ADDICTION TO ANALGESICS AND BARBITURATES[1]

HARRIS ISBELL, M.D. AND H. F. FRASER, M.D.

I. GENERAL

This review will be concerned with articles which have appeared in the literature since 1940 concerning addiction to analgesic drugs. Except in certain instances, it will not be necessary to refer to articles which appeared before 1940, since papers prior to that time were adequately covered in the monumental review of Eddy (32) and the survey by Smith (109). Since addiction to barbiturates has never been adequately treated in a general article, we will attempt to cover all the literature available to us on this subject. Addiction to marihuana, cocaine, amphetamine, alcohol, and hypnotics other than the barbiturates will not be considered.

Definition of drug addiction

Pharmacologists are accustomed to thinking of addiction as being synonymous with dependence—either physical or emotional (32). This point of view is reflected in the formulation of Tatum and Seevers (113) who defined addiction as a condition developed through the effects of repeated actions of a drug such that its use becomes necessary and cessation of the drug causes mental or physical disturbances. However satisfactory this definition may be to pharmacologists, it is not acceptable to persons who actually have to handle addicts—physicians, law enforcement officers and social workers. If dependence were the only important factor in addiction, the solution of the problem would be very simple. One would simply permit addicts to have drugs so that their dependence would be continuously satisfied. This is the conclusion reached by Lindesmith (80) who believes that dependence and its recognition by the person using the drug constitute the essential features of addiction. Actually we are concerned about addiction not because individuals who use drugs become dependent but because the effects of the drug are harmful both to the individual and to society. The harm which abuse of various drugs may cause arises in a number of ways. It may be due to a decrease in the social productivity of the addicts, as is the case in morphine addiction, to the precipitation of undesirable and dangerous behavior such as occurs with abuse of cocaine and marihuana, or to the mental confusion and impairment of motor function during intoxication with barbiturates. Dependence is important chiefly in that it causes an addiction to be continuous rather than periodic.

Any definition which makes dependence an essential feature will also not include intoxications with such substances as cocaine, marihuana and amphetamine, because dependence on these substances is no more marked than is de-

[1]From the National Institute of Mental Health of the National Institutes of Health, U. S. Public Health Service. (Research Division, U. S. Public Health Service Hospital, Lexington, Kentucky.)

pendence on tobacco and coffee and yet, in some ways, intoxication with cocaine or marihuana is more harmful than is addiction to morphine. Furthermore, definitions which exclude cocaine and marihuana from the list of addicting drugs would cause endless confusion because, in common parlance and legally, both drugs are regarded as addicting.

Any definition which makes dependence the central feature is also undesirable because of the public reaction to the term addiction. Laymen and physicians believe that the use of an "addicting" drug is an extremely bad thing. Contrariwise, it is believed that abuse of a "non-addicting" drug is not nearly so reprehensible and is not a matter of public concern. No better example can be given of the potential damage which such thinking may cause than the situation with respect to barbiturates. It has commonly been held that dependence does not occur after prolonged use of barbiturates and, therefore, measures designed to control the promiscuous use of hypnotics have been half-heartedly enforced and generally ineffective. Actually, even if no dependence occurred, chronic intoxication with barbiturates, in some ways, is far more undesirable and dangerous than addiction to morphine (61, 163).

Emphasis on dependence also fosters the idea that withdrawal of the drug is all that is necessary in treating addiction. This may account in part for the large number of irrational withdrawal schemes which have been advocated and which have clouded the literature on addiction.

In recent years, a number of psychiatrically oriented workers (54, 61, 98, 99, 117) have formulated definitions which make loss of self-control with respect to use of a drug and harm to the individual, society, or both the essential features of the definition of addiction. The chief difficulties with definitions of this sort are quantitative ones. How harmful must a drug intoxication be before it is regarded as an addiction? When has an individual lost his self-control? Despite these difficulties, this kind of definition seems to the authors to be more satisfactory than definitions based entirely on dependence. Ordinarily it is not difficult to decide whether use of a particular substance is sufficiently harmful to be classed as an addiction. Thus coffee, tea and tobacco cause so little harm that they are not regarded as addicting drugs by scientists or by the majority of the lay public, whereas the opiates, the hypnotics, alcohol and cocaine cause such obvious damage when habitually taken that they are easily classed as addicting drugs.

The Drug Addiction Committee of the National Research Council has recently considered the definition of drug addiction and, after long discussion, arrived at the following formulation, which represents an attempt at compromise between the proponents of the definition based on dependence and the proponents of the definition based on harm to the individual or society:

"Addiction is a state of periodic or chronic intoxication, detrimental to the individual and to society, produced by the repeated administration of a drug. Its characteristics are a compulsion to continue taking the drug and to increase the dose with the development of psychic and, sometimes, physical dependence on the drug's effects. Finally, the development of means to continue the administration of the drug becomes an important motive in the addict's existence."

The word "periodic" was inserted in the first sentence because cocaine and marihuana are generally used as "spree" drugs by North American addicts and are not taken continuously. One should note that physical dependence is not an essential part of this definition. Although "psychic" dependence is considered a necessary feature, it actually adds nothing to the definition. Psychic dependence is, of course, a striking and important feature of any addiction but it does not represent a specific characteristic of addiction, since strong psychic dependence can be developed on lactose, lemon juice and other innocuous substances. The authors prefer to define addiction as a state of periodic or chronic intoxication in which an individual compulsively abuses a drug to such an extent that the individual or society is harmed.

Etiology of addiction

Psychiatrists believe that the most important factor which predisposes to addiction is a personality defect. In other words, drug addiction is not a separate disease but usually represents a symptom of a number of psychiatric disorders. This point of view is reflected in the writings of Kolb (70–72), Felix (34–36), Pescor (84–87), Vogel *et al.* (117), Reichard (98, 99) and Wikler (121, 125). The majority of individuals who become addicted to any drug are usually suffering from various types of psychoneuroses or have character disorders (constitutional psychopaths). Under modern conditions, individuals with normal personalities practically never become addicted (84, 87, 117). Major psychoses play no role in the genesis of addiction (34, 36, 84, 87, 89, 90).

Reichard (99) has emphasized the importance of "tension" (anxiety) arising from a variety of somatic disorders or situational problems as an etiologic factor in addiction. Whether addiction will occur in a tense individual who has been exposed to drugs is, according to Reichard, conditioned by the individual's ability to endure discomfort and by the strength, character and orientation of his internal controls of behavior. Both Straus (110) and Rado (95) emphasized the significance of tense depressions in the etiology of drug addiction. Simmel (108) regarded intense oral and narcissistic cravings as being psychodynamically important in opiate addiction. Wikler (125) points out that these are not the only dynamic mechanisms underlying drug addiction but that the drug may also be used to express hostility or to acquire infantile dependent relationships. The depression of sexual drives by morphine may also be of importance.

The concept that addiction is based on a personality defect has been challenged by Lindesmith (80) who argues that proponents of this theory have not made use of control groups, the psychiatric disorders which are supposed to underlie drug addiction are ill-defined and, since psychiatric examinations are usually carried out after an individual has been addicted, there is no real proof that addicts were psychiatrically abnormal prior to addiction. Furthermore, Lindesmith points out that all writers admit that psychiatrically "normal individuals may become addicted. Lindesmith seems not to realise that the authors whom he criticizes have not stated that personality difficulties are the actual "cause" of addiction but merely that such psychiatric disorders predispose to addiction. Although one must admit the partial justice of Lindesmith's objections, he does

not furnish us with any satisfactory alternative hypothesis, especially since he also minimises the pleasurable effects of the addicting drugs. After reading Lindesmith one has the impression that addiction has no cause. It should also be pointed out that it would be almost impossible to find a satisfactory group of controls since such a group would have to be matched with addicts with respect to age, sex, race, religion, economic circumstances, culture, degree of drug exposure, and degree of internal controls of behavior. The writers have yet to see an addict who could not easily be shown to have been psychiatrically abnormal prior to addiction provided an adequate psychiatric examination had been made. This applies to so-called "medical" addicts as well as to "non-medical" addicts.

An individual who has personality traits which predispose to addiction will not become addicted unless he is in some way introduced to an addicting drug. The drug must, moreover, produce effects which the addicts regard, or can learn to regard, as pleasurable. Kolb (76) has written concerning addicting drugs and their effects as follows:

"In a broad sense any drug which is regularly taken to produce unusual mental reactions rather than for a specific medical need is an addicting drug. There are many such drugs—some stimulating, some depressing—and all harmful when used for non-medical purposes. The unusual reactions produced by these drugs are in the main pleasurable. By increasing physical and mental perception, a stimulating drug brings the addict into more intimate contact with the environment and gives him an increased sense of power. By decreasing physical perception and the acuity of certain mental processes, the depressing drugs enable the addict to escape from innate difficulties and disagreeable features of situations of the environment. The power to stimulate is not alone sufficient to make a drug attractive to addicts. There must be some distortion of function or sensation.

The same personality factors probably underlie various addictions; therefore, addiction to one drug predisposes to addiction to another. Thus cocaine and marihuana users are very likely to change to opiates. Alcoholics gravitate to the use of barbiturates and/or morphine.

In addition to the pleasurable effects of the drugs, the manner in which the potential addict makes contact with the drug is of great importance. Contact with the drug as a result of deliberate experimentation to experience the pleasurable effects is a far more potent cause of addiction (64, 87, 117) than is contact as a result of administration for legitimate medical purposes. Since both the drug and method of contact are important in determining whether or not addiction occurs, it is not surprising that the majority of individuals with personality traits similar to those of addicts do not become addicted. It simply means that such addiction-prone individuals have not made contact with the drugs under proper circumstances.

The tendency to relapse is one of the most striking characteristics of addiction. Relapse, according to Kolb (71) and many others, is due to the same personality factors which predispose an individual to addiction. The personality factors are strongly reinforced (71, 76) by the conditioning of the addict to use the drug as the answer to all of life's stresses.

Lindesmith (80) made such conditioning of the addict one of the main themes of his book on addiction and believes that, once established, the conditioning cannot be broken. Lindesmith's view is far too gloomy, however, since the authors know many former addicts who have been abstinent for years. Since, during addiction to morphine, there is a biological need for the drug which may be likened to the need for water or food to relieve hunger or thirst, Wikler (125) states that the gratification of the need for morphine, by analogy with other biologically determined cravings, is intensely pleasurable—perhaps the most pleasurable thing about addiction. The desire to experience the relief of the craving may be an important factor not only in maintaining addiction but also in relapse.

II. ADDICTION TO ANALGESICS

Methods for determining addiction liability. These may be divided into methods which utilize lower animals and methods which involve the use of human subjects.

In a discussion of the role of animal experimentation in studying the addiction liability of analgesic drugs, Seevers (107) pointed out that only tolerance and physical dependence can be studied in animals and that emotional dependence, or habituation, must be determined in man. According to Seevers, the monkey is the best animal to use for addiction liability experiments since signs of abstinence in monkeys are very similar to those in man; moreover, the results which have been obtained with monkeys have more closely paralleled the addiction liabilities of various drugs for man than have the results obtained with any other animal species. The study of Wikler and Frank (127) on the effects of morphine and methadone addiction on the hindlimb reflexes of chronic spinal dogs suggests the use of such preparations in determining physical dependence liability of analgesic drugs, although, as Wikler points out, such preparations may be sensitized and may give false positive results. However, the objectivity of the method of Wikler and Frank is a very strong point in favor of the technic.

Isbell (58) has reviewed the methods available for determining addiction liability in human subjects. He points out that the addiction liability of the analgesic drugs has to be considered from two points of view: 1) What is the danger of addiction under conditions of legitimate medical use? 2) What is the danger that persons with susceptible personalities will illegally abuse the drug and so become addicted? The first question is rather unimportant because the danger of addiction under conditions of medical usage is very small as long as physicians are careful in the use of analgesic drugs. The number of persons who become addicted as a result of medical contact accounts for less than five per cent of the total number of addicts (84, 87). Determination of addiction liability under conditions of medical use is usually carried out by administration of the compound under study to people with chronic painful diseases who require pain relief for long periods of time. The drug is ordinarily administered in the least dose and at the longest interval sufficient to relieve pain. The results obtained from this type of study are always extremely difficult to interpret because of the low dosage of the compound under study, the low grade of dependence produced,

the impaired physiology of chronically ill individuals and confusion of withdrawal signs with signs of the disease. Generally speaking, the difficulties of such work are so great that the results have been unreliable, especially when carried out by individuals who were not familiar with the manifestations of abstinence. Practically every new analgesic drug which has been introduced into medical practice—heroin, dilaudid, meperidine, methadone—has been judged to be non-addicting on the basis of results obtained with this type of experiment, yet further experience showed that all these compounds were addicting.

Tests of addiction liability under conditions of abuse have been much more reliable than either animal tests or tests involving clinical administration to patients requiring relief of pain. Such experiments must, of necessity, be carried out on prisoners who are, or have been, addicted to morphine. The methods used in conducting addiction liability tests in such individuals are essentially those developed by Himmelsbach (45, 56, 77). Four methods are available: administration of single doses for the detection of euphoria; determination of the effect of single doses on the intensity of abstinence from morphine; substitution of the new drug for morphine in cases strongly dependent on morphine; and direct addiction to the new drug. The first method permits one to form some judgment with respect to whether susceptible individuals will use the drug in order to experience the pleasurable effects. The second and third are based on the hypothesis that drugs which relieve or prevent the appearance of signs of physical dependence on morphine will produce dependence of a similar kind. The direct addiction technic is the best, since it gives information concerning development of tolerance, emotional and physical dependence; but it is the most laborious and time consuming of all the available technics. In conducting addiction liability tests, absolute control of the patient and his environment is essential (77). Evaluation of abstinence signs and other phenomena of addiction must be made by persons who are especially trained for such work.

