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WORLD HEALTH ORGANIZATION
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No. 116

**EXPERT COMMITTEE ON
ADDICTION-PRODUCING DRUGS**

Seventh Report

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EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Seventh Session

Geneva, 18-24 October 1956

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EXPERT COMMITTEE ON ADDICTION-PRODUCING DRUGS

Seventh Report *

The Expert Committee on Addiction-Producing Drugs held its seventh session in Geneva from 18 to 24 October 1956. The session was opened by the Deputy Director-General of the World Health Organization, who welcomed the members. Referring to the agenda and in particular to several items of general concern, he outlined the role of the Committee in the international control of drug addiction and expressed the World Health Organization's appreciation of the work of its members.

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

There are very many items of particular interest to the Committee, only a few of which can be referred to here or in connexion with other items of this report. It is noteworthy that social and health measures are being taken as means of combating the coca-leaf chewing problem, because they exemplify a shift in general attitude from attempts at strict prohibition to efforts to remove the root of the problem. It is important,

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

1. ADOPTS the seventh report of the Expert Committee on Addiction-Producing Drugs ;
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 EB19.R7, *Off. Rec. Wld Hlth Org.*, 1957, 76)

¹ United Nations, Economic and Social Council (1956) *Commission on Narcotic Drugs : report ... on the eleventh session ... 23 April to 18 May 1956* (Mimeographed document E/2891-E/CN.7/315)

too, that more countries are reporting on efforts towards treatment of addiction, giving indication of some initial success with simple methods. Burma, Iran and Singapore may be mentioned in this connexion.

The Committee took note of the resolution adopted by the Commission on Narcotic Drugs with respect to new narcotic drugs and was especially concerned that every effort should be made not only to avoid hampering but also to promote scientific and medical developments in this field. It emphasized the very great difficulty involved and the time which must elapse in the determination of relative advantages and special uses of new drugs, in spite of the quite definite recent improvements in the techniques for clinical evaluation.

2. Resolutions of the United Nations Economic and Social Council

Having taken note of the resolutions of the United Nations Economic and Social Council on technical assistance for narcotics control¹ the Committee was of the opinion that international symposia or seminars, participated in perhaps by the World Health Organization, United Nations and other international agencies, might be of particular value in this connexion. Such subjects as the following might be discussed: diagnosis of drug addiction, including the use of nalorphine for this purpose; treatment of drug addiction; prevention of drug addiction; basic research on the mechanism of addiction; sources of information and techniques for determining addiction liability of drugs; effectiveness versus disadvantages of narcotic drugs; and the relationship of chemical structure to analgesic action and other properties of narcotic drugs. Therefore, the Committee suggested that WHO should explore the possibility of organizing symposia or seminars on these and related subjects as an adjunct to technical assistance.

3. Reports of the Permanent Central Opium Board² and the Drug Supervisory Body³

Of very great interest to the Committee were the figures on the consumption of morphine and some of its derivatives, and of some of the

¹ United Nations, Economic and Social Council (1956) *Economic and Social Council. Official records: twenty-second session, 9 July - 9 August 1956. Supplement No. 1. Resolutions*, Geneva, pp. 14, 15 (Document E/2929)

² United Nations, Permanent Central Opium Board (1955) *Report to the Economic and Social Council on the work of the Board in 1955*, Geneva (Document E/OB/11)

³ United Nations, Drug Supervisory Body (1955) *Estimated world requirements of narcotic drugs in 1956*, Geneva (Document E/DSB/13)

synthetic narcotic drugs. Note was taken of the fact that both the downward trend in consumption of morphine and the upward trend in the proportion of morphine converted to morphine derivatives, such as codeine, dionine and pholcodine, were continuing. The increase in codeine consumption was very striking, as was the increase in dionine. From 1950 to 1954, world consumption of dionine increased by 36%. From 1951 to 1954, world consumption of pethidine increased by about 28%, that of methadone by about 42%, while the production of ketobemidone declined and production of other synthetic narcotic drugs was extremely small. These trends, in the opinion of the Committee, reflect diversification and development of new medical uses, particularly of new drugs, the following-up of which should be of very great interest and importance.

