the Government of the United States of America, the Committee was of the opinion that 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane, because it (1) will only partially

suppress the abstinence phenomena of a known morphine addiction, and (2) will in part sustain a morphine addiction, must be considered as having no greater addiction liability than codeine, and that 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane and its salts are assimilable to the drugs mentioned in Group II of the 1931 Convention. Therefore,

The Expert Committee on Drugs Liable to Produce Addiction

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

### 5.2.3 *4,4-Diphenyl-6-piperidino-3-hexanone*

The Committee's attention was drawn to the above substance, which has been marketed in Hungary under the name of Hexalgon and has been mentioned in the estimates for that country.

The committee noted that in previous reports 4,4-diphenyl-6-dimethylamino-3-heptanone (methadone) and 4,4-diphenyl-6-piperidino-3-heptanone were shown to be closely related chemically and to have similar pharmacological properties and similar addiction liability. It is now apparent that 4,4-diphenyl-6-dimethylamino-3-hexanone and 4,4-diphenyl-6-piperidino-3-hexanone are likewise chemically and pharmacologically similar. 4,4-Diphenyl-6-dimethylamino-3-hexanone has been shown to have addiction liability. Because of these analogies, the Committee concluded that 4,4-diphenyl-6-piperidino-3-hexanone must be considered as also having addiction liability.

### 5.3 *Synthetic substances of dithienylbutenylamine type*

#### *3-Diethylamino-1,1-di-(2'-thienyl)-1-butene (diethylthiambutene<sup>1</sup>)*

Referring to the notification of the Government of the United Kingdom of Great Britain and Northern Ireland, the Committee was of the opinion that 3-diethylamino-1,1-di-(2'-thienyl)-1-butene, 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 3-diethylamino-1,1-di-(2'-thienyl)-1-butene 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-diethylamino-1,1-di-(2'-thienyl)-1-butene (proposed international non-proprietary name

<sup>1</sup> Proposed international non-proprietary name; approved common name in the United Kingdom of Great Britain and Northern Ireland

“diethylthiambutene”) and its salts be communicated to the Secretary-General of the United Nations.

#### 5.4 *Synthetic substances of pethidine type*

*1-[2-(p-Aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester, designated also 1-[2-(p-aminophenyl)-ethyl]-4-carbethoxy-4-phenylpiperidine*

*1-(2-Hydroxy-2-phenyl-ethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester, designated also 4-carbethoxy-1-(2-hydroxy-2-phenyl-ethyl)-4-phenylpiperidine*

The Committee considered the notification of the Government of the United States of America with regard to these substances and noted particularly that, whereas the analgesic effectiveness of both compounds experimentally is about three times that of pethidine, the dose of 1-[2-(*p*-aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester to produce morphine-like effects is significantly greater than the dose of morphine for a similar effect. Recognizing that the information available at the present time is of a preliminary nature, the Committee decided to defer its opinion with respect to the addiction liability of both compounds.

#### 5.5 *Synthetic substances of hexamethyleneimine type*

##### 5.5.1 *1,3-Dimethyl-4-phenyl-4-propionoxyhexamethyleneimine*

Referring to the notification of the Government of the United States of America, the Committee was of the opinion that 1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine, 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 drug comparable to morphine, and that 1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine 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 1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine and its salts be communicated to the Secretary-General of the United Nations.

##### 5.5.2 *1-Methyl-4-phenylhexamethyleneimine-4-carboxylic acid ethyl ester, designated also 4-carbethoxy-1-methyl-4-phenylhexamethyleneimine*

*1,3-Dimethyl-4-phenylhexamethyleneimine-4-carboxylic acid ethyl ester, designated also 4-carbethoxy-1,3-dimethyl-4-phenylhexamethyleneimine*

*1,2-Dimethyl-4-phenylhexamethyleneimine-4-carboxylic acid methyl ester, designated also 4-carbomethoxy-1,2-dimethyl-4-phenylhexamethyleneimine*

Considering the notification of the Government of the United States of America with respect to these three substances, the Committee noted that the evidence on addiction liability was negative for each of them. The Committee decided, however, to make no recommendation with respect to their control at this time, but proposed that a very close watch be kept on further experimentation and any clinical use of these compounds.

#### **6. List of the Narcotic Drugs under International Control**

Having examined the preliminary draft of the "List of the Narcotic Drugs under International Control", the Committee was of the opinion that such a list can be of very great assistance to governments, control agencies, health services, and other interested parties. The Committee expressed its appreciation of the action of the United Nations in directing its Narcotics Division to prepare the list, and recognized the effort which had gone into the preparation in order to provide a file of accurate technical and related information in a form allowing of easy reference.

