An evaluation of narcotics controls discloses that our Nation's statutes are not sufficiently flexible in view of new discoveries in synthetic analgesics. Suggested changes include a redefinition of addiction and uniform national and international laws.

Addiction Liability and Narcotics Control

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AMONG the most effective measures for the prevention of drug addiction are the Federal laws and international treaties controlling the production and distribution of the drugs of addiction and the source materials from which these drugs are derived. The application and administration of these laws have steadily become more complex. A large number of synthetic drugs with pharmacological effects and addiction liability similar to that of morphine have been discovered and have created some difficult problems of classification and control. It is now also known that substances, such as the barbiturates and the amphetamines, covered by the food and drug but not by the narcotic laws, are susceptible to abuse and may produce a different addiction from that caused by the opiates. It is the purpose of this paper to review the historical origin of the present narcotic laws and to discuss changes in them which seem desirable in the light of recent knowledge.

Definition of Addiction

In 1950, at the request of the Commission on Narcotic Drugs of the United Nations, the Expert Committee on Addiction-Producing Drugs of the World Health Organization drafted a definition of addiction (*1*). The committee said, "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; (2) a tendency to increase the dose; (3) a psychic (psychological) and sometimes a physical dependence on the effects of the drug."

In its third report (*2*) in 1952, the expert committee wrote an explanation of the characteristics of addiction designed particularly to express its view on a distinction between addiction and habituation. In 1957, to clarify further this distinction, the expert committee reworded its definition of addiction without material change in its meaning (*3*).

This definition received some acceptance but also much criticism. It was not meant to be pharmacological, nor strictly speaking scientific, but practical, and was intended to include the diverse substances currently under international narcotics control. State and national narcotics laws and regulations and international narcotics conventions are designed to prevent or at least limit abuse of cocaine and marihuana as well as of opium and the potent analgesics. Though all of these substances are commonly and loosely termed narcotics, their properties

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differ so widely that they are similar only in being subject to abuse and in creating social dangers. Of necessity, any definition attempting to cover all of them had to be very broad.

National Control

When control was first considered (1909–12) and for a considerable time thereafter, only cocaine and opium and its alkaloids were taken into account. Their abusive use was recognized and considered of sufficient importance to warrant strict control, even at the expense of placing a burden upon drug manufacturers, pharmacists, and physicians, as well as upon the government which had to implement the control. Relatively few individuals abused both opiates and cocaine, the effects of which are different and in some respects opposite; yet both were called narcotics and both were subjected to the same control measures.

An excellent chronological review of the steps in the development of national and international control of narcotic drugs was published in 1953 (*4*).

Merely listing the principal acts of Congress on this subject with their chief intent will indicate the progress of events and the development of thought on the problem of control:

February 9, 1909. Prohibition of importation of opium and its preparations and derivatives except for medicinal purposes and absolute prohibition of importation of smoking opium.

January 17, 1914. Prohibition against exportation of opium and cocaine and salts, and derivatives and preparations thereof, except to a country which regulated the entry of such drugs; absolute prohibition of exportation of smoking opium.

January 17, 1914. Prohibitive tax upon opium manufactured for smoking purposes.

December 17, 1914. Harrison Narcotic Law, an internal revenue measure by tax and registration limiting the availability of narcotic drugs to medical and scientific uses, and regulating production, manufacture, and distribution, through channels of medical supply to the dispensing registrants, the qualified practitioner, and druggist.

May 26, 1922. Narcotic Drugs Import and Export Act, an extensive revision of the act of 1909 authorizing the importation of such quantities only of opium and coca leaves as were found to be necessary for medical and legitimate needs. Importation of any form of narcotic drug except crude opium and coca leaves was prohibited. Exportation of manufactured drugs was permitted under a system of control designed to assure their use for medical needs only in the country of designation.

June 7, 1924. Amendment to the Narcotic Drugs Import and Export Act prohibiting the importation of opium for the manufacture of heroin.

June 14, 1930. An act establishing the Bureau of Narcotics in the Department of the Treasury.