The Committee took note also of the view of the Permanent Central Opium Board and the Drug Supervisory Body that weight (in absolute figures or per million inhabitants) is probably not the best criterion for studying the consumption of the various drugs, whether it be for the purpose of making comparisons between drugs or between countries. A more satisfactory method would be to group together drugs which can be substituted for each other or used concurrently in their main applications, and to express consumption in terms of therapeutic efficacy. The Committee felt that a comparison on the basis of therapeutic efficacy would provide additional information of definite value and hoped that a yardstick for such a comparison could be devised.

4. Morphine and its Derivatives

4.1 *Situation regarding diacetylmorphine (heroin)*

The Committee, noting the persistence of a relatively small residuum of licit use of diacetylmorphine, as indicated in the reports of the Commission on Narcotic Drugs¹ and of the Permanent Central Opium Board,² nevertheless maintained its stand that diacetylmorphine is not indispensable and urged continuation of all possible measures, consistent with effective clinical practice, to bring about the replacement of diacetylmorphine by other agents which may be used with less risk to public health.

¹ United Nations, Economic and Social Council (1956) *Commission on Narcotic Drugs : report . . . on the eleventh session . . . 23 April to 18 May 1956*, paragraphs 272-281 (Mimeographed document E/2891-E/CN.7/315)

² United Nations, Permanent Central Opium Board (1955) *Report to the Economic and Social Council on the work of the Board in 1955*, Geneva, p. 12 (Document E/OB/11)

5. Synthetic Substances with Morphine-like Effect

5.1 *Synthetic substances of morphinan type*

(+)-3-Hydroxy-N-phenethylmorphinan, designated also d-3-hydroxy-N-phenethylmorphinan

Referring to the notification from the Government of Switzerland requesting the exemption of (+)-3-hydroxy-N-phenethylmorphinan from the obligations of the International Conventions on Narcotic Drugs, the Committee considered carefully the argument in the memorandum accompanying that notification, and reviewed the recommendations made with respect to 3-hydroxy-N-phenethylmorphinan in its sixth report¹ to which exception is taken. The Committee was of the opinion that, when a substance existed as a racemate and its optical isomers, and evidence was available on the addiction liability of the racemate or one of its isomers, the only course compatible with public safety was the application of narcotics control to all isomeric forms of the substance, as has been done in the present instance, until or unless there was specific evidence to the contrary. The Committee was further of the opinion that argument by analogy could not in general be considered an adequate basis for exemption from narcotics control, more especially so for exemption of an optical isomer whose antipode had been shown to have strong addiction-producing properties. For such an exemption to be recommended there must be specific evidence on the absence of addiction liability, and specific or strong presumptive evidence on the impracticability of racemization or conversion to the optical form having addiction liability. Therefore, the Committee concluded that action on the request for exemption of (+)-3-hydroxy-N-phenethylmorphinan must be deferred until the necessary evidence became available.

5.2 *Synthetic substances of dithienylbutenylamine type*

3-Piperidino-1,1-di-(2'-thienyl)-1-butene

The Committee's attention was drawn to the above substance and to an inquiry regarding its manufacture which raised the question of its liability to produce addiction. Evidence had been presented previously that three members of the dithienylbutenylamine group, namely, 3-dimethylamino-1,1-di-(2'-thienyl)-1-butene² (dimethylthiambutene³); 3-ethylmethylamino-1,1-di-(2'-thienyl)-1-butene² (ethylmethylthiambutene³); and

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1956, **102**, 8 (section 5.1.4)

² See *Wld Hlth Org. techn. Rep. Ser.*, 1954, **76**, 9 (section 4.4).

³ Proposed international non-proprietary name

3-diethylamino-1,1-di-(2'-thienyl)-1-butene¹ (diethylthiambutene²), were addiction-producing substances comparable to morphine, and on the basis of this evidence each of these substances was subjected to international control measures in accordance with the provisions of the 1948 Protocol.³ Furthermore, in its fourth report, the Committee expressed the opinion that "the closest watch should be kept upon the development of new dialkyl-dithienylamines because those so far examined are so closely similar in their properties as to make the group of dialkyl-dithienylamines as a whole suspect with respect to addiction-producing properties."⁴

It should be noted also that 3-piperidino-1,1-di-(2'-thienyl)-1-butene was shown to have an analgesic effectiveness equivalent to that of morphine.⁵

A survey on the relationship between analgesic action and addiction liability showed that there existed for most of the drugs considered a parallelism in the order of intensity of these two effects and that this parallelism was apparent for the members of the dithienylbutenylamine group which were included.⁶

Since the order of analgesic effectiveness was very similar for the piperidino-dithienyl derivative and for the other dithienyl compounds whose addiction liability was known, the Committee believed it could be justifiably concluded that the addiction liability of 3-piperidino-1,1-di-(2'-thienyl)-1-butene would be comparable to that of morphine.