The Committee suggested the desirability of having the list reviewed for technical accuracy by a small group, possibly of three or four, with such technical assistance as may be necessary. Such a group might be obtained by invitation to selected members of the Expert Advisory Panel on Drugs Liable to Produce Addiction. Any necessary changes to ensure accuracy should be made as soon as possible to permit of early publication. In view of the continuing production of new drugs, the Committee considered that the list will require addenda and revisions, the accuracy of which should be provided for by a small reviewing group, as with the initial publication.

#### **7. Abuse of Amphetamine**

The Committee took note of the memorandum presented by Dr T. Masaki on the amphetamine problem in Japan,<sup>1</sup> and had its attention drawn to the occurrence of abuse of amphetamine and amphetamine-like substances in other areas to an extent which constitutes a hazard to public health. The Committee noted that stern measures are already being taken by one of

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<sup>1</sup> See Annex, page 14.

the governments concerned to meet the situation, and that suggestions have been made for local measures for improvement in other areas. The Committee proposed, as it had done previously, to keep close watch on the situation, but was of the opinion that abuse of amphetamine continued to be a local problem and not one for international action.

### 8. Pethidine

The Committee took note of the replies which had been received to the circular letter of the Director-General, pursuant to its recommendation,<sup>1</sup> bringing to the attention of governments and the medical profession throughout the world the dangerousness of the addiction potentiality of pethidine and the need for care in its use as with morphine. The replies indicate a willingness to assist in the implementation of the warning. The Committee was pleased to note the publication of the warning in a number of medical journals and the intent of the World Medical Association to prepare a document on the subject for distribution to all national medical associations.

The Committee drew attention to one source of difficulty in the recognition of the danger with respect to pethidine, namely, the multiplicity of names under which the drug is marketed, so that, in some instances at least, the physician is not aware that the drug with which he is dealing is in fact pethidine. The same difficulty can arise when a new drug which is liable to produce addiction is introduced in different countries under different names.

The Committee was of the opinion that the difficulty could be met, as is already done in some countries, by the identification of the new drug in each instance by its recommended (or proposed) international non-proprietary name—for example, by the use of the international non-proprietary name on labels and in all descriptive matter—and suggested that WHO should consider the appropriateness of drawing the attention of governments to such a procedure.

In this connexion the Committee noted that the Commission on Narcotic Drugs had already recommended governments to use, whenever possible, in documents concerned with the implementation of the international treaties on narcotics, the non-proprietary names proposed by WHO in addition, where they so desire, to the chemical or proprietary names or both.<sup>2</sup>

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1955, **95**, 10 (section 7.3.2)

<sup>2</sup> See *Wld Hlth Org. techn. Rep. Ser.*, 1952, **57**, 12 (section 10).

## 9. International Non-Proprietary Names

The Committee was pleased to note the favourable response to the suggestions made at its fifth session,<sup>1</sup> and transmitted in the circular letter of the Director-General under the date of 21 April 1955, designed to speed up the selection of an international non-proprietary name for a drug which may come under international narcotics control. Replies from governments indicated that efforts are being made to implement the Committee's suggestions.

### Annex

#### THE AMPHETAMINE PROBLEM IN JAPAN \*

##### 1. Varieties of Wake-Amine (Amphetamine)

The habit-forming wake-amines which pose a present-day social problem in Japan are classified into two kinds :

- (1)  $\beta$ -phenylisopropylamine or rac. 1-phenyl-2-amino-propane  
Trade name : Zedrine (Takeda)
- (2)  $\beta$ -phenylisopropylmethylamine or *d*-1-phenyl-2-methylamino-propane  
Trade names : Philopon (Dainippon Seiyaku)  
Hospitan (Santendo Seiyaku)

Philopon, the general term for these amines in Japan, originates from the brand name for  $\beta$ -phenylisopropylmethylamine hydrochloride of the Dainippon Pharmaceutical Co.