August 2, 1937. The Marihuana Tax Act. Imposition of registration and occupational tax on all persons who produced, imported, manufactured, sold, or transferred marihuana.

August 9, 1939. Contraband Seizure Act, authorizing confiscation of any vessel, vehicle, or aircraft used to facilitate transportation and so forth of contraband narcotics or marihuana.

December 11, 1942. Opium Poppy Control Act, prohibiting the growth of the opium poppy in the United States, except under special license issuable when need is shown for domestic production for medical and scientific uses.

July 1, 1944. A statute making the Federal narcotic laws applicable to pethidine (meperidine, Demerol) under the statutory designation "Isonipecaine."

March 8, 1946. The Opiates Act, or Robertson Amendment, establishing a general procedure for the expeditious application of control measures to any drug found to be dangerous from the addiction-liability standpoint.

1955–59. The Karsten bill, designed, among other things, to implement our obligation under the 1948 protocol to bring new substances under narcotics control. This bill is still pending. Consideration is being given to its possible amendment looking to greater flexibility in our system of narcotics control, tailoring, so to speak, the degree of control to the degree of risk to public health. Among those giving thought to the desirability of such amendment, the Committee on Drug Addiction and Narcot-

ics of the National Research Council discussed the problem at length at its 20th meeting, January 11, 1959, and passed unanimously a resolution embodying its views (*5*).

International Control

The first effective effort toward obtaining international action to control the traffic in opium and the dangerous drugs obtained therefrom was the conference of the International Opium Commission convened in Shanghai in February 1909, on the initiative of the U.S. Government. The successive steps or agreements on international narcotics control, again reflecting the development of thought on this problem, have progressed as follows:

International Opium Convention of 1912. Designed to bring about the gradual suppression of the abuse of opium, morphine, and cocaine, as also of the drugs prepared or derived from these substances which give rise or might give rise to similar abuses. The contracting parties agreed to enact effective laws or regulations for the control of the production and distribution of raw opium. A less definite obligation was imposed with respect to smoking opium, and the contracting parties' best efforts were to be used with respect to morphine and cocaine and their salts to restrict their import and export to authorized persons and to enact laws limiting exclusively to medical and legitimate purposes the manufacture, sale, and use of these dangerous drugs.

Geneva Narcotics Convention of 1925. Intended to impose somewhat more specific obligations with respect to control of national and international trade. It established the Permanent Central Opium Board to watch continuously the course of international trade in the drugs covered by the 1912 convention, collect and examine statistics, and obtain and communicate to all parties explanations of apparently excessive accumulations of the dangerous drugs in any country.

Convention of 1931. Limited the manufacture and regulated the distribution of narcotic drugs by requiring all countries, whether or not parties to the convention, to supply annual estimates of their needs of stated derivatives of opium and coca leaves, based solely on medical and scientific requirements. Thereafter, each country was obligated to limit its manufacture of each of the drugs in accordance with its estimate and to supply periodically to the Permanent Central Opium Board statistics of actual manufacture, consumption, importation, and exportation of those drugs. In other words, the convention contemplated the adjustment of world manufacture to legitimate world demand, the control of all channels of distribution, both national and international, and provision for a recording system of all narcotic drug operations. It entrusted to international organizations the task of supervising and coordinating throughout the world. The convention specified the drugs to be controlled and made some provision for additions to the list.

Protocol of 1946. Transferred to the Commission on Narcotic Drugs of the United Nations Economic and Social Council the functions previously carried out by the Opium Advisory Committee of the League of Nations.

Protocol of 1948. Established an international procedure, analogous in principle to that of our Opiates Act of 1946, whereby new drugs found to have dangerous addiction liabilities are promptly brought under the control imposed by the 1931 convention, the definitive finding in this case being made by the World Health Organization.

Opium Protocol of 1953. Designed to limit definitely the production of opium to medical and scientific needs and to establish the areas of production and sources of world supply. This protocol has not yet become effective.