At the same time the Committee suggested that direct evidence on the addiction-producing properties of 3-piperidino-1,1-di-(2'-thienyl)-1-butene should be sought if clinical application of the compound is intended.

5.3 *Synthetic substances of pethidine type*

5.3.1 *1-[2-(p-Aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester, designated also 1-[2-(p-aminophenyl)-ethyl]-4-carbethoxy-4-phenylpiperidine*⁷

A notification from the Government of the United States of America regarding, inter alia, the above designated drug, was before the Committee

¹ See *Wld Hlth Org. techn. Rep. Ser.*, 1956, **102**, 10 (section 5.3).

² Proposed international non-proprietary name

³ Protocol bringing under international control drugs outside the scope of the Convention of 13 July 1931 for limiting the manufacture and regulating the distribution of narcotic drugs, as amended by the Protocol signed at Lake Success on 11 December 1946 (United Nations, document E/NT/7).

⁴ *Wld Hlth Org. techn. Rep. Ser.*, 1954, **76**, 9 (section 4.4)

⁵ Green, A. F. (1953) *Brit. J. Pharmacol.*, **8**, 2

⁶ Eddy, N. B., Halbach, H. & Braenden, O. J. (1956) *Bull. Wld Hlth Org.*, **14**, 353

⁷ The name anileridine has been suggested, but has not yet been accepted, as a proposed international non-proprietary name.

at its sixth session in 1955.¹ A complete report on the testing of this compound for addiction-producing properties now being available, the Committee was of the opinion that 1-[2-(*p*-aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester, 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 1-[2-(*p*-aminophenyl)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

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

5.3.2 α -1-Methyl-3-ethyl-4-phenyl-4-propionoxypiperidine
(*alphameprodine* ²)

Referring to the notification of the Government of the United States of America, the Committee was of the opinion that α -1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine,³ 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 α -1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, paragraph 2, Group I. Therefore,

The Expert Committee on Addiction-Producing Drugs

RECOMMENDS that its opinion with respect to α -1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine (*alphameprodine*) and its salts be communicated to the Secretary-General of the United Nations.

6. 2,4-Diamino-5-phenylthiazole and β -Ethyl- β -methylglutarimide

The Committee took note of current research with these products as possible antagonists to some of the undesirable effects of morphine and

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1956, **102**, 11 (section 5.4)

² Proposed as international non-proprietary name.

³ The substance having this chemical designation has been examined under the code numbers Nu-1932 and Nu 2-1932, and without any doubt it corresponds stereochemically to *alphaprodine*.

related substances, and as possible adjuvants to analgesic action. It was particularly interested in the work going forward in several research centres to determine whether or not these agents affect the rate of development of addiction. The progress of these experiments will be watched very closely.

7. Abuse of Amphetamines

The Committee's attention was drawn to a progress report on the use and abuse of amphetamines in Japan, in which it was shown that a serious situation still exists, but that substantial amelioration had been attained by the vigorous enforcement of local control measures. The Committee was pleased to note, as a step towards lessening amphetamine abuse in other areas, the unanimous adoption by the Commission on Narcotic Drugs of a resolution in which "it took note of the dangers arising from the abuse of amphetamines and recommended that governments should provide adequate measures of control to prevent such abuse".¹

8. Definition of Habit-Forming Drugs

Reviewing at this time the definitions of addiction-producing and habit-forming drugs as drafted in its second report² and clarified in its third report,³ the Committee was of the opinion that the time was ripe for emphasizing again the distinction between addiction and habituation (see Annex, page 12). To this end the following definitions were approved:⁴

Drug addiction

Drug addiction is a state of periodic or chronic intoxication 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;

Drug habituation

Drug habituation (habit) is a condition resulting from the repeated consumption of a drug. Its characteristics include:

- (1) a desire (but not a compulsion) to continue taking the drug for the sense of improved well-being which it engenders;

¹ United Nations, Economic and Social Council (1956) *Commission on Narcotic Drugs: report . . . on the eleventh session . . . 23 April to 18 May 1956*, paragraph 328 (Mimeographed document E/2891-E/CN.7/315)

² *Wld Hlth Org. techn. Rep. Ser.*, 1950, **21**, 6-7 (sections 6.1-6.3)

³ *Wld Hlth Org. techn. Rep. Ser.*, 1952, **57**, 9 (section 6.1)

⁴ The definition for drug addiction is substantially the same as the one given in the second report of the Committee; that for drug habituation is new.