##### 2. Number of Addicts to, and Persons Misusing, Wake-Amine

Abuse of wake-amine was first noted in 1945, and the number of persons misusing this drug has increased markedly since the summer of 1948. A survey of addicts throughout Japan is now being made by the Ministry of Welfare, but the final exact number has not yet been announced. A survey

<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1955, 95, 11 (section 10)

\* Memorandum submitted by Dr T. Masaki, Professor of Pharmacology, Hokkaido University School of Medicine, Sapporo, Japan.

of the number of addicts in a small region revealed that in the city of Kurume, in Kyushu Island, about 1.1% of the whole population and about 5% of the 16- to 25-year-old population were wake-amine addicts.<sup>1</sup> According to an investigation by the Ministry of Welfare in May 1954, 9107 (7.2%) out of 127 142 interviewed persons had taken wake-amine and 2241 (1.8%) were abusing it. In May and June 1954, 10 148 persons were taken into custody because of offences against the Awakening Drug Control Law. Among these offenders, 5320 persons (52%) were found to be addicts. The total number of misusers of wake-amine in Japan in June 1954 was estimated at between 500 000 and 600 000, of whom half were considered to be addicts. On the other hand, the Japan Pharmacist Association assumes the number of wake-amine misusers to be 1.5 million. All reports agree, however, that the highest incidence occurs in persons in their teens and twenties.

Kaga<sup>2</sup> investigated the cases of 117 addicts who were admitted to a certain hospital between 1948 and 1953, and found that those between 21 and 25 years accounted for 40% of all cases, while those from 16 to 30 years comprised 80% of the total. There were no addicts over 40 years old. Of the addicts 40% first used wake-amine between the ages of 15 and 20, while 30% first used it between the ages of 21 and 25.

In the survey in August 1954 of juveniles confined in reformatories, it was found that 33% were familiar with the use of wake-amine. Geographically, the percentages ran: Osaka 33%, Sapporo 14%, Sendai 33%, Takamatsu 58%, Tokyo 26%. Such data provide good evidence for the statement that there is a close relationship between juvenile delinquency and wake-amine abuse.

### 3. Amount of Wake-Amine Produced and Consumed

Since the Awakening Drug Control Law took effect, the amount of wake-amine legally produced and distributed for the purposes of therapy or research has been very small. Up to the time of completion of this report it was not possible to obtain information as to the exact amount of the annual legal production of wake-amine in Japan. Yet there are very many addicts on the streets, as described above, so there is little doubt that the supply of wake-amine to addicts is obtained through an illegal route. In fact, a large quantity of wake-amine in various forms has been confiscated already; for example, according to an official report of the Hokkaido Committee for Awakening Drug Counter-measures, the kinds and amount of wake-amine

<sup>1</sup> Noda, K. (1950) *Kurume Igakkai Zassi*, **13**, 294

<sup>2</sup> Kaga, T. (1954) *Seishin Shinkeigaku Zassi*, **55**, 891

confiscated in Hokkaido (district with about 5% of the whole population of Japan) during the period January-July 1955 are as follows : concentrated solution, 9086 ml ; solution for injection, 137 555 ml ; undissolved powder, 1206.3 g.

#### 4. Motives for Addiction

During the post-war period (1945-49), when wake-amine was available to anyone, it was used by students who desired to be more effective in study or in sports, by night workers for overcoming sleepiness, and by some for curiosity or because they wanted to enjoy night life.

Now cases are increasing where addicts were first induced to take up the drug as a result of solicitation by illegal distributors. Data collected in an investigation made in March 1955 in the Hokkaido district, on 116 wake-amine addicts who were admitted to psychiatric hospitals because of their mental impairment, reveal the following motives for using the drug :

<i>Motive</i>	<i>Number of cases</i>
Night amusements, such as mah-jongg . . . . .	43
Solicitation . . . . .	31
Curiosity . . . . .	24
Deceived . . . . .	8
Improving working abilities . . . . .	8
Desperation . . . . .	2
Studying . . . . .	1
Slimming . . . . .	1

Those who became addicted to wake-amine have mostly the psychological dispositions tabled below :

	<i>Male</i>	<i>Female</i>	<i>Total</i>
Weak-mindedness . . . . .	53	8	61
Emotional instability . . . . .	20	5	25
Lack of confidence . . . . .	13	3	16
Conceitedness . . . . .	3	2	5
Explosive temper . . . . .	1	—	1
Total . . . . .	90	18	108

Besides the motives mentioned above, there are two other factors which stimulated wake-amine abuse in Japan. One was the ready availability of the large military stock of wake-amine immediately after the surrender of Japan, and the other was the spiritual collapse of the people and the attitude of indifference of the community and the family towards the education of young people during the post-war period. Wake-amine addiction has much to do with the prostitution and gambling prevalent in Japan in the post-war years.