Single Convention. Originally intended to incorporate into a single agreement by codification the provisions of the various international narcotics conventions but actually undergoing elaboration. It is still in the drafting stage.

Need for Flexibility

It is apparent that, initially, thought and effort toward narcotics control were centered upon the crude materials, opium and coca leaves, or upon the potent drugs obtained from them, morphine and its derivatives and cocaine. In the United States marihuana was added to the list of substances controlled because of evidence

of widespread abuse. The picture changed with the discovery and introduction into medicine of the first synthetic morphine-like pain-relieving drug (pethidine, meperidine, Demerol), the tremendous impetus to research on analgesics which followed that discovery, and the important advances which have been made in the study of addiction. It would seem desirable to consider how the picture has changed and to try to understand the implications of the change.

Pethidine was but the first of a very large number of substances prepared entirely by synthesis in the laboratory which exhibited in animals and man wide differences in analgesic and physical dependence properties. These substances also are widely different in chemical structure. Some are built upon moieties of the morphine molecule. Others differ so greatly in chemical structure that the tentative relationships of structure and analgesic action described by Braenden, Eddy, and Halbach (*6*) as recently as 1955 cannot always be discerned.

It is well recognized from clinical experience and direct evaluation experiments under controlled conditions that substances derived from morphine differ in analgesic potency and addiction liability and present different degrees of risk to public health, ranging from the great danger of heroin, the main drug in the present-day illicit traffic in the United States, to relatively low risk with codeine, which with proper therapeutic use rarely results in addiction.

Examples of all the synthetic chemical types have been evaluated for addiction liability as well as for analgesic effect and have exhibited a range of activity from much greater than morphine to substantially less than codeine. In this connection the expert committee (*7*) has stated "that synthetic analgesic drugs differ from one another in addiction liability just as do drugs derived from natural sources 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 synthetic drugs is neither greater nor less than the risk encountered through the use of morphine, related opium alkaloids, or substances derived therefrom."

For the natural alkaloids, that is, for substances which are modifications of morphine whether occurring in opium or produced in the laboratory, the 1931 convention recognized a difference and established groups I and II for which control regimens would be different. Group I was further subdivided into subgroup (a) comprising morphine and similarly addicting substances, and subgroup (b) comprising ecgonine, thebaine, and other drugs regarded as not themselves addicting but convertible into drugs capable of producing addiction. Group II was established to include codeine, dionin, and related substances, likewise then regarded by many as not capable of producing addiction but also convertible into addiction-producing drugs. The distinction was drawn between subgroup (b) and group II not on theoretical but on practical grounds, namely, that the drugs in group II were very extensively used in medicine all over the world, whereas those in subgroup (b) were hardly used at all by the medical profession (*8*). All measures of control were applicable to all drugs in group I (both subgroups), but a somewhat modified control was permitted for the drugs of group II. For the latter the substances themselves were controlled internationally in essentially the same way as those in group I with only minor modifications such as greater leeway in estimates of needs and other statistical matters. However, under the convention, compounds of the drugs in group II, if they were adapted to normal therapeutic use, were exempted from international narcotics control.

The U.S. laws do not recognize a distinction in the regimen of control such as that between group I and group II of the 1931 convention except insofar as specifically described preparations of not greater than specified concentration may be sold as conditionally exempt preparations without a narcotics prescription. These limited exemptions were authorized before the discovery of pethidine and the many other synthetics, and the Opiates Act of 1946 made no provision for their extension to a preparation of any synthetic. This situation must be discouraging to pharmaceutical manufacturers and may act as a deterrent to research programs designed to develop analgesics of low addictiveness. Since under present

conditions any such agent could be controlled only in the same manner as morphine, our narcotics laws are in a sense hampering the search for a nonaddicting pain-relieving drug.

Clinical experience and direct addiction experiments indicate that cocaine does not produce physical dependence, and abrupt withdrawal after prolonged use is not followed by an abstinence syndrome. In the amounts taken by addicts in the United States, however, cocaine can cause a dangerous psychosis, and taken chronically it causes tachycardia, insomnia, and anorexia with resultant impairment of nutrition. Cocaine does produce strong psychic dependence, and its prolonged use is undoubtedly detrimental, hence its control by the narcotics laws. Similarly, marihuana does not produce physical dependence manifested by a withdrawal syndrome. Here, too, control is exercised because of the harmful effects of the drug under conditions of abuse.