Drug addiction

- (2) a tendency to increase the dose;
- (3) a psychic (psychological) and generally a physical dependence on the effects of the drug;
- (4) detrimental effect on the individual and on society.

Drug habituation

- (2) little or no tendency to increase the dose;
- (3) some degree of psychic dependence on the effect of the drug, but absence of physical dependence and hence of an abstinence syndrome;
- (4) detrimental effects, if any, primarily on the individual.

9. Barbiturates

Evidence presented to the Committee indicated that the consumption of barbiturates continues to increase; the situation with respect to them has not ameliorated. It must be stated that barbiturates are habit-forming as defined above (see section 8) and in some circumstances can produce a drug addiction dangerous to public health (see Annex, pages 13-14), although differentiation among them with respect to the intensity of this liability cannot yet be made. The Committee continued to be of the opinion that control measures at the national level are sufficient at the present time but need close attention and, in some instances, definite strengthening:

- (1) Barbiturates, whatever the dose or admixture, should be dispensed only on prescription;
- (2) a prescription should specify the number of times it may be refilled or repeated;
- (3) there should be a record of such prescriptions.

10. "Tranquilizing" Drugs

The Committee's attention was drawn to the very rapidly increasing use of those agents which are being described as "tranquilizers" and "ataraxics". The Committee believed that these substances, diverse in their chemical characteristics but similar in their central sedative action, must be classed as potentially habit-forming. In addition, some evidence has been presented that, under conditions of excessive use, a characteristic withdrawal syndrome can appear (see Annex, page 14). In this respect, the "tranquilizers" and "ataraxics" resemble the barbiturates and should be subjected to national control. Their continuing clinical use should be followed very closely for an eventual evaluation of their relation to public safety.

11. Bibliography of Drug Addiction

The advantages and the difficulties of initiating and maintaining a compilation of material on drug addiction, not only titles of published papers but also informative abstracts, as a centralized source of information in this field were discussed. The Committee was of the opinion that such a compilation would be very valuable and suggested that even a modest beginning towards the over-all objective of such a compilation would be worthwhile. Members of the Committee offered to assist by making available some of their own material and it was suggested that correspondence with members of the WHO Expert Advisory Panel on Addiction-Producing Drugs might result in additional offers of the same sort.

12. International Non-Proprietary Names

Attention has been drawn again to the need for overcoming difficulties in the initiation of suggested international non-proprietary names for substances to be brought under narcotics control.¹

In compliance with the 1948 Protocol,² notifications were transmitted to the Secretary-General of the United Nations as soon as practicable after evidence had become available on addiction liability, in some instances at a quite early stage in the development of a new compound, even before any decision as to marketing had been made. For some such compounds, the mechanism for selection of an international non-proprietary name has not yet been initiated.

The Committee is of the opinion that the procedure outlined in its fifth report³ still offers a means for facilitating and speeding up the selection of an international non-proprietary name. However, if this provision has not been or cannot be carried out so that a suggestion for a proposed name is not available when a notification with respect to a new narcotic drug is transmitted to the Secretary-General of the United Nations, the government concerned might at that time request the World Health Organization to suggest an appropriate name. Lacking such a request, WHO should on its own initiative devise a proposed non-proprietary name.

¹ See United Nations, Economic and Social Council (1956) *Commission on Narcotic Drugs: report . . . on the eleventh session . . . 23 April to 18 May 1956*, paragraphs 60-65 (Mimeographed document E/2891-E/CN.7/315).

² See footnote 3 on page 7.

³ *Wld Hlth Org. techn. Rep. Ser.*, 1955, **95**, 11 (section 10)

The Committee suggested that WHO should consider the appropriateness of again drawing the attention of governments to the procedure for speeding up selection of international non-proprietary names outlined in its fifth report, together with the alternative proposals mentioned above.

Annex

HABIT-FORMING DRUGS

At its second session, the Expert Committee on Drugs Liable to Produce Addiction defined a habit-forming drug as "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".¹ The characteristics of drug addiction as set forth in the definition adopted at the same session are "(1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means; (2) a tendency to increase the dose; (3) a psychic (psychological) and sometimes a physical dependence on the effects of the drug".¹ The definition said also that addiction is detrimental to the individual and to society.