### 5. Usual Method of Administration

Addicts administer wake-amine to themselves chiefly by the intravenous or subcutaneous route. The concentration of wake-amine (Philopon) is 3 mg per millilitre ; most illegal products allegedly contain the same proportion.

Some illegal products, however, have no wake-amine ingredient at all and are a fake (personal communication from Professor M. Akagi). The following data show the results of a chemical analysis of the so-called "illegal Philopon" carried out by the Hokkaido Hygiene Institute during the period between August 1951 and September 1952.

<i>Ingredient</i>	<i>Number of cases</i>	<i>Percentage</i>
Wake-amine . . . . .	118	94
Ephedrine hydrochloride . . . . .	2	} 6
Procaine hydrochloride . . . . .	2	
Caffeine and sodium benzoate . . . . .	1	
Vitamin B <sub>1</sub> . . . . .	1	
Sodium chloride . . . . .	2	

The frequency of injection and the dosage used by addicts vary quite markedly from 1-5 ampoules (one ampoule contains 3 mg) per day up to 200 ampoules per day.<sup>1</sup>

Some wake-amine addicts are barbiturate (especially hexobarbital) users at the same time. This twofold addiction is caused by the patients' desire to regain the sleep/wakefulness balance which has been impaired by the abuse of wake-amine. For the same reason some people use an antihistamine drug which has a hypnotic effect—e.g., Lestamine (2-(benzhydryloxy)-N,N-dimethylamine hydrochloride)—and others use intravenous alcohol or "shochu" (a kind of Japanese brandy). Occasionally, opiates or Ohton (3-dimethylamino-1,1-di-(2'-thienyl)-1-butene hydrochloride) are combined with them.

According to the above-mentioned report of Kaga,<sup>2</sup> the proportion of addicts using either one or more than one drug is as follows :

<i>Drugs used</i>	<i>Number of addicts</i>
Wake-amine alone . . . . .	83
Wake-amine + narcotic . . . . .	7
Wake-amine + hypnotic . . . . .	5
Wake-amine + narcotic + hypnotic . . . . .	1
Wake-amine + other drugs . . . . .	11
Wake-amine + hypnotic + other drugs . . . . .	10
Total . . . . .	117

<sup>1</sup> Noda, K. (1950) *Kurume Igakkai Zassi*, **13**, 294

<sup>2</sup> Kaga, T. (1954) *Seishin Shinkeigaku Zassi*, **55**, 891

## 6. Symptoms of Wake-Amine Intoxication

Hara et al.<sup>1</sup> studied 52 chronic intoxicated males who took Philopon for an average of 25 months and whose heaviest dose per day varied between 10 and 160 ml. Their survey revealed the following findings :

### (1) *Clinical symptoms*

Physical : Anorexia, loss of weight, insomnia, thirst, palpitation, and marked impairment of autonomic nervous system.

Mental : Auditory hallucination and delusion of reference were observed in most cases. Talkativeness and hyperkinesis, as well as "gemachtes Erleben", were noticed in some cases.

Abstinence : Serious cases are rare. Sleepiness, tiredness, and apathy are noticed.

### (2) *Laboratory findings*

(a) Urine-urobilinogen reaction was positive in most cases.

(b) No change in blood-cell count or blood-protein content. In the electrocardiogram the right form was more frequent. Myocardial damage was found in only one case.

(c) Frequently, light or moderate degree of liver damage was proved by icterus index, Takata reaction, cobalt chloride reaction, BSP (phenyl-pyruvic acid) test, and Lugol test.

(d) Stomach acidity, low blood-sugar level, labile autonomic nervous system were noticed.

(e) Out of 12 addicts, 5 cases were diagnosed as adrenal-insufficient by the Thorn test.

Other investigators agreed with the report just described—among them Professor Sakurai of Tokushima University, who concludes that 90% of 110 wake-amine addicts who were admitted to hospital or to the observation ward were complicated with the following types of mental impairment :

### (1) *Sensation and thinking*

Auditory hallucination (67%)

Delusion of reference (60%)

<sup>1</sup> Hara, Z. et al. (1954) *J. Jap. Soc. intern. Med.*, **43**, 663

Delusion of persecution (53%)  
Visual hallucination (32%)

(2) *Feeling*

Restlessness (50%)  
Anxiety (13%)  
Irritability (13%)

(3) *Sensorium*

Clear (39%)

These symptoms very much resemble those of schizophrenia, yet, within 30 days of giving up wake-amine, they had disappeared in almost all cases, although in some more than 50 days were needed.