In recent years the Addiction Research Center of the Public Health Service Hospital at Lexington, Ky., has been investigating the possibility of development of physical dependence during prolonged administration of barbiturates, meprobamate, and similar drugs. It has been shown conclusively that physical dependence could develop when large doses of these substances were taken chronically and that a characteristic abstinence syndrome followed abrupt withdrawal (*9–11*). It was also shown, however, that no clinically significant degree of dependence developed in persons taking only 0.4 gram or less daily of secobarbital or pentobarbital, that is, two to four times the usual daily oral dosage (*12*). It is clear from the work at Lexington that the symptomatology of abstinence with barbiturates or meprobamate is distinctly different from abrupt withdrawal of an opiate. Further, physical dependence or addiction with barbiturates and meprobamate has been observed in clinical practice (*13–15*).

It should be clear that addiction and its relation to narcotics control are complex qualitatively and quantitatively and that our present system of control is not realistically adjusted to this complexity. The Opiates Act says, for example, that the criterion for control of a new substance shall be ability to produce or sustain an addiction similar to that of morphine or cocaine. If, in this connection, the word similar is interpreted as implying quantitative similarity, difficulty must be encountered in bringing under control a substance of low addiction liability, substantially less than that of codeine, as has been the case with propoxyphene, a weak synthetic analgesic of the methadone group. This particular situation might be clarified by making the criterion for control "qualitatively similar to morphine," leaving to the judgment and experience of the responsible authority whether or not the addiction liability of a particular substance is sufficient in degree to constitute a risk to public health and thus warrants narcotics control. It is possible that control at the manufacturing and wholesale level only would be adequate for substances of low addiction liability where the risk to public health is small, leaving retail trade in drugs of minor addictive potential free of narcotics control, not requiring narcotics prescriptions, narcotics records, and the like.

It has been pointed out that our narcotics laws and regulations, while providing for exempt preparations of codeine and other substances derived from morphine and even for preparations containing up to a certain concentration of morphine itself, make no provision for exempt preparations of synthetic analgesics. Since it is known that the "natural" alkaloids, morphine and substances derived from it, and the synthetic analgesics vary in addictiveness and therefore in risk to public health, both the "natural" and synthetic classes of drugs should be treated in the same way. If exempt preparations are safe and permissible in the "natural" class, they should be safe and permissible in the synthetic class. On the other hand, if the argument is that there is some risk in exempt preparations of morphine and opium because of the possibility of abuse by the consumption of multiple doses, a similar risk would be expected with exempt preparations of synthetic substances with morphine-like addiction liability. The Expert Committee on Addiction-Producing Drugs of the World Health Organization has pointed out repeatedly the risk of

addiction through the use of multiple doses of preparations of strongly addicting substances (*16*, *17*) and that admixture with other substances cannot be relied upon to avoid such risk (*18*).

In contradistinction to what has just been said about exempt preparations of morphine, of opium, and of synthetics with comparable addiction liability, a very desirable measure of flexibility in narcotics control would be provided by extension of the exempt preparation provisions to substances of low addiction liability, irrespective of origin. Provided such a modification does not contravene any international agreement, the substances in pure form would be subjected to narcotics control, but preparations or combinations of them, in mixtures with other therapeutic non-narcotic agents from which the addicting substance would not be readily recoverable, would be exempt from narcotics control.

Our national laws make no provision for control of a substance not itself addicting but readily convertible into another substance known to be addicting. This lack could lead to grave danger, allowing free trade in the parent substance and giving opportunity for clandestine transformation into the addicting agent. It would seem desirable to control the convertible substance as one would control any substance into which it can be converted.