In determining the degree of abstinence from the various drugs the point-score system developed by Himmelsbach (56, 77) has been invaluable. The point-score system makes use only of objective signs of abstinence, some of which are measurable (temperature, blood pressure, body weight, respiratory rate, and caloric intake) and some of which are ordinarily non-measurable (yawning, lacrimation, rhinorrhea, perspiration, gooseflesh, mydriases, tremor, restlessness, and vomiting). Under close environmental control, observations for these signs of abstinence are made by trained personnel at regular intervals following abrupt and complete withdrawal of the drug under test. Arbitrary numerical values are assigned to the various signs of abstinence. The total of these numerical values represents the intensity of abstinence at any given time and can be compared with the intensity of abstinence from morphine by reference to Himmelsbach's control curve.

Objections have been raised to the use of morphine addicts in conducting addiction liability tests on the ground that such subjects are peculiarly liable to the development of physical dependence on any new drug and, therefore, the results obtained with former addicts are not applicable to the general population.

It has never been definitely proved that individuals who have once been addicted to morphine develop physical dependence more readily than do persons who have never been addicted. Such a situation, if it exists, is really an advantage and not a disadvantage because it permits one to obtain definite useful information in a relatively short period of time. Furthermore, the method has always been reliable. Every drug which has been judged to be addicting on the basis of results obtained with former morphine addicts has finally been proved to be addicting under non-experimental conditions. From a practical point of view, morphine addicts are the only subjects who can ethically be used for addiction liability testing so that, regardless of one's feelings in the matter, the results of tests using morphine addicts have to be accepted until disproved by many years of clinical experience.

Addiction liabilities of various analgesic drugs of the morphine series. Using the substitution technic, Himmelsbach (45) found that dihydromorphine, alpha-isomorphine, dihydro-alpha-isomorphine, dihydromorphinone, dihydrodesoxymorphine-D, codeine, dihydrocodeine, isocodeine, dihydroisocodeine, and dihydrodesoxycodeine-D would all support physical dependence in patients strongly addicted to morphine, although satisfaction of physical dependence with dihydroisocodeine was not prompt or complete. Definite signs of abstinence were seen following withdrawal of all drugs after substitution for morphine. Himmelsbach concluded that, so far as the ability of these drugs to support physical dependence was concerned, methylation of the phenolic hydroxyl group of morphine reduced the potency of the compound and prolonged its action. Replacement of the alcoholic hydroxyl by hydrogen or oxygen increased potency and shortened the action. Spatial shift of the alcoholic hydroxyl resulted in irregular effects and saturation of the bond between positions 7 and 8 tended to increase both potency and duration of action.

Fraser and Isbell (39) have studied the addiction liability of 6-methyldihydromorphine, morphinan (3-hydroxy-N-methylmorphinan) and dihydrocodeinone. In a single dose, both 6-methyldihydromorphine and dihydrocodeinone reduced signs of abstinence from morphine. Morphinan was not tested in this respect. All the drugs produced euphoria in former morphine addicts. All three compounds were administered to former morphine addicts for 38 days. Signs of abstinence, which were as intense as those that would have been expected after addiction to equivalent doses of morphine for a comparable period of time, were observed after withdrawal of morphinan. Intensity of abstinence after withdrawal of both dihydrocodeinone and 6-methyldihydromorphine was much milder than would have been expected following withdrawal of morphine after administration of comparable doses for comparable times. The addiction liability of dihydrocodeinone appears to lie between that of codeine and morphine and is approximately of the order which would have been expected from the analgesic potency of the compound. However, 6-methyldihydromorphine is as potent as morphine in inducing analgesia which, in mice, persists for twice as long as that following morphine (33). The results suggest that some separation of physical dependence liability and analgesic potency has been achieved in 6-methyldihydromorphine.

Longer direct addiction experiments will be necessary in order to establish this point definitely.

Isbell (66) obtained very interesting results with N-allylnormorphine. This drug has been shown to be an effective antagonist to the analgesic and respiratory depressant actions of morphine in experimental animals (42, 115). In a single dose, it increased the intensity of abstinence from morphine and prevented relief of abstinence symptoms by morphine. Following administration of 80 to 120 mgm. of N-allylnormorphine hydrobromide daily to former morphine addicts for 30 days, no signs of abstinence were detected following abrupt withdrawal. The addicts did not like the effect of the drug and refused increases in dosage which were offered them. It is not known whether N-allylnormorphine will have analgesic properties under clinical conditions in man. The results obtained with experimental animals have varied. Unna (115) found that the drug was not an effective analgesic in rats, whereas Hart and McCawley (42) found that the drug did elevate pain thresholds of rats. Since N-allylnormorphine does elevate the pain thresholds as measured by the Hardy-Wolff technic in humans (66), an investigation of relief of clinical pain by this compound would be of interest.

Meperidine series. Himmelsbach (49) found that meperidine partially suppressed signs of abstinence when substituted for morphine. Following withdrawal of merperidine after administration of large doses to former morphine addicts for 10 weeks, signs of abstinence appeared which were somewhat more severe than those observed after withdrawal of codeine. In further experiments, Himmelsbach (50) observed clinically insignificant abstinence syndromes after administration of 75 mgm. of meperidine three times daily for three months, while clinically significant syndromes occurred after administration of 75 mgm. four times daily for two months followed by 75 mgm. eight times daily for two weeks. Himmelsbach felt that previous addiction to meperidine might facilitate the development of physical dependence on meperidine. After administration of 100 mgm. eight times daily for two weeks to patients previously addicted to meperidine, stronger grades of abstinence were observed than after administration of the same amounts of meperidine to subjects never before addicted to that drug. This result was, however, not obtained in all patients who were readdicted to meperidine. Himmelsbach concluded that meperidine possessed addiction liability which was of a lower order than that of morphine.

Whether meperidine will produce physical dependence under ordinary conditions of medical use is a matter which has caused considerable controversy. Batterman (17–20) has maintained that no cases of addiction have occurred following medical use of the drug and believes that all persons who have become addicted to meperidine (in the sense of becoming physically dependent) were formerly addicted to morphine. This point of view was reflected in the popular article by De Kruif (79) which appeared in the Reader's Digest. A large number of clinical reports (13, 27, 29, 41, 82, 93, 100) have appeared which describe cases of habituation or addiction to meperidine. The most significant article is that of Polonio (93) who collected 17 cases from the literature and reported on an additional 15 cases which he had personally observed. Polonio emphasizes the danger of meperidine when taken in amounts which will satisfy addicts.

Five deaths occurred among the 32 cases which Polonio summarized. Wieder (119) described 3 cases of addiction to meperidine, two of which were undoubtedly cases of primary addiction. One of these cases definitely followed medical use of meperidine. In the experience of the U. S. Public Health Service Hospital at Lexington, Kentucky, addiction to meperidine is much more common than is addiction to codeine (58, 117). Definite signs of abstinence have been observed following withdrawal of meperidine from "primary addicts" at Lexington even though the withdrawals were conducted gradually and not abruptly. Addiction to meperidine is quite common among physicians, perhaps because so many doctors believe the drug to be non-addicting.

Andrews (6) found that tolerance to the pain threshold elevating action of meperidine developed rapidly during the course of experimental addiction. This tolerance persisted for at least 30 days after meperidine was withdrawn. Meperidine reduced the psychogalvanic response to thermal stimulation and no tolerance developed to this action during addiction. Tremors, toxic psychoses and convulsions (7) were observed during experimental addiction to meperidine. These symptoms were associated with the appearance of large slow waves in the electroencephalogram. Andrews concluded that, in quantities sufficient to satisfy the desires of addicts, meperidine was a drug which had dangerous effects on the nervous system. Andrews' work has been borne out by the deaths reported by Polonio (93) and by the condition of patients admitted to the U. S. Public Health Service Hospital at Lexington, Kentucky.

The following conclusions appear to be warranted by the available evidence: meperidine is an addicting drug which will produce physical dependence in individuals who have never been addicted to morphine, as well as in former morphine addicts. Although physical dependence on meperidine is milder than dependence on morphine, the toxic effects of the drug are so pronounced that addiction to this compound is even more undesirable than is addiction to morphine.

Isbell (60) has studied the addiction liability of five derivatives of meperidine. The drugs tested were bemidone (ethyl-1-methyl-4-[3-hydroxyphenyl]-piperidine-4-carboxylate hydrochloride), keto-bemidone (4-[3-hydroxyphenyl]-1-methyl-4 piperidyl ethyl ketone hydrochloride), Nu-1196 (*dl*-alpha-1, 3-dimethyl-4-phenyl-4-proprionoxy piperidine hydrochloride), Nu-1779 (*dl*-beta-1, 3-dimethyl-4-phenyl-4-proprionoxy piperidine hydrochloride), and Nu-1932 (1-methyl-3-ethyl-4-phenyl-4-proprionoxy piperidine hydrochloride). In sufficient dose, all these drugs induced euphoria in former morphine addicts and all relieved abstinence from morphine. The comparative potency in inducing both effects increased in the following order: bemidone, Nu-1196, Nu-1779, Nu-1932 and keto-bemidone. Keto-bemidone appeared to be at least as effective as morphine in inducing euphoria and in relieving abstinence from morphine. Following experimental addiction of former morphine addicts to keto-bemidone for 59 days, signs of very intense abstinence appeared after withdrawal. All five drugs had addiction liability. Keto-bemidone was outstanding and appeared to be as addictive as heroin.

Methadone series. Scott and Chen (105) found that tolerance did not develop

to the pain threshold elevating action of methadone following administration of 2 mgm./kgm. daily to dogs for 28 days. In further experiments, Scott *et al.* (106) found that tolerance to the analgesic action developed rapidly in dogs which received 5 to 20 mgm./kgm. of methadone intraperitoneally twice daily for 14 to 32 days. Tolerance to other effects of methadone was also noticed in these experiments. Following withdrawal of methadone from these dogs and from an additional group of dogs which received methadone subcutaneously three times daily in amounts increasing to 5 mgm./kgm., tachycardia and fever appeared. Wikler and Frank (127) observed the development of tolerance to the effects on the hindlimb reflex of chronic spinal dogs that received 1 to 5 mgm./kgm. of methadone four times daily for 37 to 63 days as well as tolerance to other actions. Following withdrawal of methadone from these chronic spinal dogs and from intact dogs (62), vomiting, mydriasis, shivering, tachycardia, hyperpnea, fever and weight loss were observed. Changes in the reflexes of the paralysed limbs of chronic spinal dogs following withdrawal of methadone were very similar to changes in the reflexes of addicted chronic spinal dogs following withdrawal of morphine. Abstinence signs came on more rapidly after withdrawal of methadone than after withdrawal of morphine, were more severe, and subsided more quickly. Woods, Wyngaarden and Seevers (132) observed that 4 monkeys that received 5 to 13 mgm./kgm. of methadone for 75 to 96 days became more sensitive to the toxic effects of methadone rather than developing tolerance. Addiction of monkeys to methadone did not confer cross-tolerance to morphine. Following withdrawal of methadone, no abstinence signs were noticed in these monkeys whereas definite abstinence phenomena were observed in control monkeys which received morphine. Cochin, Gruhzit, Woods and Seevers (28) administered methadone to monkeys three times daily and again observed no definite symptoms upon withdrawal. It appears that striking differences exist between the dog and the monkey with respect to the development of tolerance and physical dependence on methadone.

Isbell and his collaborators (58, 59, 62, 64, 65) found that, in sufficient dose, methadone was as potent as morphine in inducing euphoria in former morphine addicts. The euphoric effects of methadone were longer lasting than was the euphoria induced by morphine. When methadone was injected intravenously, addicts could not distinguish its effects from those of heroin or dilaudid. Methadone was just as effective as morphine in relieving symptoms of withdrawal from morphine. One mgm. of methadone could be substituted for each four mgm. of the accustomed dose of morphine in individuals strongly dependent on morphine without signs of abstinence appearing. After substitution of methadone for 10 to 14 days, abrupt withdrawal of methadone was followed by a definite but low-grade type of abstinence which was characterized by slow onset, relatively few autonomic signs, great weakness and slow recovery. Fifteen former morphine addicts were experimentally addicted to methadone in doses ranging up to 400 mgm. daily for 28 to 186 days. Definite tolerance to the pain threshold elevating, sedative, electroencephalographic, nauseant and miotic effects were observed in these patients. Probably tolerance to the circulatory and respiratory depressant effects developed as well. Following withdrawal of methadone from these subjects,

signs of abstinence appeared which were identical with those seen after withdrawal of methadone following substitution for morphine. The slow recovery from abstinence from methadone was more unpleasant to some of the subjects than was abstinence from morphine. Most of the patients experimentally addicted to methadone came to prefer it to all other drugs. Although abstinence from methadone is comparatively mild, the euphoric effects of methadone are so marked and emotional dependence so strong that the total addiction liability of methadone is probably almost as great as that of morphine (58, 117). The drug is also more toxic than morphine and, in the amounts used by addicts, would cause even greater physical degeneration and social loss. No clear-cut evidence of physical dependence has been observed following the administration of the drug to non-addicts who require pain relief for considerable periods of time (62, 68, 69). Methadone, however, immediately became very popular with morphine addicts (14) and therefore spread of addiction to this substance will probably be rapid.