The Committee was of the opinion that the use of the expression "habit-forming", when the meaning is clearly "addiction-producing" should be discontinued. It reiterated this opinion in its third report,² declaring "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 went further in its third report, seeking by a series of statements to clarify the differences between addiction-producing and habit-forming drugs. It did not re-define the latter.

The original definition of a habit-forming drug is ambiguous since it implies that any one or more of the characteristics of an addiction-producing drug may not be apparent. It is also doubtful whether it was

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1950, **21**, 6-7

² *Wld Hlth Org. techn. Rep. Ser.*, 1952, **57**, 9

correct to say that a habit-forming drug is not generally considered to be detrimental to the individual. It is this very point of possible harm to the individual which makes further consideration of the question important.

The statements in the third report point out the possibility of individual and sociological damage and emphasize one point of distinction with respect to a habit-forming drug, namely: the lack of compulsive craving, but the development of a habit of administration because the effect of the drug is found desirable to the individual. These statements in the third report seem to have been largely overlooked, perhaps because they are not as explicit in setting forth the characteristics of a habit-forming drug as they might be, and the two expressions addiction-producing and habit-forming are still too commonly used interchangeably.

In the USA, the term "habit-forming" to include addiction-producing and some other drugs, was and still is employed in the regulations under the Food, Drug and Cosmetic Act, in which it is expressly stated that packages containing any one of a given list of drugs must carry a warning on the label: "May be habit-forming". The expression "habit-forming" seems to have been employed in the regulations partly because at the time it was a generally used term in the sense of addiction-producing and partly in order to apply the warning to substances for which there was no evidence then of their addiction potentiality but for which there must have been admitted habit-forming liability. These included the barbiturates and some other sedative drugs. The expression "habit-forming" still has the connotation of addiction-producing in the minds of many, and the situation cannot be clarified as long as "habit-forming" is used in a dual sense or as long as there is not a more precise differentiation of terms by a more explicit definition.

Many authorities have expressed the view that all drugs which are used therapeutically for a central sedative or tranquilizing effect, to promote sleep or to relieve anxiety, may be habit-forming. Some drugs which are used for a central stimulating or exhilarating effect may also be habit forming. With both types, the essential factor presumably is improvement in the sense of well-being. Habituation with these agents is not primarily or essentially an abuse, except that it may lead to unduly prolonged or excessive administration not related to symptomatic relief. Such excessive administration may result in physical dependence and development of a true addiction. With the barbiturates, for example, Fraser and his associates¹ have established that there is a critical dosage level for some barbiturates above which definite addiction with all of its characteristics

¹ Fraser, H. F. et al. (1956) *Fed. Proc.*, **15**, 423

is demonstrable. Whether this is so for sedatives generally is not known, but the possibility of their producing habituation should be recognized and becomes of greater and greater importance with the widespread and ever-increasing use of the so-called "tranquilizing" agents.

Lemere¹ has commented on the possibility of habituation to one of these agents, meprobamate. He said:

"A psychologic dependency on the drug is also undoubtedly created in certain patients. Many feel so much less tense when taking the drug that there may be an exaggerated feeling of well-being. Some may even experience a degree of exhilaration or euphoria. In most cases, this does not appear to be harmful, but in a few patients it leads to overdosage . . . I have had 13 cases among over 600 patients for whom I have prescribed meprobamate in which the drug had to be discontinued because of excessive self-medication . . . I personally have seen patients under the influence of 6 or more tablets a day manifest all the signs of intoxication, including euphoria, dysarthric speech, and generalized incoordination. Other patients simply take so much of the drug that their relatives complained of their 'lying around sleeping all day' . . ."

Lemere mentions one patient who had been taking 6.4 g of meprobamate daily for a month and who had a convulsion ten hours after discontinuing the drug. H. Isbell (personal communication) reports that a similar case has come to his attention. These cases call to mind the convulsions which may occur as a part of the abstinence syndrome after abrupt discontinuance of large doses of barbiturates and suggest that meprobamate may, like the barbiturates, have a critical dose level above which a true physical dependence develops, but below which only habituation occurs.