The categories of control now provided by law or suggested herein for a realistic relationship between degree of narcotics control and risk to public health then should include: full control for substances having high or intermediate addiction liability; the oral prescription list of substances or mixtures having little addiction liability; exempt status for preparations and mixtures of safe concentration from the standpoint of abuse; and control at the manufacturing and wholesale level only for substances with very low addiction liability. In addition, there would be advantage in an official listing of certain compounds to which no narcotics control is presently applied. This listing would include substances related to those under some degree of narcotics control or other substances with clinical usefulness which, because of their general chemical or pharmacological characteristics, might be considered to have addiction potentiality, but concerning which there is no conclusive evidence of such liability. The listing would make interested parties aware that the status of such compounds would be reviewed from time to time as experience accumulated so that if evidence of addiction or other abuse appeared the proper degree of control would be applied.

To maintain the flexibility of narcotics control and to keep the degree of control applied to all drugs commensurate with the degree of risk to public health, the authority designated by law to make a finding in this field should be empowered to revise such a finding in the direction of either greater or less control, including complete removal of a substance from narcotics control, when experience warrants such revision. The designated authority too should have for its guidance adequately representative technical advice and, before a finding is made, recommendations of that advisory body should be published and an opportunity provided for a hearing and presentation of additional or counter evidence by any interested party, as in the 1946 Opiates Act procedure. Also it is to be understood that any revision of national control with respect to a particular substance must be consistent with our obligations under international agreements.

Addiction Redefined

Two general criteria for narcotics control are available, "addiction-producing and addiction-sustaining similar (or qualitatively similar) to morphine," as in our 1946 Opiates Act; or "liable to the same kind of abuse and productive of the same kind of harmful effects," as in the 1948 protocol. With either would it not be well to substitute for the heterogeneous, albeit comprehensive, definition of addiction of the World Health Organization's expert committee, a definition which would be specifically descriptive of the various qualitative types of addiction already alluded to? The following text is suggested:

For an understanding of the need and scope of narcotics control, drug addiction may be defined as a state of periodic or chronic intoxication produced by the repeated consumption of

a drug (natural or synthetic). Three qualitatively different types may be recognized, the characteristics of which are:

Opiate addiction, of which morphine addiction is the prototype, has three major components: tolerance, physical dependence, and emotional (psychic or psychological) dependence. Tolerance, the need for an increasing dose to produce an effect, is an inevitable accompaniment of opiate addiction but does not develop equally to all effects nor necessarily parallel to physical dependence. Physical dependence is an altered physiological state which requires continued administration of a drug to prevent the appearance of a characteristic illness, termed an abstinence syndrome. Emotional dependence is substitution of the use of the drug for other adaptive behavior, the use of the drug becoming the answer to all of life's problems. The abstinence syndrome is a self-limited illness, beginning with yawning, perspiration, rhinorrhea, and lacrimation, progressing to dilatation of the pupil, waves of gooseflesh, twitching of various muscle groups, hot and cold flashes, and restlessness which may become extreme. There is elevation of systolic blood pressure, respiratory rate, and rectal temperature. Retching, vomiting, and diarrhea ensue in the more severe syndromes. There is complete or almost complete anorexia and rapid loss of weight. The time course varies: it may appear in 2 to 4 hours after the last dose of drug and run its course in not much more than 48 hours; it may be delayed in onset for as much as 48 hours and persist for at least 14 days. The abstinence syndrome is precipitable in whole or in part when physical dependence is present by the administration of an opiate antagonist (nalorphine). Opiate addiction is always associated with a drive or compulsion to continue taking the drug and to obtain it by any means.

Cocaine addiction has as its chief characteristic emotional (psychic or psychological) dependence. Tolerance does not develop, there is no physical dependence, and consequently no abstinence syndrome follows withdrawal of the drug. There may be a drive or compulsion to continue taking the drug, depending upon the degree of psychic dependence. In some areas cocaine abuse is a periodic indulgence progressing to a toxic psychosis, characterized by paranoid delusions.