Other methadone drugs. Isbell and Eisenman (63) found that *l*-methadone accounted for all the addiction liability of racemic methadone as well as for all its analgesic effect. *d*-Methadone was inactive in both respects. Isomethadone, though less potent than methadone, induced euphoria in former morphine addicts and relieved abstinence from morphine. Following withdrawal of isomethadone from 10 former morphine addicts who had received dosages ranging from 270 to 360 mgm. daily for 42 to 59 days, signs of abstinence appeared which were considerably more intense than signs of abstinence from methadone but less intense than signs of abstinence from morphine. Following substitution of 1 mgm. of isomethadone for each 1.33 mgm. of the stabilization dose of morphine, mild signs of abstinence appeared in 5 morphine addicts who had been stabilized on 480 mgm. of morphine daily. Following withdrawal of isomethadone, an abstinence syndrome similar to that seen after direct addiction to isomethadone was observed. Methadol (6-dimethylamino-4-4-diphenyl-heptanol-3) did not induce euphoria in former morphine addicts and did not relieve abstinence from morphine. The drug is also inactive as an analgesic. Racemic acetylmethadol (6-dimethylamino-4-4-diphenyl-3-acetyl-heptanol) induced striking euphoria in former morphine addicts and was very effective in relieving abstinence from morphine (40). Heptasone (6-morpholino-4-4-diphenyl-heptanone-3 hydrochloride) was relatively inactive in inducing euphoria in former morphine addicts. Doses of 90 to 100 mgm. subcutaneously were required to produce definite results (40). Such effects as were observed were also very transient and lasted only an hour. In doses of 10 mgm. intravenously, heptasone produced marked euphoria and sharp rises in the thermal radiation pain threshold. Both effects were transient and disappeared within 45 minutes to one hour. Doses of 100 mgm. of heptasone subcutaneously had only minor effects on symptoms of abstinence from morphine. Twenty mgm. of heptasone intravenously produced striking relief from abstinence which persisted for only an hour. Intravenous injection of 20 to 30 mgm. of heptasone caused precipitous drops in blood pressure, marked respiratory depression and coma in non-tolerant individuals. Only minor signs of abstinence were observed after withdrawal of heptasone following ad-

ministration of doses ranging up to 260 mgm. daily for 40 days to former morphine addicts. The addiction liability of heptasone is quite low; but the drug is a relatively ineffective and short acting analgesic, and it is potentially so dangerous, if inadvertently injected into the blood stream, that it probably has no clinical value.

Electroencephalograms in addiction. Andrews (5) found that, during maintained addiction, the electroencephalograms of a series of 50 patients who were actively addicted to morphine were characterized by an abnormally high percentage of waves with frequencies of approximately 10 per second (alpha waves). In some patients who were receiving very large amounts of morphine, large slow waves with frequencies of less than six per second (delta) were observed. In some cases, the high alpha percentage was maintained during and following withdrawal and was felt by Andrews to be an irreversible change. In a further study of 2 men who were observed through an experimental cycle of morphine addiction, Andrews (8) found that morphine addiction increased the alpha percentage in an individual with a low alpha index prior to addiction and induced slow waves in another individual with a high alpha index before addiction. In other words, the effect of addiction was to slow the electroencephalogram. Andrews postulated that morphine produced this effect by reducing the cortical excitatory state but not by decreasing the number of exteroceptive stimuli received by the brain, since measurements of auditory thresholds showed no significant changes throughout the cycle of addiction. In unpublished work, Andrews (11) observed similar changes in the electroencephalograms of morphine addicts who had been stabilized on eight different morphine derivatives. During addiction to codeine, Andrews (4) noted a high occipital alpha percentage which was maintained during withdrawal despite the mental unrest associated with abstinence. Isbell and his collaborators (62, 64) observed progressive shifts of the electroencephalographic spectrum to the slow side during experimental addiction to methadone. The alpha percentage decreased, alpha frequency was slowed, delta activity appeared and later dominated the record. As addiction to methadone progressed, definite evidence of partial tolerance was shown by a shift of the frequency spectrum toward the pre-addiction pattern. Following withdrawal of methadone, the slow electroencephalographic pattern persisted for two days after which the pre-addiction state was gradually regained. During meperidine addiction, Andrews (7) noted the appearance of large slow waves in the electroencephalogram. Altschul and Wikler (3) reported a marked shift of the electroencephalogram to the slow side of the frequency spectrum during addiction to keto-bemidone. Large slow waves (delta) and subsequent development of tolerance to this effect were observed during addiction to this drug. One individual exhibited paroxysmal slow spike and dome activity while receiving 480 mgm. of keto-bemidone daily. Twelve hours after abrupt withdrawal of keto-bemidone, the percentage of delta waves was again increased and in one subject several bursts of high frequency waves of frequencies of 18 cycles per second were observed.

Clinical picture of addiction to morphine. This subject has been summarized

by Himmelsbach in two excellent papers (47, 48) which should be carefully studied by any individual who has to manage addicts or evaluate the addiction liability of new drugs. Andrews and Himmelsbach (12) found that the intensity of the morphine abstinence syndrome was related to the dosage of morphine required to prevent signs of abstinence from appearing (the stabilization dose). These investigators found that if the stabilization dose were known, the intensity of abstinence in a given individual could, within limits, be predicted mathematically. From the shape of the curve relating intensity of abstinence to stabilization dosage, these authors predicted that the maximum intensity of abstinence which can possibly be attained would be achieved with doses of about 500 mgm. of morphine daily. This prediction is in accord with clinical experience. Pfeffer (89) found that psychoses were seldom precipitated by withdrawal of morphine.

Pathology of morphine addiction. There is still no evidence that prolonged addiction to morphine produces any pathological changes which cannot be attributed to malnutrition, neglect of personal hygiene, and infections resulting from unsterile injections. The frequency of bacterial endocarditis and of malaria among morphine addicts has been commented on by a number of writers. Swain (111) found histological alterations in the brains of 3 individuals who presumably died from morphine addiction. The changes described included acute and chronic neuronal alterations, destruction of neurons and irregular perivascular demyelinization. Two of Swain's cases, however, were definitely cases of acute morphine poisoning and the changes reported may have been due to anoxia. The third patient was a woman who was treated with insulin during withdrawal of morphine and her death and the pathological changes observed could very well have been due to severe hypoglycemia.

Physiology of physical dependence. Wikler and his collaborators (122–127) have carried out an important group of experiments on the neurophysiology of physical dependence in addiction, using chronic spinal dogs, chronic decorticated dogs, and experimentally "neurotic" dogs and cats. In the non-tolerant and non-addicted chronic spinal dog, morphine depressed the flexor, crossed extensor, "mark time" and Phillipson's reflexes. The ipsilateral extensor thrust reflex was enhanced by morphine and the knee-jerks were little affected. These effects of morphine on the patellar and flexor reflexes of chronic spinal dogs fitted in well with the effects of morphine on two-neuron and multineuron reflexes as recorded by electrophysiological technics in cats (122). When chronic spinal dogs were experimentally addicted to morphine, tolerance developed to the depressant effects of morphine on the hindlimb reflexes as well as to the general sedative actions of the drug, the temperature lowering effects, etc. Tolerance to the stimulant effects of morphine on the ipsilateral extensor thrust reflex did not occur. Following withdrawal of morphine, in addition to signs of abstinence above the level of the cord section (rhinorrhea, salivation, mydriases, fever, hyperpnea, tremors, restlessness and weight loss), marked alterations in the hindlimb reflexes of the chronic spinal dogs were observed. The flexor reflex, the crossed extensor reflex, the "mark time" and Phillipson's reflexes were markedly exaggerated whereas the ipsilateral extensor thrust was greatly reduced. These

changes are exactly opposite to the acute changes induced by morphine in non-tolerant dogs. Similar changes were seen after addiction of chronic spinal dogs to methadone. Eserine in doses of 0.25 mgm./kgm. induced alterations in the hindlimb reflexes which were very similar to those noticed in withdrawal of morphine (125, 127). The changes following eserine could be prevented or abolished by injections of morphine. In experimentally addicted chronic decorticated dogs, tolerance developed to the sedative and pain threshold elevating actions of morphine. It was noteworthy that conditional salivation did not occur in the chronic decorticated animals. Increasing motor restlessness and irritability were noted in these decorticated dogs as tolerance increased. Following abrupt withdrawal of morphine from decorticated dogs, a stereotyped abstinence syndrome ensued which was abolished by morphine. Wikler's results show that physical dependence on morphine is due to changes in the organism which have no symbolic significance for the animal. This is another way of stating that the abstinence syndrome represents a physiological rather than a "psychic" derangement. The results also show that the changes responsible for the abstinence syndrome involve the spinal cord and probably other parts of the central nervous system.

The effects of morphine on conditional responses depended upon the stability of the reflex, the effects the drug had on the unconditional response, and on the general adaptive pattern of the individual dog (123, 125). More recently learned and unstable conditional responses were impaired by morphine whereas older and more stable conditional responses were depressed to a lesser degree or not impaired at all. If the dose of morphine was large enough to impair the unconditional response, the conditional response was also impaired. Morphine tended to accentuate the general adaptive pattern which was most predictable for any given animal. Wikler suggested that, in man, morphine may abolish more recently learned reaction patterns and release more firmly established reaction patterns regardless of whether the firmly established patterns are normal or neurotic. Thus in highly narcissistic individuals, morphine is apt to release fantasies of omnipotence and grandiosity with a corresponding feeling tone of unusual well-being and overt behavior characterised by garrulity, boastfulness and increased psychomotor activity. In other individuals, mild depression and anxiety or only a general sedative effect may be observed. Whether or not the reaction induced by morphine is sufficiently pleasant to induce addiction depends upon the meaning of the effects to the individual and upon the strength of his personality controls. Since morphine does not affect differentiation of stable conditioned stimuli unless a dose sufficient to impair the unconditional response is given, one would not expect morphine to impair intellectual functioning seriously in man even though the drug affects the individual's motivations and emotional attitudes toward life problems.

Himmelsbach (46, 53) has studied the relationship of addiction to the autonomic nervous system as reflected by changes in cold pressor tests and by changes in peripheral blood flow. In non-addicts and in former morphine addicts, morphine reduced the elevation in blood pressure following a standard cold stimulus and accelerated the return of the blood pressure level to the normal

level following removal of the stimulus (46). In addicts, the pressor response to cold was greater than in the controls and the time required for the blood pressure to return to the normal level was increased. The increased response to cold slowly reverted to normal following withdrawal of morphine. Using a plethysmographic method, Himmelsbach (53) found that morphine significantly increased the rate of blood flow to the hand and forearm. This effect on blood flow was dependent upon an intact sympathetic nerve supply. The resting blood flow in the hands and forearms of addicts and former addicts was less than that of marihuana users or non-addicts. Himmelsbach felt that his results indicated that morphine addicts were "tense" and that morphine relieved tension by depression of the sympathetic division of the nervous system. Himmelsbach postulated that morphine addiction increased the hyperirritability of autonomic centers.

Williams and Oberst (130) carried out extensive metabolic investigations throughout a cycle of morphine addiction, using 2 former morphine addict volunteers. The results of this study were largely negative. Addiction was accompanied by small increases in body water, water content of blood, blood sedimentation rate, carbohydrate intake and nocturnal activity. Small decreases were noted in body weight, hemoglobin, packed cell volume, pulse rate, basal metabolism, and diastolic blood pressure. No significant changes were noted in acid-base balance, blood hydrogen ion concentration, serum protein level, and sodium, potassium, calcium, phosphorus and CO_2 content of blood.

Water metabolism. Barbour and his collaborators (15, 16) found that morphine addiction altered water metabolism in dogs and that withdrawal of morphine induced hydration of the blood (and probably of the tissues in general). The observations of these investigators appeared to fit in with the experiments of Pierce and Plant (92) who observed sharp decreases in red blood cell count and hemoglobin levels following withdrawal of morphine from strongly addicted dogs. Dietrick and Thienes (30) found that the hydration of the tissues was increased in experimentally addicted rats; but, following withdrawal, there was a partial or complete recovery from the edema with a tendency to relapse on the second or third day of withdrawal. Administration of calcium and parathyroid hormone caused a greater loss of tissue water during withdrawal and partially prevented the increased edema on the second and third day of withdrawal (30, 114). The results of Dietrick and Thienes were not in accord with those of Flowers, Dunham and Barbour (38) who found that tissue water was increased in the first day of withdrawal of morphine from chronically morphinized rats. Williams (128, 129) found that the water content of blood of morphine addicts was increased as compared with the blood of former morphine addicts and non-addicts whereas plasma water was the same in all groups. Changes in blood and plasma specific gravity paralleled the changes in blood water content. The packed cell volume was also diminished during addiction. Williams felt that these findings indicated that addiction and physical dependence were associated with hydration of the blood. However, one can calculate from Williams' figures that the increase in blood water is due to the decrease in the hematocrit and that the water content of the blood cells is unchanged. Following withdrawal, Williams found a tem-

porary increase in the hematocrit and a decrease in the blood water. The decrease in blood water during withdrawal would be much more in line with the clinical picture of abstinence in man than would an increase since, during abstinence, water intake is reduced and the amount of water lost by all routes is greatly increased. Isbell (57) studied the blood, plasma and extra-cellular fluid volumes during a cycle of addiction in 5 former morphine addicts. He found that the packed red cell volume, the red blood cell count, and the circulating red cell mass were reduced during addiction to morphine. The water content of plasma and of blood cells was unchanged. The water content of whole blood was increased but the increase was due to the increased proportion of plasma to cells and not to an increase in the water content of either cells or plasma. The apparent hydration of the blood in addiction is, therefore, really due to a mild anemia. Plasma volume was not altered by morphine addiction. Changes in the extracellular fluid volume, as measured by the thiocyanate technic, were more difficult to interpret. Thiocyanate fluid volumes were increased in 3 of 5 subjects during addiction. The increases were present only after the daily dosage of morphine had been elevated to 550 mgm. or more and were more likely to be found during a period when the dosage was being rapidly elevated or shortly after a dosage plateau had been reached. Since all the subjects had developed strong physical dependence on morphine before any alterations occurred in the thiocyanate fluid volume, Isbell concluded that changes in extra-cellular fluid did not play a significant role in the physiology of physical dependence on morphine in man. In other experiments, Isbell (66) found that tolerance to the anti-diuretic action of morphine (21) developed in a few days during experimental addiction, using former morphine addicts as subjects.