The time is ripe for emphasizing again the distinction between "addiction" and "habit" and the strict application of the terms "addiction-producing" and "habit-forming" that there may be appropriate warning in both instances on labels and in all literature, so that the occurrence of abuse may be watched for and guarded against. Addiction-producing drugs need strict control, international and national; for habit-forming drugs the warning and national control measures should suffice, at least until such time as the seriousness of habituation in a particular case is fully established, but any warning concerning habituation should not carry the stigma of addiction.

Three things then are necessary: (1) the drafting of as precise a definition as possible of a "habit-forming drug" and of "drug habituation"; (2) the recommendation that these terms, as well as "addiction-producing" and "drug addiction", be used in compliance with their established definitions in all literature, including warning labels, and (3) the establishment of criteria by which the development of habituation may be determined.

¹ Lemere, F. (1956) *Arch. Neurol. Psychiat. (Chicago)*, 76, 205

A *habit-forming drug* is one which produces habituation (habit) but not addiction when used continuously at about the usual therapeutic dose level. Some habit-forming drugs when used excessively, in terms of dosage and/or frequency of administration, may produce a true physical dependence (addiction), superimposed upon a psychic dependence.

Drug habituation resulting from the repeated administration of a drug must have certain characteristics: a degree of psychic dependence; a desire, but not a compulsive craving, to continue taking the drug for the sense of improved well-being which it engenders. A tendency to increase the dose to maintain or increase the effect may or may not be present, and physical dependence, with its concomitant of a withdrawal syndrome is always absent. Any detrimental effect of habituation is primarily directed to the individual. Abuse, with habit formation, may, however, become so widespread as to be detrimental to society, usually a geographically localized society. The abuse of amphetamines in some areas, the excessive use of barbiturates, and the extensive and spreading use of tranquilizing agents are examples of such widespread abuse.

The most difficult part of all may be the establishment of satisfactory criteria for determining the presence of habituation, but a few suggestions may be made. Proof of psychic dependence is essential, and it is doubtful that any animal experiment can furnish such proof even though animals can develop a habit of performance. Regularity of administration in man, with or without a change in dose or frequency, and ability to distinguish between the drug of habituation and a placebo are possible criteria. A questionnaire could be developed to be filled out periodically during administration of the drug and of a placebo, which would throw light on the presence of psychic dependence. A psychically dependent—that is, an habituated—individual would probably seek the same or similar medication if administration were interrupted and in order to obtain resumption of such medication would tend to exaggerate the recurrence of symptoms said to be relieved by the drug. Undoubtedly there are other useful criteria for habituation. A carefully thought-out, carefully controlled double-blind study with a group of sedative agents and a placebo, on patients seeking relief for anxious or nervous states, would seem a useful line of attack which would go far to clarify the whole situation.

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First report	84	1/9	0.25	1.—
Alcohol and Alcoholism				
Report of an expert committee	94	1/9	0.30	1.—
Alcoholism Subcommittee				
See under Mental Health.				
Amputees and Prostheses				
Report of a conference on prosthetics	100	3/6	0.60	2.—
Antibiotics, Expert Committee on				
Report on the first session	26	9d.	0.10	0.40
Biological Standardization, Expert Committee on				
Report on the third session	2		<i>Out of print</i>	
Report on the fourth session	36	9d.	0.10	0.40
Fifth report	56	1/3	0.15	0.60
Sixth report	68	1/6	0.20	0.80
Seventh report	86	1/9	0.25	1.—
Eighth report	96	1/9	0.30	1.—
Ninth report	108	1/9	0.30	1.—
Report of the Subcommittee on Fat-Soluble Vitamins	3	9d.	0.10	0.40
Diphtheria and Pertussis Vaccination				
Report of a conference of heads of laboratories producing diphtheria and pertussis vaccines	61	4/3	0.55	2.20
Environmental Sanitation, Expert Committee on				
Report on the first session	10	2/—	0.25	1.—
Second report	47	1/3	0.15	0.60
Third report	77	1/9	0.25	1.—
Fourth report ("Food Hygiene")	107	1/9	0.30	1.—
Food Additives, Joint FAO/WHO Conference on				
Report	104	1/9	0.30	1.—
Health Education of the Public, Expert Committee on				
First report	89	1/9	0.25	1.—
Malnutrition, Prevention and treatment of severe, in times of disaster				
Report of a group of consultants	45	2/9	0.35	1.40
Maternity Care, Expert Committee on				
First report: a preliminary survey	51	1/3	0.15	0.60
Meat Hygiene, Joint FAO/WHO Expert Committee on				
First report	99	3/6	0.60	2.—