Marihuana (cannabis), like cocaine, produces emotional (psychic or psychological) dependence only. Physical dependence does not develop and there is no abstinence syndrome. Also little, if any, tolerance develops. Abuse is often sporadic, consisting of a periodic intoxication characterized by elation and distortion of time and space perception.

The amphetamines (benzedrine, *d*-amphetamine) also produce only emotional dependence. There is no physical dependence, no abstinence syndrome, and very little tolerance. Chronic intoxication resulting from abuse resembles in symptomatology chronic intoxication with cocaine.

Barbiturate addiction is characterized by emotional (psychic or psychological) dependence, physical dependence, and partial tolerance, but it implies habitual consumption of amounts far in excess of usual therapeutic doses. While barbiturate addiction has the same three components as opiate addiction, there are two significant differences. First, with the opiates there is evidence to indicate that physical dependence may begin to develop with the first dose; with the barbiturates there is no evidence that significant physical dependence occurs in patients who consume only usual therapeutic doses. Second, the abstinence syndromes with the opiates and with the barbiturates are characteristically different. The barbiturate abstinence syndrome is characterized by anxiety, nervousness, disturbances of cardiovascular responses, twitching of muscle groups, and tremor progressing to convulsions of petit mal or grand mal type and confusion or both, disorientation, and hallucinations predominantly visual. The abstinence syndrome, as with the opiates, is self-limited. Some degree of compulsion to continue taking the drug will occur in barbiturate addiction.

Meprobamate, as well as other hypnotics, may produce an addiction with the same characteristics as the barbiturates.

Non-Opiates and Narcotics Control

The consensus today, nationally and repeatedly affirmed by the Expert Committee on Ad-

diction-Producing Drugs of the World Health Organization, is that, although abuse occurs, narcotics control should not be extended to the amphetamines, the barbiturates, or other sedatives. There are several reasons for this opinion.

Clinical experience leads us to believe that most persons will handle and use these drugs as prescribed and will not develop a chronic intoxication or addiction. This is not believed to be true of the opiates, cocaine, or marihuana. Cocaine and opium are derived from plants whose production is limited to certain areas of the world from which they are transported to processing and consuming countries. International control is absolutely necessary. Amphetamines, barbiturates, and other hypnotics are produced primarily by local manufacturers, making control of imports and exports less of a problem and control of these drugs by local measures effective. Furthermore, indications for the medical use of the amphetamines or of the hypnotics are more numerous and far broader than indications for the opiates, cocaine, or marihuana. The barbiturates are widely used in the treatment of epilepsy, peptic ulcer, hypertension, mild neuroses, and simple insomnia. Meprobamate is finding wide application in mental disease. The amphetamines are used medically as anorexic agents, for the treatment of narcolepsy, to elevate mood in depressed individuals, to elevate blood pressure in shock, and in many other situations.

On the other hand, the main indication for use of opiates is the presence of severe pain; the use of cocaine is practically limited to local anesthesia; and marihuana has no medical indication. To place the restrictive regulations of narcotic laws on the amphetamines, the barbiturates, and other sedatives would hamper proper medical use and would not be justified in view of the relatively low public health risk which is already mitigated through regulations in respect to these drugs in the food and drug statutes, both Federal and State.

Conclusions

It is concluded that implementation of suggestions made in the discussion with respect to changes in our national narcotics control regimen would:

1. Remove any distinction between substances of natural or purely synthetic origin with respect to the possibility of exempt preparations.
2. Provide flexibility of narcotics control based upon the degree of risk involved, varying from full control for substances of high addiction liability to control at the manufacturing and wholesale level only for substances of low addiction liability. Alternatively for the latter group, control of the pure substance and exemption from control of its preparations with other therapeutic agents might be provided.
3. Bring local regulations into line with the international narcotics conventions.
4. Encourage the development of much needed analgesics of an efficacy more or less comparable to codeine which might have low addiction liability by making possible a commensurate degree of narcotics control.
5. Clarify the meaning of addiction in relation to narcotics control, by descriptive definition and by basing the application of control to new substances upon properties qualitatively similar to those of morphine.

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