Theories of physical dependence and tolerance. The older theories (oxydimorphine, antitoxic substances, allergy, replacement of cell constituents, reversible coagulation, pathobiosis, etc.) have been reviewed by Eddy (32) and by Kolb and Himmelsbach (77). They are all unsatisfactory and need not be considered here. Water metabolism was discussed above. The writers know of no new information concerning the distribution, excretion, and metabolism of the opiate drugs which has any bearing on tolerance and dependence. The hypothesis that withdrawal symptoms are entirely "psychic" is not tenable in view of the definite abstinence syndromes which have been produced in various lower animals and in view of the work of Wikler with chronic spinal and decorticated dogs. There remain only two hypotheses to be considered: 1) that of Tatum, Seevers and Collins (112, 113) who state that abstinence symptoms arise because the stimulant effects of morphine outlast the depressant effects; 2) Himmelsbach's (51) hypothesis that tolerance to morphine is due to the enhancement of homeostatic mechanisms which oppose certain actions of morphine. In Himmelsbach's theory, physiological counter-responses become better developed as injections of morphine are repeated. When morphine is withdrawn the counter-responses are still operative but are unchecked because no drug is present to oppose them.

There have always been a number of difficulties in accepting the concept of Tatum, Seevers and Collins. Signs of abstinence from morphine in almost any

species are different from the signs produced by the stimulant actions of the drug. For example, Tatum and Seevers state that miosis and vagal slowing of the heart are stimulant actions. During withdrawal one sees mydriasis and increase in the pulse rate. Convulsions, one of the most striking stimulant actions of morphine in the dog, are certainly not a feature of abstinence in this species. The stimulant actions of codeine are greater in proportion to its depressant actions than are those of morphine. One would therefore expect on the basis of the theory of Tatum, Seevers and Collins that dependence on codeine would be more severe than on morphine. The reverse is the case. The experiments of Wikler (126) on addiction in chronic spinal dogs also does not support the hypothesis of Tatum and Seevers. If the diminution of the flexor reflex in nontolerant spinal dogs is regarded as a depressant effect and accentuation of the extensor thrust reflex as a stimulant effect of morphine, one would expect that, following withdrawal of morphine from addicted chronic spinal dogs, the flexor reflex would be unchanged or altered very little whereas the extensor thrust would be markedly accentuated. Actually, the flexor reflex becomes hyperactive during withdrawal and the extensor thrust is greatly depressed.

The theory that abstinence is due to the release of enhanced homeostatic mechanisms from the brake imposed by the presence of morphine appears to fit the facts better than any other hypothesis yet advanced. Many of the signs of abstinence from morphine are qualitatively the opposites of some of the acute effects of morphine. Morphine depresses body temperature and, during abstinence, one observes fever. Morphine constricts the pupils and in abstinence one sees mydriasis. In the spinal dog, morphine depresses the flexor reflex and during abstinence the flexor reflex becomes hyperactive. Himmelsbach (51) suggested that the homeostatic responses which opposed the actions of morphine are mediated largely by the hypothalamus and the autonomic nervous system. While this may be true, Wikler's work shows that other parts of the nervous system are also involved. Wikler (125) believes that the physiological mechanisms which oppose the actions of morphine in tolerant animals may become conditioned to meaningful stimuli in the manner of ordinary conditioned reflexes. Therefore, in the intact organism, physical dependence may be partly conditioned and partly unconditioned (*i.e.*, both "pharmacological" and "psychic"). According to Wikler, only the adaptive responses to drugs are conditionable whereas direct effects of drugs cannot be conditioned (125).

Since eserine induced changes in the hindlimb reflexes of chronic spinal dogs which resemble abstinence from morphine and since these effects of eserine are abolished or prevented by morphine, Wikler (125) suggests that abstinence from morphine may be related to cumulative depression of cholinesterase. The effects of the depression of cholinesterase would become manifest only in the absence of morphine which is an anticholinergic drug as well as a depressant of cholinesterase. This hypothesis will require further study.

Residual tolerance. It is still uncertain whether individuals who have once been addicted to morphine lose their tolerance completely following withdrawal of the drug or continue to maintain some degree of tolerance to certain effects of

morphine for indefinite periods of time. Andrews (9) found that opiates had much less effect on the pain thresholds, (as measured by the thermal radiation technic) of former morphine addicts than would have been expected from the results obtained on 3 non-addicts by Hardy, Wolff and Goodell. Andrews interpreted his findings as indicating residual tolerance to the pain threshold elevating effect of morphine in former addicts. It is difficult to accept this evidence, however, because of the unreliability of the Hardy-Wolff-Goodell method. In the hands of the majority of observers, elevations of the pain threshold are not consistently obtained following administration of morphine to non-addicts. Isbell (66) found no differences in the effects of small doses of morphine on the pain thresholds of normal individuals and former morphine addicts. The changes in the pain thresholds of both groups were unpredictable. When elevations occurred, they were of much less magnitude than those observed by Hardy, Wolff and Goodell and a lowering instead of an elevation of the pain threshold after morphine was seen in some individuals in both groups. In further work, Andrews (11) found that there was no difference between addicts and non-addicts with respect to the ability of morphine to depress the psychogalvanic reflex elicited by thermal stimulation. Andrews (5) felt that the fact that the percentage of alpha waves was higher in former morphine addicts than in normals was evidence for some irreversible change produced by morphine addiction. This conclusion should, however, be checked by using as controls a group of prisoners analogous in all characteristics except for addiction rather than by using published data gathered from an ordinary population. Williams (129) was unable to show any differences in the degree of respiratory depression, slowing of the pulse, and depression of body temperature after administration of 20 mgm. of morphine subcutaneously to non-addicts and former morphine addicts.

Psychological studies of addiction. Partington (83) studied the mental efficiency of drug addicts using the revised Babcock examination for the measurement of mental deterioration. He found that the Babcock efficiency index of drug addicts was significantly lower than that of the non-addicts studied by Babcock. This difference was due to the fact that addicts made low scores on tests of learning and motor abilities. Older addicts were significantly more deficient than young addicts but the duration of drug use was not a significant factor affecting mental efficiency as measured by this test. There are several objections to accepting these results. The Babcock test is not regarded as reliable by many psychologists, has not been widely used and is probably insufficiently calibrated. Partington used the subjects studied by Babcock as his controls and these may have differed significantly from the group of addicts who served as subjects for the experiments. Furthermore, the results are not in agreement with results obtained with other intelligence tests. Brown and Partington (25) administered the Wechsler-Bellevue Test of Adult Intelligence to 371 native white male narcotic drug addicts. They found no significant difference in the intelligence of the addicts as compared with Wechsler's normal group. The mean intelligence quotient of the addicts was 101 (normal IQ is 100). Fewer of the drug addicts were defective and fewer fell into the superior and very superior classifications when compared with the control group of Wechsler. In a further study, Brown and Partington (26) found no

differences in the measures generally employed for the estimation of intelligence in a group of 42 former morphine addicts who were matched with a group of hospital attendants with respect to age, sex, intelligence quotient and nationality. Drug addicts were superior to the hospital attendant group in tests involving cancellation of forms, distributed attention and arithmetic speed. Addicts, however, showed greater tendencies to persevere than did the hospital attendants. It therefore appears that morphine addiction does not cause any permanent reduction in intelligence.

Brown (23) studied the effect of single doses of morphine upon the personality of former morphine addicts as measured by the Rorschach test. The results indicated that administration of morphine in amounts sufficient to cause satisfactory euphoria resulted in increased capacity for imaginative living with the personality shifting in the direction of introversion. Emotional life was somewhat stimulated but the energy was directed into channels of fantasy living more than in the direction of attention to outer stimuli. In a study of psychological changes during addiction to methadone, Isbell *et al.* (64) noted results similar to those obtained by Brown.

Brown (24) studied two patients through a complete cycle of addiction to morphine. Mental efficiency was reduced as reflected by a slowing of the voice and hand response time, delay in improvement in code learning, and decrease in tapping speed. The amplitude of the electrodermal response elicited by disturbing words was significantly reduced whereas the blood pressure response to the same stimuli was increased. During addiction, the difference between the effects of non-disturbing and disturbing word stimuli on the electrodermal response, respiratory rate, and voice response time was reduced. Brown concluded that morphine may ameliorate the disturbing effects of emotional stress. This conclusion is in accord with clinical experience.

Treatment

Treatment of drug addiction is divided into two phases: withdrawal and rehabilitation. The subject of treatment has been exhaustively covered by Wolff (131) in a recent monograph.

Withdrawal. Withdrawal is necessarily the first step in the treatment of drug addiction but, nonetheless, it is the least important phase of therapy and is the only part of treatment which is easily carried out (61, 117). The fixation which so many physicians have on withdrawal therapy is reflected in the fact that about 10 new withdrawal schemes which are frequently termed cures are devised each year (131). Many of these withdrawal schemes are based on erroneous theories of addiction and are more harmful than is abrupt withdrawal of drugs (73, 77). The advocates of many of these withdrawal treatments have been uncritical and have not compared their results with control cases that were subjected to abrupt withdrawal of drugs. Many of the authors of new withdrawal systems appear to be ignorant of the manifestations and course of abstinence from morphine and, in general, practically all neglect the very essential factor of complete control of environment of the addict.

Withdrawal schemes which involve purgation, hyoscine, belladonna, lecithin,

blisters, auto-hemotherapy, psychotherapy treatments and hypnosis have been reviewed by Kolb (73) and by Kolb and Himmelsbach (77). All these schemes are valueless and some are dangerous so that no further comment is necessary. The use of insulin during withdrawal, as advocated by Sakel (101, 102), has been studied by Wieder (120). He found that not only was insulin valueless in preventing or ameliorating abstinence signs but that it also increased the discomfort of addicts undergoing withdrawal. Wolff (131) adopted the strange position that, although the treatments mentioned above, particularly the insulin treatment, have been shown to have no beneficial effects on objective withdrawal phenomena, they should nevertheless be used because the "suggestive effect" of these treatments is of value. Withdrawal of morphine or similar drugs is actually a very simple procedure provided adequate control of the environment can be achieved, and no complicated symptomatic treatment is necessary. Abrupt withdrawal is seldom used since it carries a small risk of death (77) and because it is unnecessary and cruel. Slow withdrawal (gradual reduction of the drug over a period of a month or more) is also seldom used except in cases complicated by serious organic disease. Rapid withdrawal (reduction of the drug over a period of less than 14 days) is now most popular. Generally the drug is reduced over a period of 7 to 10 days. Only mild to moderate signs of abstinence will be observed when this system is used. Himmelsbach (47) recommends the administration of one full stabilization dose of morphine during the first day of withdrawal, one single injection of three-quarters of the stabilization dose of morphine during the second day and two injections of one-half and one-quarter of the stabilization dose of morphine during the third day. Diminishing amounts of codeine are given during the fourth, fifth and sixth days. Himmelsbach's method is based on the observation that one stabilization dose of morphine will significantly reduce the total intensity of abstinence without prolonging its course. This system is popularly known as the "pick-up" system and is very effective. Substitution of methadone for morphine followed by withdrawal of methadone is the most recent advance in rational withdrawal therapy (65, 117). This method is based on the observation that methadone suppresses signs of abstinence from morphine and, during rapid withdrawal of methadone, signs of abstinence are milder than those observed during rapid withdrawal of morphine (62). However, treatment by methadone substitution and reduction is only slightly better (65) than simple reduction of morphine.

Adjunctive therapy during withdrawal includes the judicious use of sedatives and hypnotics, maintenance of fluid balance, hydrotherapy, and simple psychotherapeutic technics such as assurance directed against the emotional reaction to withdrawal (47, 61, 73, 75–78, 98, 99, 116, 121).

Himmelsbach studied the effects of certain adjuncts which have been recommended by various authors as being useful in withdrawal of morphine and found all the following to be of little or no value: pyrahexyl compound (1, 2, 52), large doses of thiamine (37, 44), prostigmine (55), pyridoxine (56), pentobarbital (56) and atropine (56). Isbell (66) found that although dibenamine, tetraethylammonium and dibutoline abolished some of the autonomic signs of abstinence, they did not reduce the actual suffering of the patient.

More recently, Kells (67) reported that pyribenzamine alleviates withdrawal symptoms. Schlan and Unna (104) found that myanesin abolished objective abstinence signs without affecting the craving of the addicts for drugs. The results of both Kells and Schlan and Unna will have to be checked under controlled conditions before they can be accepted.