There are very many cases where addicts, driven by such hallucinations and delusions, committed crimes of cruelty. Out of 60 murder cases in Japan during May and June 1954, 31 convicted murderers had some connexion with wake-amine misuse. Moreover, there have been cases of crimes committed by addicts just for the purpose of getting wake-amine.

### 7. Therapy of Chronic Wake-Amine Intoxication

Unlike the severe psychic craving, physical dependence is not very pronounced, and abstinence symptoms are comparatively light. Prompt prohibition of the taking of the drug is therefore indicated, and it is regarded as illegal to administer wake-amine to the addict for therapeutic purposes.

It has been reported that, after prohibition of the drug, the use of electroshock therapy when the patient craves an injection has worked very well and aided in breaking the habit.<sup>1</sup> K. Nakae recommends the combination of intravenous injection of 1 g of caffeine and sodium benzoate and subcutaneous injection of 5 mg of apomorphine hydrochloride after several electroshock treatments. This technique, applied to 20 patients, not only quickly cut the habit, but also lessened such troubles as mob rule, disorderliness, attempts to escape, and sexual dissoluteness, which are likely to occur when addicts are placed in one ward.

The Department of Psychiatry of Osaka University reports that continuous administration of chlorpromazine or of a mixture of chlorpromazine and Serpasil was quite satisfactory for the treatment of the schizophrenic state in 2 cases of wake-amine addicts.

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<sup>1</sup> Watanabe, G. (1951) *Yonago Igaku Zasshi*, 3, 53

## 8. Measures Taken to Control Abuse

### 8.1 *Legislative counter-measures*

In July 1949 the Japanese Government restricted the use of wake-amine to cases under doctor's prescription only. In June 1951 the Awakening Drug Control Law was enacted, by which the importation of wake-amine into Japan was prohibited, while the possession, manufacture, sale, and purchase of the drug were severely restricted. From the beginning the penal clauses of this law were strict, yet they were revised and made even more severe on 30 June 1954. Furthermore, the Awakening Drug Control Law was again revised by Parliament in 1955. According to the latest revision of 30 September 1955, the following substances which can be converted into wake-amine or used to synthesize wake-amine will be controlled as strictly as the latter :

1-Phenyl-2-methylaminopropanol-1 and its salts  
 1-Phenyl-1-chloro-2-methylaminopropane and its salts  
 1-Phenyl-2-dimethylaminopropanol-1 and its salts  
 1-Phenyl-1-chloro-2-dimethylaminopropane and its salts  
 1-Phenyl-2-dimethylaminopropane and its salts  
 Phenylacetic acid and its salts  
 Phenylacetonitrile  
 Phenylacetone  
 Other substances, which can be used for making wake-amine, and are listed by the Ministry of Welfare

### 8.2 *Medical care and rehabilitation of addicts*

It is necessary to treat the addict in a special institution for a certain period in order to rid him of the habit and to correct his way of life.

There is at present only one special hospital (200 beds) near Tokyo for such cases ; other patients are treated in ordinary psychiatric hospitals. Among such psychiatric hospitals, the following were assisted by appropriations from the national budget in 1954 :

Hospitals owned by prefectural governments (Hyogo and Kanagawa) . . . . .	110 beds
Hospitals owned by corporations (Osaka, 85 beds; Tokyo, 40 beds) . . . . .	125 "
Hospital owned by a municipality (Toyooka City) . . . . .	20 "
Total . . . . .	255 beds

In 1955 the national budget was to provide for 2100 beds.

The investigation which was made by the Hokkaido Government in March 1955 revealed that 133 patients had been hospitalized within the previous year, and that 43 addicts were at that time in hospital. It is really surprising to realize that such inadequate medical facilities are provided for an estimated 250 000-300 000 patients at present in Japan.

### 8.3 *Movement to overcome the wake-amine tragedy*

In January 1955 the Cabinet set up the Awakening Drug Counter-measure Headquarters. The Minister of Welfare heads this office to which are attached prefectural branches headed by prefectural governors. The function of this institution is to make the public realize how tragic is the evil of wake-amine abuse and to gain public co-operation in the movement to eliminate it. This educational movement is now progressing on a nationwide scale. As a first step, efforts are being made to educate youth and especially to supervise those who live in and near such areas of addiction as the red-light districts.

At the present stage no one can tell exactly how effective this campaign will prove to be, but it is believed that the public is becoming more and more aware of the danger and increasingly concerned about measures for its control.

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