It has recently been reported (81, 94, 103) that, following prefrontal lobotomy, abstinence symptoms did not appear after withdrawal of morphine from individuals presumably addicted to that drug. In none of these studies was the presence of dependence proved by preliminary withdrawal prior to operation, environmental control was poor, withdrawal of drugs after operation was usually gradual, and the authors did not appear to be sufficiently familiar with the manifestations and course of abstinence.

Watts and Freeman (118) observed manifestations suggestive of abstinence (fever, tachycardia, etc.) after withdrawal of morphine from a leucotomized patient. Dynes and Poppen (31) also mention abstinence signs of such severity that morphine had to be withdrawn gradually from lobotomized patients. It is difficult to understand how lobotomy would abolish withdrawal symptoms in view of the strong abstinence syndromes observed in chronic decorticated and chronic spinal dogs by Wikler, although it is not surprising that the emotional reaction to withdrawal would be greatly altered by this surgical procedure. Again, further observations carried out under properly controlled conditions will be necessary to settle the point definitely. Regardless of whether lobotomy alleviates withdrawal symptoms, the procedure would not be justified as a treatment for drug addiction *per se*, since the personality defects which commonly follow this procedure are more devastating to the patient than is addiction.

Rehabilitative treatment. The treatment of drug addiction can be carried out successfully only in institutions (74–76, 98, 99, 116, 117). Attempts at treatment in the home practically never succeed and in fact complete withdrawal of drugs is seldom accomplished under such circumstances. It follows that a certain degree of coercion is usually desirable and necessary in the treatment of drug addiction. Coercion may take the form of pressure from relatives, friends or law enforcement officers. In many instances the only solution is to arrest the addict and have him sentenced for violating the narcotic laws (74). Individuals, however, who are not criminals or whose criminal activities arose merely as a consequence of their addiction should not be sent to an ordinary penal institution but to an institution devoted entirely to the treatment of drug addiction (75, 96). The contacts and associations which the addict builds up in ordinary penal institutions are often more damaging than the addiction itself. Sentences imposed for narcotic addiction should not be long (74). The deterrent effect of incarceration is as great if sentences of one year are imposed as if sentences of five years are given (74). Long sentences may engender attitudes of hostility and may foster the development of dependence on institutional existence (96, 99). Wherever possible, sentences should be probated conditionally upon completing treatment (74–76, 96, 97) since this permits an addict to be discharged once he has reached maximum benefit from his treatment. It also provides for

a period of supervision following discharge and, if the addict relapses prior to the expiration of the probationary sentence, he can be returned to the institution without the trouble and expense of another trial. Time is an important element in the treatment of drug addiction. The optimum period of time varies in individual cases but, in general, several months are required before maximum benefit from treatment is reached (74–76, 116, 117, 121).

After drugs have been withdrawn, any curable physical disease which the addict may have should receive appropriate medical or surgical treatment. In patients suffering with chronic diseases which are not curable, the treatment should be designed to achieve the maximal amount of physical benefit possible and to teach the patient to live with and manage his disease without resorting to narcotics (61). In individuals whose addiction is attributable to the presence of chronic pain, appropriate surgical procedures (sympathectomy, dorsal root section, cordotomy, or prefrontal lobotomy) should be considered.

Occupational therapy forms an exceedingly important part of treatment of drug addiction (61, 75, 76, 78, 117). All patients who are able to work should be provided with an opportunity to engage in a useful, productive occupation of a nature which will maintain and add to any existing skills. Patients with chronic diseases should not be allowed to vegetate on infirmary wards but should, within the limits imposed by their diseases, be given some type of useful activity to pursue and, if possible, should be trained in some occupation which they can carry on despite their infirmity and which will enable them to support themselves when discharged. Occupational therapy should be reinforced by a program of recreational therapy including a program of athletics, motion pictures, music and other amusements, and an ample supply of reading material.

Psychotherapy. The psychotherapeutic treatment of drug addiction is essentially not different from the psychotherapeutic treatment of non-addicted individuals who suffer with neuroses or character disorders. It is therefore a very broad subject which cannot be adequately covered in this review. Psychotherapy always has to be individualised and is dependent both upon the training, orientation and skill of the therapist (61, 117) and on the nature of the psychiatric problem. The first decision which must be reached in any given case is whether psychotherapy should be offered at all. Many addicts with intense infantile fixations obtain very little benefit from psychotherapy and, in such instances, the best procedure is to provide a short period of intensive institutional supervision followed by a long period of supervision of the patient in his home environment (117). Other patients who developed a higher level of emotional maturity prior to becoming addicted should be offered intensive individualised psychotherapy. There are, unfortunately, not enough psychiatrists to administer psychotherapy to all the patients who need and will accept it. This deficiency in psychiatric facilities can perhaps be partially bridged by organizing group psychotherapeutic sessions.

Many addicts appear to derive great benefit from participation in the inspirational approach of the group known as Alcoholics Anonymous or the more recently organized Addicts Anonymous (61, 116). These groups also provide a

continuing stimulus to remain abstinent from drugs after the patient is discharged.

Whenever possible, treatment should be continued after the patient is discharged from the institution. Prior to discharge, the patient should have a definite plan of life. He should have a job and a place to live. Arrangements should be made for continuing supervision of the addict by his family physician, parole officer (97), minister or friends. The addict should not be returned to an environment where frequent contact with other addicts is unavoidable. Resources of an efficient, well organized, social service department are invaluable in assisting the patient to make proper plans for post-institutional treatment.

Results of treatment. Results of treatment of drug addiction are very difficult to assess because the clientele of institutions treating addicts is drawn from the entire United States so that adequate follow-up studies would be prohibitive in cost. Discharged patients are also naturally reluctant to maintain contact with an institution devoted to the treatment of addicts because of the danger that their employers and friends may learn of their addiction. They therefore use false names and addresses and do not readily respond to follow-up letters. The best study of the results of treatment was made by Pescor (88) who attempted to obtain information on the status of 4766 male patients discharged from the U. S. Public Health Service Hospital at Lexington, Kentucky, between January 1, 1936 and December 31, 1940. Pescor found that the addiction status of these patients could not be determined in 39.6 per cent of the cases, 7 per cent had died following discharge, 39.9 per cent had definitely relapsed to the use of drugs and 13.5 per cent were known to be still abstinent. It is possible that a large number of the individuals, whose status was unknown, were still abstinent because the institution would have been notified if any of the patients had been arrested for any reason and fingerprints taken. In another study, Vogel (116) found that, of 11,041 addicts admitted between May 1, 1935 and January 1, 1948, 6,788 or 61.4 per cent had been admitted only once. The known relapse rate is only 39.6 per cent which is surprisingly low. In the same paper, Vogel states that 22.3 per cent of male patients and 29.8 per cent of female patients who were discharged from the Lexington hospital between 1942 and 1946 and who had remained in the institution for a period of time sufficient to obtain maximum benefit were reliably believed to be still abstinent. 35.1 per cent of the men and 36.6 per cent of the women were reliably believed to have relapsed to the use of drugs. The status of 42.6 per cent of the men and 33.6 of the women was unknown. One must conclude from the figures of Pescor and Vogel that the treatment of drug addicts is still far from satisfactory. Improvement in the results is probably dependent more upon advances in psychiatric treatment than on any other single factor. On the other hand, it also seems fair to conclude that treatment of drug addiction is far from hopeless. Furthermore, many addicts who do relapse remain abstinent for a number of years before returning to the use of drugs. Such periods of abstinence must be regarded as a considerable gain, just as a long remission is counted as a gain in the case of other chronic relapsing diseases such as tuberculosis or arthritis.

III. ADDICTION TO BARBITURATES

In the United States and England it has been commonly held that barbiturates did not produce dependence and were therefore not addicting. For this reason these drugs have not been subjected to as intensive investigation with respect to addiction liability as have morphine and other analgesics.

Incidence of chronic intoxication with barbiturates. It is very difficult to obtain any worthwhile statistics on the incidence of addiction to barbiturates. Chronic barbiturate poisoning is not a reportable condition and the manifestations of barbiturate addiction are not familiar to many physicians. Chronic barbiturate intoxication is frequently misdiagnosed and masquerades as intoxication with alcohol (163) or as organic disease of the nervous system (149, 166, 168, 175). Barbiturates are frequently used in conjunction with some other drug, particularly opiates or alcohol. In hospital records, such cases are usually listed as addiction to narcotics or as alcoholism without mention of barbiturates.

There is evidence that addiction to barbiturates was increasing in Germany prior to 1939. In the years 1923 to 1928, Pohlisch and Panse (181) observed only 14 cases of chronic barbiturate intoxication in the material of the psychopathic hospitals in the Berlin area. Between 1928 and 1932, 117 cases were admitted to these hospitals. Schubert (193), working in Bonn, could find reports of no cases in that locality between 1925 and 1929. Between 1929 and 1935, Schubert states that chronic intoxication with barbiturates accounted for 1.1 per cent of admissions and exceeded the number of cases of morphinism. In the United States, the situation is less clear. In 1940, Hambourger (161) stated that addiction to barbiturates was not rare and accounted for one of every 15,000 hospital admissions. In 1942, Wagner (209) sent a questionnaire to all members of the Connecticut State Medical Society. Of 937 doctors who replied, 306 stated that they "frequently" saw cases of addiction to barbiturates. On the other hand, Goldstein (157) stated that, in 1947, barbiturate addiction was not only rare in the United States but was also actually decreasing. Lowy (167), on the basis of responses to questionnaires circulated to all types of hospitals, estimated the incidence of barbiturate addiction as being only 615 in 2,500,000 hospital admissions.

There is other evidence which suggests that chronic intoxication with barbiturates is increasing in the United States. This includes the increased incidence of barbiturate addiction among narcotic addicts admitted to the United States Public Health Service Hospital at Lexington, Kentucky (163), the increased number of inquiries relative to treatment of barbiturate addiction which have been received in recent years at the same institution, and the increased number of tips investigated by narcotic agents which finally proved to be cases of chronic barbiturate intoxication and not cases of narcotic addiction. A number of articles which have appeared in popular magazines (138, 145, 146, 211) also state that abuse of barbiturates is increasing and, in fact, has become serious. These popular articles give descriptions of illegal sales of barbiturates by unscrupulous pharmacists and by peddlers. Both State (208) and Federal (183) Food and Drug officials confirm the fact that an illegal market exists. Food and Drug

officials have records of prescriptions for barbiturates which were refilled hundreds of times. The seriousness of the situation is also reflected by the large number of states that have enacted legislation regulating the distribution and sale of barbiturates (144, 155) and by the continuing agitation for Federal controls.

No one questions the tremendous increase in acute intoxication with barbiturates and, as pointed out by Trichter (208) and Camp (145), many of the cases of acute intoxication probably represent instances of super-imposition of acute poisoning on a pre-existing barbiturate addiction. The production of barbiturates in the United States now amounts to more than 300 tons yearly. Between 1933 and 1945, the number of fatal cases of poisoning with barbiturates in the United States increased 300 per cent (133, 135, 157, 158, 176, 208). The number of cases of poisoning with barbiturates is exceeded only by the number of cases of poisoning with carbon monoxide (158, 208). Despite the low mortality rate, which averages only about 8 per cent, barbiturates cause more deaths than any other solid or liquid poison (135, 154, 157). They are also the most common agents used in suicidal attempts but, as Tatum (205), Camp (145) and Trichter (208) point out, many of the suicides are probably not intentional but are due to impairment of judgment and memory. Individuals chronically intoxicated with these drugs forget the number of capsules they have ingested, continue to take more and more and, finally, unintentionally kill themselves. This condition has been termed "automatism" in England. It seems very probable that the rise in chronic intoxication with barbiturates has paralleled the rise in acute intoxication with barbiturates.

Types of abuse of barbiturates. In the United States addicts prefer the potent short-acting barbiturates (pentobarbital, seconal, amytal) to the milder long-acting drugs (barbital and phenobarbital). The drugs are usually taken orally although some narcotic drug addicts inject them intravenously. Barbiturates may be used for single debauches lasting for only a night or for "sprees" of several days or weeks duration. In many instances, they are taken continuously for months and years. The use of barbiturates to reinforce the effect of alcohol is quite common and appears to be increasing. The concomitant use of barbiturates and amphetamine is also popular and is reminiscent of the combined use of morphine and cocaine by narcotic drug addicts. It is difficult to determine from clinical histories the amount of drugs used by barbiturate addicts since such patients actually do not know how much they have been taking because of the confusion and mental impairment produced by these drugs. It is, however, unlikely that any individual can continue to ingest more than 2.0 grams of pentobarbital or seconal or 4.0 grams of amytal daily for any extended period of time. Probably the average intake during continuous chronic intoxication is about 1.5 grams of either pentobarbital or seconal and about 3 grams of amytal daily.

Etiology. As in morphine addiction and alcoholism, personality disorders appear to be the most important predisposing cause of addiction to barbiturates (136, 137, 149, 150, 170, 172, 180, 181, 187, 188, 199, 214). Statistics on the

personality characteristics of barbiturate addicts are scant in number but the majority of barbiturate addicts are either psychoneurotics or are suffering with character disorders (constitutional psychopathy). Pohlisch and Panse (181) state that psychically normal individuals do not become addicted to barbiturates. Individuals with sleep disturbances, either "inherited" or due to psychoneuroses, are particularly prone to barbiturate addiction. According to Pohlisch and Panse, psychoneurotic individuals usually begin the use of barbiturates to induce sleep. In the beginning of addiction, psychoneurotics usually take reasonable amounts of barbiturates but later increase their dosages rapidly. The drug then becomes a means of intoxication and not a method of obtaining sleep. Psychopaths begin the use of barbiturates in order to become intoxicated rather than to induce sleep and, therefore, elevate their dosage very rapidly from the onset.

In contradistinction to the situation in addiction to analgesics, a large number of individuals are introduced to barbiturates as a result of medical administration. Introduction of the potential addict to the drug in illegal fashion does occur, however, and is apparently increasing (158, 208).

Other types of intoxication definitely predispose to barbiturate addiction. Morphine addicts take the drug when they are unable to buy morphine. This frequently leads to concomitant use of barbiturates and morphine. Many alcoholics use barbiturates to relieve the symptoms which follow an alcoholic debauch and soon begin taking barbiturates to augment the effects of the alcohol. Many alcoholics, after being introduced to hypnotics, abandon alcohol completely and use only barbiturates.

Addiction of experimental animals to barbiturates. Seevers and Tatum (197) administered 100 mgm./kgm. of barbital daily to dogs for periods ranging up to three and one-half years. After two to six months, characteristic signs were seen 24 hours following withdrawal of the drug. These included muscle tremors and incoordination. After 48 hours of abstinence, marked irritability, motor unrest and convulsions were observed. Pathological changes were observed in the nervous systems of 2 dogs which received barbital for 33 to 37 months. Carratala (147, 148) administered barbital, dial and somnifen to dogs in increasing doses for periods of 44 to 57 days. After withdrawal of the drug for periods of 48 hours, Carratala reported increased irritability and convulsions. Stanton (198) found no increase in the pre-dose irritability of rats that received 8 to 23 mgm. of sodium phenobarbital or 6 to 36 mgm./kgm. of sodium pentobarbital subcutaneously daily for seven weeks. Irritability also did not increase following complete withdrawal of these drugs at the end of the experiment. Stanton did observe shortening of the sleeping time as addiction proceeded. Swanson, Weaver and Chen (204) gave 40 mgm./kgm. of sodium amytal to dogs and 35 to 40 mgm./kgm. to monkeys intravenously three times weekly for periods of two to four months. Two monkeys received 35 to 40 mgm./kgm. daily for two months. No evidence of abstinence was observed following withdrawal in any of these animals. Swanson, Weaver and Chen therefore concluded that sodium amytal did not produce "true" addiction. They did admit the possibility of abuse of the drug by individuals with abnormal personalities.

Clinical evidence concerning abstinence from barbiturates. The majority of the papers on chronic barbiturate intoxication which have appeared in the American and English literature state that no abstinence symptoms follow withdrawal of barbiturates (149, 150, 156, 158, 160, 176, 205, 208, 210, 213) or else do not mention whether abstinence appeared after discontinuation of the drug (136, 137, 162, 182, 186–189, 207, 214). These papers are useful chiefly for clinical descriptions of maintained chronic barbiturate intoxication.

The German investigators have been more astute and have recognized since 1912 that convulsions and delirium may follow the abrupt withdrawal of medication from individuals chronically intoxicated with barbiturates (142, 143, 152, 168, 169, 174, 180, 181, 192, 193). The monograph of Pohlisch and Panse (181) is outstanding in this respect and reviews the findings in 131 cases of chronic barbiturate intoxication. Most of the German authors were strongly impressed by the resemblance of the barbiturate abstinence syndrome to alcoholic delirium tremens.

Since 1940 a small number of articles have appeared in the American literature which describe the occurrence of convulsions following withdrawal of barbiturates (141, 153, 164, 178). The occurrence of delirium during abstinence from barbiturates, although mentioned by Osgood (178), has not been stressed by the American authors. Both German and American authors have described the increased incidence of convulsions following withdrawal of phenobarbital from epileptics (151, 185, 191).

Although the clinical papers on withdrawal of barbiturates were very suggestive, it was actually impossible from the data in these communications to determine whether the phenomena observed after withdrawal of barbiturates were due solely to abstinence from barbiturates. The histories of the barbiturate addicts were unreliable with respect to dosage and length of addiction. Barbiturate addicts may deliberately exaggerate the amounts of drugs they take, and also may be unable to recall the amounts used on account of the drunkenness and confusion produced by the drugs. Many of the cases reported represented examples of mixed addiction to morphine and barbiturates, to alcohol and barbiturates, and frequently to other drugs as well. The possibility therefore existed that convulsions and psychoses during withdrawal were due either to direct poisoning or to abstinence from a combination of drugs. Many of the patients were suffering from other diseases and large numbers of them were emaciated and malnourished. In many instances, withdrawal of barbiturates was not abrupt and usually barbiturates and other drugs were administered to these patients during withdrawal of barbiturates. The physical and mental status of these patients prior to chronic intoxication with barbiturates was unknown so that it was difficult to determine whether the development of convulsions and psychoses was dependent upon an underlying psychotic epileptic diathesis or whether any permanent physical or mental damage followed chronic barbiturate intoxication.

In order to obviate the difficulties mentioned in the preceding paragraph, Isbell and his collaborators (163) administered large amounts of pentobarbital,

seconal, and amytal to 5 former morphine addicts for periods ranging from 92 to 144 days. Following withdrawal of barbiturates from these experimentally addicted individuals, convulsions occured in 4 of the jubjects and psychosis of delirium-like nature occured in 4. These symptoms did not appear as long as the patients were taking barbiturates.. Recovery following abstinence was apparently complete. Isbell *et al.* therefore concluded that true abstinence symptoms do follow withdrawal of barbiturates from chronically intoxicated individuals. The abstinence symptoms were not due to a combination of intoxication, to malnutrition, or to a pre-existing psychotic or epileptic diathesis. Chronic barbiturate intoxication did not produce any permanent damage which could be detected by clinical or psychometric examination.

The clinical picture of chronic barbiturate intoxication in man. Practically all authors are agreed on the manifestations of chronic barbiturate intoxication in man (136, 137, 149, 150, 163, 170, 180, 181, 193, 199, 207, 214). The symptoms are identical with those seen in the milder types of acute barbiturate intoxication. The signs observed are chiefly due to the effects of the drugs on the central nervous system. The clinical picture is strikingly similar to that of individuals who are chronically intoxicated with alcohol except for the fact that persons who are addicted only to barbiturates continue to eat and maintain a good state of nutrition (163). The mental signs include confusion, impairment of intellectual ability, defective judgment, loss of emotional control and accentuation of pathological features in the personalities of the addicts. Individuals who are chronically ingesting barbiturates become hostile, or even assaultive, at fancied insults or minor incidents. They are slovenly in their dress, spill food on themselves, and live like pigs. They regress psychically and behave like small children. Frequently they are so depressed that suicide becomes a distinct possibility. The degree of mental impairment is so great that they are totally unable to work or to care for themselves. Though they may be so intoxicated that they cannot stand, they will try to obtain even more barbiturates. True toxic psychoses are, however, probably rare during maintained barbiturate addiction. Although patients are confused and think with difficulty they are usually oriented in time, place, and person and hallucinations and delusions are seldom observed. When a psychosis does occur it is probably due to the superimposition of an acute intoxication on the chronic state.

The neurological signs of chronic barbiturate intoxication are predominantly motor in nature and suggest cerebellar disease, multiple sclerosis, Parkinsonism or alcoholism. Neurological signs include ataxia in gait and station, dysarthria, dyssynergia, adiadokokinesis, hypotonia, tremor, depression of the abdominal reflexes, and occasionally transient clonus and positive Babinski signs. The pupils and deep reflexes are little altered. There are no sensory changes. The other findings include mild depression of systolic and diastolic blood pressures and lowering of body temperature. Pulse and respiratory rates are little altered. Gastrointestinal, urinary, respiratory or cardiac symptoms are rare. The total amount of sleep per day is increased only an hour or two.

One of the most striking features of chronic barbiturate intoxication in the

experiment of Isbell *et al.* (163) was the great variation in the effect of the barbiturates in different individuals and in the same individual on different days. One man who took 1.8 to 2.0 grams of seconal daily, exhibited only mild to moderate signs of intoxication while another individual who was receiving only 1.3 grams of seconal daily can best be described as a staggering drunk. On certain days, a dose of barbituate would produce little effect in a given individual and on other days the same dose would cause severe intoxication and even light coma. Variations in the same individual were partly related to differences in food intake on different days but even after food intake was controlled considerable variation persisted. The variations in the inherent tolerance of different individuals to barbiturates has been commented on by Newman (177). Even with short acting barbiturates, such as seconal, cumulative effects were observed in Isbell's subjects.

It is apparent from the foregoing description that chronic intoxication with barbiturates is a very formidable and dangerous condition. Even if no abstinence followed withdrawal of barbiturates, the effects are so harmful that chronic use of barbiturates would have to be classified as an addiction under the terms of the definition proposed by the National Research Council's Committee on Drug Addiction.

Tolerance to barbiturates

Animal experiments on tolerance. This subject has been ably reviewed by Tatum (205, 206) and by Seevers and Tatum (197). As Tatum states, the majority of the investigators who have studied this problem agree that some tolerance to the hypnotic effect does occur (147, 148, 171, 198). The degree of tolerance is not great and is usually manifested by a decrease in sleeping time following administration of the barbiturates. Only Swanson, Weaver and Chen (205) deny the existence of any tolerance. Agreement is less general with respect to tolerance to the toxic effects. Seevers and Tatum did not demonstrate any increase in the lethal dose of barbiturates during chronic intoxication of dogs with sodium barbital and Stanton (198) found no tolerance to the toxic effects in rats. Carratala (147, 148) reported tolerance to both the hypnotic and toxic effects in dogs. Gruber and Keyser (159) administered butisol, amytal, cyclopal, pentobarbital, ortal, seconal and evipal to dogs, rabbits and albino rats. As measured by the duration of sleeping time, all these species developed partial tolerance to the hypnotic action of these various barbiturates when they were chronically administered. Tolerance to one barbiturate conferred partial cross-tolerance to others. Tolerance to the hypnotic action conferred no protection against the toxic effects of the drug. It therefore appears that one must conclude, as did Tatum (205, 206), that some tolerance is developed to the hypnotic effects of the barbiturates but it is unlikely that chronic administration will raise the LD_{50}.

Tolerance in man. The German writers, particularly Pohlisch and Panse (181), state very definitely that individuals who chronically ingest large amounts of barbiturates develop tolerance to the hypnotic effects regardless of the type of

barbiturate used. A greater degree of tolerance can be developed against the hypnotic effect of phanodorn than against those of any other barbiturates known to these German authors. Isbell and his associates (163) found that it was very difficult to determine whether tolerance developed during the course of experimental addiction to pentobarbital, seconal, and amytal because of the marked fluctuation in the effects of the drugs from day to day. Tolerance to hypnotic and sedative effects was much less developed in barbiturate addiction than in morphine addiction. After 4 of Isbell's patients had recovered following withdrawal, they were abruptly placed on the same dosage of barbiturates they had attained gradually during addiction. All 4 patients became much more intoxicated than they were at any time during addiction. Some degree of tolerance must, therefore, have developed during chronic administration of barbiturates.

Intolerance to barbiturates. Seevers and Tatum (197) found that, during chronic experimental barbital poisoning, dogs first became tolerant and then reached a stage of intolerance in which barbiturates produced such severe effects that the animals were in danger of death. Seevers and Tatum ascribed this intolerance to the development of pathological changes in the central nervous system. Pohlisch and Panse (181) state that humans first become tolerant to barbiturates and finally reach a stage in which small doses of barbiturates cause pathological intoxication. This state of intolerance, according to Pohlisch, frequently precedes abstinence and is similar to the state of intolerance noted in alcoholics before the onset of delirium tremens. Isbell and co-workers (163) did not observe any intolerance in their experimental subjects but the period of intoxication in this experiment was much shorter than the period of intoxication in many of the cases of Pohlisch.

Pathological changes in chronic barbiturate intoxication. The majority of investigators who have studied chronic barbiturate intoxication in animals have reported the occurrence of pathological changes in the central nervous system. Mott, Woodhouse and Pickworth (173) administered 150 to 300 mgm. of barbital, dial, phenobarbital and soneryl daily to cats for periods varying between one and six weeks. 300 to 600 mgm. of these same drugs were administered daily to monkeys for comparable periods of time. Following withdrawal of these drugs, both cats and monkeys made a rapid recovery and showed no obvious clinical signs of permanent anatomical damage. Histological examination revealed the presence of masses of mucinoid material in the central nervous system of the animals. The mucinoid material was especially abundant in the white matter of the cerebellum but also occurred in the white substance of the midbrain and spinal cord, and to a lesser extent, in the gray matter of the cord, brain stem and cerebral cortex. Occasionally globules of mucinoid material were observed within the nerve cells, especially in the anterior horn cells of the spinal cord. This mucinoid material was not present in the tissues of animals that had not received barbiturates and slowly disappeared from the nervous systems of chronically poisoned animals following withdrawal of barbiturates. In addition to the mucinoid material, Mott, Woodhouse and Pickworth observed degenera-

tive changes in the Purkinje cells in the cerebellum, in the anterior horn cells of the spinal cord and in the Betz cells of the motor cortex. These changes were not specific for chronic barbiturate poisoning but also appeared after a chronic administration of sulfonal, trional or urethane. Examination of the brains of two of the dogs used by Seevers and Tatum (197) showed thickening of the leptomeninges, changes in the endothelial linings of the blood vessels, and alterations in glial cells and the oligodendroglia. Shrinkage, pyknosis and encrustation of the ganglion cells were observed. Seevers and Tatum also reported the presence of mucin-like material which was present intra- and extra-cellularly. Carratala (147, 148) described thickening of the leptomeninges and perivascular hemorrhages in the central nervous system of dogs chronically poisoned with various barbiturates. Schulte (194) did not find any histologic evidence of damage to the skin, liver, spleen or heart muscle of dogs who received 50 mgm./kgm. of pentobarbital or amytal intraperitoneally twice weekly for 205 days. Since the intoxication was not continuous in Schulte's experiment, the lack of pathological changes is not surprising. Schulte did not examine the central nervous systems of his animals histologically. Swanson, Weaver and Chen (204) also found no pathological changes in dogs and monkeys after intermittent and continuous chronic administration of sodium amytal intravenously. The investigators who have reported negative findings generally have not administered the drug at sufficiently short intervals for sufficiently long periods of time to make their results convincing. One must, therefore, conclude that, in animals, chronic barbiturate intoxication produces pathological changes in the nervous system. It is, however, difficult to relate the pathological changes to the symptoms seen during intoxication or withdrawal.

The authors know of no reports on the pathology of chronic barbiturate intoxication in man. So far as can be ascertained by clinical methods, most human subjects appear to recover completely from chronic barbiturate intoxication. The German authors, notably Pohlisch (180) and Pohlisch and Panse (181), comment on the fact that peripheral neuritis and Korsakoff's syndrome are not seen following abstinence from barbiturates. Since both of these conditions are now believed to result from nutritional deficiency, it is not surprising that they do not occur following chronic barbiturate intoxication because barbiturate addicts continue to eat and maintain a good state of nutrition (163). If irreversible pathological changes do occur in man they are so slight as to be undetectable by clinical means and are not sufficient to cause any permanent physical handicap to individuals who have abused these drugs. Barbiturate addicts are much more likely to develop permanent damage as a result of trauma resulting from a fall while intoxicated or from a convulsion during abstinence than as a result of pathological changes due to direct effects of the drug.

Clinical picture of abstinence in man. The following description of withdrawal of barbiturates is based primarily on the five cases of Isbell *et al.* (163). These represent the only instances in which the actual dosage of barbiturates and length of chronic intoxication were definitely known. The 5 patients, who were addicted only to barbiturates, were subjected to complete abrupt withdrawal

under conditions so controlled as to minimize the possibility of the patients smuggling in drugs of any sort. The description, however, agrees well with the descriptions of other authors (141, 142, 143, 152, 153, 168, 169, 174, 178, 180, 181, 192, 193).

During the first 12 to 16 hours of abstinence from barbiturates, patients improve and the signs suggestive of cerebellar dysfunction disappear. As the signs of intoxication decline, patients become apprehensive and so weak that they can hardly stand. Fasciculation of various muscles appears and a coarse tremor of the hands and face is evident. The deep reflexes become hyperactive and slight stimuli may cause excessive muscular responses. The patients cannot sleep, are nauseated, have abdominal cramps and frequently vomit. Systolic blood pressure is elevated about 20 mm. of mercury, and the pulse rate is increased about 10 to 20 beats per minute. Patients may lose as much as 5 kgm. of body weight in the first 36 hours of abstinence. The weight loss is due to loss of body water by all routes, to decreased intake of fluid, or to both. Elevation of the non-protein nitrogen content of the blood, hyperglycemia and hemoconcentration appear and are attributable in part to dehydration. Patients also develop difficulties in making cardiovascular adjustments on assuming the upright posture. On standing, their pulse rates rise 40 to 80 beats per minute and systolic blood pressure, while fluctuating widely, generally falls 15 to 50 mm. of mercury while the diastolic blood pressure increases. The pulse pressure is therefore narrowed. The cardiovascular changes, unlike those observed in normal individuals, become more marked the longer the patients remain standing. These changes are not similar to the disturbance in postural hypotension in which both systolic and diastolic blood pressures decrease upon standing and in which the normal increase in the pulse rate fails to occur. This derangement in cardiovascular physiology resembles the disturbance seen during or after many severe febrile illnesses, particularly severe infections. No clinical or electrocardiographic evidence of myocardial damage can be detected.

As serious and severe as these symptoms are, they are followed by even more dangerous phenomena. Between the 16th hour and the fifth day of withdrawal, usually about the 30th hour of abstinence, the patients may have one or more convulsions which are indistinguishable from those observed in idiopathic grand mal epilepsy. The patients usually regain consciousness within a few minutes after the onset of the convulsion. They may be slightly confused for an hour or two following the convulsion but prolonged stupor such as is seen in grand mal epilepsy was not observed. Ordinarily, patients have no more than three convulsions but numerous minor episodes characterized by clonic twitching of one or more extremities, without loss of consciousness, or by athetoid movements of the extremities which may occur between and after major convulsions. Hyperventilation resulting in alkalosis with concomitant paresthesias of the hands and feet is ocasionally observed. Between or following the convulsions, patients continue to exhibit weakness, disturbed cardiovascular adjustments on changes in posture, anorexia and nervousness. Unless the patient develops a psychosis, these symptoms gradually disappear and after two or three weeks the patients recover completely.

Independent of the occurrence of convulsions, patients may develop a psychosis which usually appears between the third and seventh day of abstinence. The onset of the psychosis is often heralded by insomnia of 24 to 48 hours duration, after which patients begin to experience visual and auditory hallucinations. Visual hallucinations are more prominent. Hallucinations at times are amusing and at other times very disturbing. Patients may see little people, giants, absent relatives, animals, insects, birds, snakes, fish, etc. The patients may believe that imaginary persons are trying to harm them. They may state that they have been blown up, "cut with knives", or forced to drink poison. Non-existent people talk to and threaten them, and radios, which no one else can hear, play beautiful music. The patients are confused and usually disoriented in time and place but not in person. They may misidentify objects, persons and noises. They have a marked coarse tremor. The attention span is short; patients who are experiencing hallucinations will start to answer a question, stop before completing the answer, and begin to stare at their imaginary visitors. The emotional reaction to the psychosis appears to be influenced by basic personality traits of the patient. Some individuals become extremely agitated, try to fight or escape from their imaginary persecutors and may become dangerously exhausted. Other patients lie quietly and watch the strange visitors and listen to the imaginary music without taking any action. Some patients are so quiet that, even though they are having hallucinations, the psychosis may not be detected unless it is specifically looked for. Occasionally schizophrenic-like reactions are observed. Patients may show mutism or bizarre affect, have ideas of control and influence, build up a system of paranoid delusions and experience sexual hallucinations. Characteristically, the psychosis appears more readily and is more severe during the night. Untreated patients will usually recover from psychosis within two weeks of its onset. Some will recover in three or four days and some may require two or three months. Improvement usually occurs with the return of the ability to sleep. Hallucinations become less vivid and finally disappear. The patients may have delusions for a few days and believe that their hallucinations are real. After recovery, most patients can recall and describe some of the hallucinations they experienced during the psychosis.

The manifestations of withdrawal of barbiturates, like abstinence from morphine, vary from person to person. Certain individuals may escape with anxiety, weakness, anorexia, etc. as the only symptoms. Others may develop convulsions and not a psychosis. Still others may have a psychosis but no convulsions. Convulsions may precede or follow the psychosis.

It is probable that signs of abstinence will occur following long intoxication with any of the known barbiturates. Reports in the literature show that convulsions, psychosis, or both have occurred after the withdrawal of barbital (174, 180, 181, 192), phenobarbital (180, 181), pentobarbital (163, 178), amytal (163, 178) and phanodorn (142, 143, 152, 169, 181, 193). Whether the barbiturate abstinence syndrome is more likely to occur and is more severe after intoxication with any particular barbiturate is unknown, although Pohlisch (181) found that psychoses and convulsions occurred more frequently after withdrawal of phanodorn than after withdrawal of barbital or phenobarbital.

Electroencephalograms in chronic barbiturate intoxication. During acute intoxication with barbiturates of mild degree, the characteristic change in the electroencephalogram consists of the appearance of an increased number of waves with frequencies of 15 to 30 per second (140, 201, 202, 203). As the degree of barbiturate narcosis increases the fast (beta) activity is largely replaced by large slow waves (delta) which are similar to, or identical with, those occurring in natural sleep. In very intense narcosis, complete absence of electrical activity for short periods may be observed (201, 203). The changes during chronic barbiturate intoxication are similar to those observed during mild acute barbiturate narcosis. Characteristically, the electroencephalogram in maintained chronic barbiturate intoxication reveals an increased number of high voltage waves with frequencies of 20 to 30 per second (163). During the early stages of addiction to barbiturates, slow waves are seen; but, as addiction proceeds, these disappear. This may indicate some degree of tolerance. During the first 12 to 48 hours after barbiturates are withdrawn, the number of beta waves decreases and paroxysmal bursts of high amplitude waves with frequencies of four to six cycles per second appear (163). These paroxysmal slow waves indicate that grand mal seizures may be imminent. Electroencephalograms recorded during grand mal seizures in abstinence from barbiturates are identical with those obtained from individuals during seizures of idiopathic grand mal epilepsy. Following seizures due to abstinence from barbiturates, large slow "stupor" waves (1 to 6 cycles per second) are seen. Following the convulsive phase of withdrawal, increased percentages of waves with frequencies of six to seven cycles per second persist for about two weeks. One month after the beginning of withdrawal, the electroencephalograms are indistinguishable from electroencephalograms obtained prior to chronic barbiturate intoxication.

Psychological studies during chronic barbiturate intoxication. Sargant (190) found that 0.065 to 0.195 gram of sodium amytal reduced the average intelligence quotients of 103 soldiers about 4 per cent. The reduction was slightly less than that obtained with 20 cc. of absolute alcohol. Isbell *et al.* (163) and Kornetsky (165) found marked deterioration in the ability of former morphine addicts to perform psychometric tests after the administration of 0.4 to 0.7 gram of either pentobarbital or seconal or 0.9 to 1.2 grams of amytal. During chronic intoxication with barbiturates, a marked decline in the ability of the subjects to carry out a simple digit-symbol test was observed. As the experiment proceeded, the performance on this test improved but learning may have contributed significantly to the improved performance. Changes in projective tests (Bender-Gestalt, "Draw-a-Man" and Rorschach) all indicated accentuation of the basic personality characteristics of the subjects during maintained intoxication. After the acute withdrawal symptoms subsided, the results obtained with all types of psychological tests rapidly returned to the levels observed prior to chronic barbiturate intoxication.

Mechanism of abstinence from barbiturates. This is practically an untouched field and very little information is available. Schütz (195, 196) reported that the serum cholinesterase content was decreased during continued administration of

barbiturates to epileptic patients. He postulated that the decrease of cholinesterase in the serum reflected a similar decrease in the nervous tissue and attributed the occurrence of convulsions during withdrawal to an increased tissue content of acetylcholine. Isbell *et al.* (163), using different analytical methods, were unable to demonstrate any depression of the serum cholinesterase or any increase in the amount of acetylcholine in the serum of individuals who were either chronically intoxicated with barbiturates or were undergoing withdrawal. It should also be pointed out that serum cholinesterase is chiefly pseudo-cholinesterase and its physiological significance is unknown. Moreover, it is not justifiable to assume that a depression of the cholinesterase activity of the serum reflects a change in the tissue cholinesterase concentration.

The pathological studies of Mott, Woodhouse and Pickworth (173) suggest that the barbiturate abstinence syndrome is due to pathological changes in the nervous system. As mentioned above, these authors found that chronic barbiturate intoxication is associated with the presence of abnormal mucinoid material which is widely distributed throughout the central nervous system. Apparently the amount of the mucinoid material decreases rapidly following withdrawal of barbiturates from cats and monkeys. Further pathological investigations will have to be undertaken to establish or disprove this hypothesis.

Relationship of barbiturate addiction to other intoxications. The clinical manifestations of abstinence from barbiturates are strikingly similar to those of alcoholic delirium tremens (139, 142, 143, 164, 181). Similar abstinence syndromes have been described following withdrawal of chloral or paraldehyde from individuals chronically poisoned with those drugs (139, 164, 180). This suggests that delirium tremens is not a symptom complex which is specific for alcoholism but is a condition which can arise after long intoxication with hypnotics of diverse chemical structure. If this is true, the constellation of symptoms known as delirium tremens must be based on some action which these drugs possess in common.

Treatment of chronic barbiturate intoxication. Abrupt withdrawal of barbiturates from individuals chronically intoxicated with those drugs is absolutely contraindicated (61, 180–212). Even rapid reduction of the dose is dangerous since withdrawal phenomena may appear if the dosage is suddenly reduced to 50 per cent or less of that which the individual is accustomed to taking. The first point in treating chronic intoxication with barbiturates is to determine the dosage of any barbiturate which will maintain the patient in a mild state of continuous intoxication. Usually 0.2 to 0.3 gram of pentobarbital four times daily will accomplish this purpose. After this "stabilization" dose has been determined, barbiturates should be withdrawn very gradually. Dosage of barbiturates should not be reduced more than 0.1 gram per day and, occasionally, reduction should be stopped for periods of three or four days. The appearance of anxiety, weakness, and insomnia indicate that reduction should be stopped and the patient maintained on the dosage level at which the symptoms appeared for several days. It usually requires 14 to 21 days to withdraw barbiturates safely. Withdrawal of barbiturates and analgesics can be conducted simultaneously without

increasing the danger of appearance of signs of abstinence from barbiturates. Whether anticonvulsants or hypnotics other than barbiturates are of value in withdrawing patients from barbiturates has not yet been determined.

After withdrawal of barbiturates is completed, the rehabilitative and psychotherapeutic treatment is identical with that for morphine addiction. There is no information available on the long-range results of the treatment of chronic barbiturate intoxication. The same tendency to relapse, which is characteristic of addiction to opiates and alcohol, is present in addiction to barbiturates so that the prognosis must be guarded.

SUMMARY

Drug addiction is a condition in which an individual has lost the power of self-control with reference to a drug and abuses the drug to such an extent that the individual, society, or both are harmed. Dependence, either physical or psychic, is not an essential feature of drug addiction.

The most important factor which predisposes to drug addiction is a personality disorder. In addition to the personality disorder, contact with a drug which produces mental reactions that are regarded as pleasurable is necessary. Contact with the drug as a result of curiosity about the pleasurable effects is a much more potent factor in inducing addiction than is contact as a result of legitimate medical administration.

Animal methods have only a limited place in determining the addiction liability of new drugs. Dogs and monkeys are the best species to use for such experiments. The final determination of the addiction liability of any new analgesic drug is dependent upon experimentation or clinical observations with human beings.

There is no drug in the morphine series which is known to be an effective analgesic that does not also possess addiction liability. The addiction liabilities of compounds of the morphine series generally parallel the analgesic potencies of the drugs. However, it is possible that some separation of addiction liability and analgesic potency has been achieved in the compound 6-methyldihydromorphine. N-allylnormorphine does not produce physical dependence in man, but it is not known whether this drug is an effective analgesic.

There are also no known compounds in either the meperidine or methadone series which do not possess addiction liability. Addiction to meperidine is fairly common and physical dependence can be developed in individuals who have never been previously addicted to any other analgesic drug. Addiction to meperidine, because of the toxic effects of the drug, is more undesirable than addiction to morphine.

Recent neurophysiological investigations have shown that the spinal cord, and probably other parts of the central nervous system, are involved in physical dependence on morphine. Physical dependence is not entirely due to changes in the autonomic nervous system.

The theory that the manifestations of abstinence are due to the stimulant effects of morphine outlasting the depressant effects is probably not tenable.

The most satisfactory theory of dependence at the present time is that certain homeostatic responses, which oppose some of the actions of morphine, are enhanced by repeated administration of the drug. When morphine is withdrawn, these enhanced physiological counter-responses are still operative and, therefore, signs of abstinence appear. The mechanisms responsible for the enhancement of the homeostatic responses are unknown.

During addiction to morphine and other analgesics, the electroencephalogram is characterized by general slowing. Following withdrawal the electroencephalogram returns to normal.

It has not been established that partial tolerance to certain actions of morphine persists for long periods of time following withdrawal of the drug. Furthermore, it has not been established that individuals who have been addicted to one analgesic drug will develop physical dependence on another analgesic drug any more rapidly than a comparable individual without addiction experience.

There is no real evidence that addiction to morphine produces permanent anatomical damage to the central nervous system. Morphine addiction does not produce any permanent impairment of intelligence.

Treatment of morphine addiction involves withdrawal of the drug followed by a long period of rehabilitative and psychiatric therapy. Withdrawal of morphine is very easy to accomplish provided adequate environmental control of the addict can be achieved. The best and only rational method of withdrawal consists of the administration of decreasing doses of either morphine or some equivalent drug. The results of treatment of addiction, although not completely satisfactory, are much better than is commonly thought.

Barbiturates are addicting drugs no matter how the word addicting is defined. In fact, addiction to barbiturates is far more dangerous and harmful than is addiction to morphine or other analgesic drugs. Barbiturate addiction is apparently increasing in the United States.

The clinical picture of chronic barbiturate intoxication resembles that of chronic intoxication with alcohol and is characterized by impairment of mental ability, impairment of emotional control, psychic regression and dangerous neurological symptoms.

Withdrawal of barbiturates from individuals chronically intoxicated with those drugs is followed by a very definite and severe type of abstinence syndrome which is characterized chiefly by the appearance of convulsions and delirium.

Physical recovery from chronic barbiturate intoxication in man is, so far as can be judged by clinical and psychological examination, complete unless the addict incurs an accidental injury during chronic intoxication or during a convulsion in withdrawal.

The barbiturate abstinence syndrome has been produced experimentally in dogs.

Chronic barbiturate poisoning in animals is accompanied by definite pathological changes in the central nervous system.

The mechanism of symptoms of abstinence from barbiturates is unknown.

Treatment of chronic barbiturate intoxication consists in a very careful gradual withdrawal of the drug followed by a long period of rehabilitative and psychiatric therapy.

REFERENCES

PART I—ANALGESICS

1. Adams, R.: Marihuana. Harvey Lect., 37: 166-197, 1941-42. Reprinted in Bull. New York Acad. Med., 18: 705-730, 1942.
2. Allentuck, S., and Bowman, C. M.: The psychiatric aspects of marihuana intoxication. Am. J. Psychiat., 99: 248-251, 1942.
3. Altschul, S., and Wikler, A.: Electroencephalogram during a cycle of addiction to keto-bemidone hydrochloride. (In press.)
4. Andrews, H.L.: Studies on codeine addiction. Pub. Health Rep., Suppl. No. 158, Part III. The effects of codeine on the electrical potentials of the cerebral cortex. pp. 20-31, 1940.
5. Andrews, H. L.: Brain potentials and morphine addiction. Psychosom. Med., 3: 399-409, 1941.
6. Andrews, H. L.: The development of tolerance to demerol. J. Pharmacol. & Exper. Therap., 75: 338-341, 1942.
7. Andrews, H. L.: Cortical effects of demerol. J. Pharmacol. & Exper. Therap., 76: 99-04, 1942.
8. Andrews, H. L.: Changes in the electroencephalogram during a cycle of morphine addiction. Psychosom. Med., 5: 143-147, 1943.
9. Andrews, H. L.: The effect of opiates on the pain thresholds in post-addicts. J. Clin. Investigation, 22: 511-516, 1943.
10. Andrews, H. L.: Skin resistance changes and measurements of pain threshold. J. Clin. Investigation, 22: 517-520, 1943.
11. Andrews, H. L.: The effect of 8 morphine derivatives on the electroencephalogram. Unpublished data.
12. Andrews, H. L., and Himmelsbach, C. K.: Relation of the intensity of the morphine abstinence syndrome to dosage. J. Pharmacol. & Exper. Therap., 81: 288-293, 1944.
13. Anslinger, H. J.: Demerol. Correspondence. J. Am. M. A., 132: 43-44, 1946.
14. Anslinger, H. J.: Methadon addiction. Correspondence. J. Am. M. A., 136: 609, 1948.
15. Barbour, H. G., Hunter, L. G., and Richey, C. H.: Water metabolism and related changes in fated and fat-free fed dogs under morphine addiction and acute withdrawal. J. Pharmacol. & Exper. Therap., 36: 251-277, 1928.
16. Barbour, H. G., Russel, B. E., Flowers, S. H., Durham, E. S., and Hunter, L. G.: The significant redistribution of water between internal and surface tissues and the blood at the height of morphine withdrawal. Am. J. Physiol., 90: 373, 1929.
17. Batterman, R. C.: Demerol: A new synthetic analgesic: its indications as a substitute for morphine. Connecticut M. J., 8: 13-17, 1944.
18. Batterman, R. C.: The clinical aspects of evaluating analgesic agents. With notes on the safety of morphine. Yale J. Biol. & Med., 18: 597-607, 1946.
19. Batterman, R. C.: The importance of addiction to the newer synthetic analgesics in human therapy. Ann. New York Acad. Sc., 51: 123-130, 1948.
20. Batterman, R. C., and Himmelsbach, C. K.: Demerol—a new synthetic analgesic: A review of its present status and comparison with morphine. J. Am. M. A., 122: 223-226, 1943.
21. Bodo, R. C. de: The antidiuretic action of morphine and its mechanism. J. Pharmacol. & Exper. Therap., 82: 74-85, 1944.
22. Brown, R. R.: The order of certain psychophysiological events following intravenous injection of morphine. J. Gen. Psychol., 22: 321-340, 1940.
23. Brown, R. R.: The effect of morphine upon the Rorschach pattern in post-addicts. Am. J. Orthopsychiat., 13: 338-343, 1943.
24. Brown, R. R.: A cycle of morphine addiction, Part II: Psychological investigations. Pub. Health Rep., 61: 37-53, 1946.
25. Brown, R. R., and Partington, J. E.: The intelligence of the narcotic drug addict. J. Gen. Psychol., 26: 175-179, 1942.
26. Brown, R. R., and Partington, J. E.: A psychometric comparison of narcotic addicts with hospital attendants. J. Gen. Psychol., 27: 71-79, 1943.
27. Brucke, S. v.: Dolantin abuse and one case of dolantin delirium. Wien. klin. Wchnschr., 53: 854-856, 1940.
28. Cochin, J. C., Gruhzit, C. C., Woods, L. A., and Seevers, M. H.: Further observations on addiction to methadon in the monkey. Proc. Soc. Exper. Biol. & Med., 69: 430-431, 1948.
29. Curry, J. J.: Habituation to meperidine hydrochloride (demerol hydrochloride). J. Am. M.A., 133: 343-344, 1947.
30. Dietrick, L. E., and Thienes, C. H.: Tissue hydration during morphine addiction and withdrawal in rats on low calcium diets and on high calcium diets with parathyroid hormone injections. Arch. internat. de pharmacodyn. et de thérap., 66: 130-137, 1941.
31. Dykes, J. B., and Poppen, J. L.: Lobotomy for intractable pain. J. Am. M. A., 140: 15-19, 1949.
32. Eddy, N. B.: Tolerance and addiction. Chapter 10 in Krueger, H., Eddy, N. B., and Sumwalt, M.: The Pharmacology of the Opium Alkaloids. Part I. Pub. Health Rep. Supp., 165: 687-758, 1941.

33. Eddy, N. B.: Personal communication.
34. Felix, R. H.: Some comments on the psychopathology of drug addiction. Ment. Hyg., 23: 567-583, 1939.
35. Felix, R. H.: Studies on codeine addiction. Pub. Health Rep. Supp. 156, Part IV. The effect of codeine on behavior. pp. 33-49, 1940.
36. Felix, R. H.: An appraisal of the personality types of the addict. Am. J. Psychiat., 100: 462-467, 1944.
37. Fitzhugh, O. G.: The effect of vitamin B_1 on morphine abstinence symptoms. J. Pharmacol. & Exper. Therap., 67: 422-428, 1939.
38. Flowers, S. H., Dunham, E. S., and Barbour, H. G.: Addiction edema and withdrawal edema in morphinized rats. J. Pharmacol. & Exper. Therap., 36: 572, 1929.
39. Fraser, H. F., and Isbell, H.: The addiction liability of some morphine derivatives. Unpublished data.
40. Fraser, H. F., and Isbell, H.: Addiction liabilities of heptazone and of the acetylmethadones. Unpublished data.
41. Garda, D.: The clinical use of dolantin and its abuse by toxicomanics. Dia med., 13: 1053-1054, 1941.
42. Hart, E. R., and McCawley, E. L.: The pharmacology of N-allylnormorphine as compared with morphine. J. Pharmacol. & Exper. Therap., 82: 339-345, 1944.
43. Himmelsbach, C. K.: Studies on codeine addiction. Pub. Health Rep. Supp. 156, Part I. A review of the literature on codeine addiction. pp. 1-10. Part II. Studies on physical dependence on codeine. pp. 11-19, 1940.
44. Himmelsbach, C. K.: Thiamine in the treatment of the morphine abstinence syndrome in man. J. Pharmacol. & Exper. Therap., 70: 393-396, 1940.
45. Himmelsbach, C. K.: The effects of certain chemical changes on the addiction characteristics of drugs of the morphine, codeine series. J. Pharmacol. & Exper. Therap., 71: 42-48, 1941.
46. Himmelsbach, C. K.: Studies on the relation of drug addiction to the autonomic nervous system; results of cold pressor tests. J. Pharmacol. & Exper. Therap., 73: 91-97, 1941.
47. Himmelsbach, C. K.: The morphine abstinence syndrome, its nature and treatment. Ann. Int. Med., 15: 839-896, 1941.
48. Himmelsbach, C. K.: Clinical studies of drug addiction. Physical dependence, withdrawal and recovery. Arch. Int. Med., 69: 766-772, 1942.
49. Himmelsbach, C. K.: Studies of the addiction liability of "demerol" (D-140). J. Pharmacol. & Exper. Therap., 75: 64-67, 1942.
50. Himmelsbach, C. K.: Further studies of the addiction liability of demerol (1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester hydrochloride). J. Pharmacol. & Exper. Therap., 79: 5-9, 1943.
51. Himmelsbach, C. K.: With reference to physical dependence. Federation Proc., 2: 301-308, 1943.
52. Himmelsbach, C. K.: Treatment of the morphine abstinence syndrome with a synthetic cannabis-like compound. South. M. J., 37: 26-29, 1944.
53. Himmelsbach, C. K.: Studies on the relationship of drug addiction to the autonomic nervous system: results of tests of peripheral blood flow. J. Pharmacol. & Exper. Therap., 80: 343-353, 1944.
54. Himmelsbach, C. K.: Comments on drug addiction. Hygiea, May, 1947.
55. Himmelsbach, C. K., Ohrbst, F. W., Brown, R. R., and Williams, E. G.: Studies of the influence of prostigmine on morphine addiction. J. Pharmacol. & Exper. Therap., 76: 50-55, 1942.
56. Himmelsbach, C. K., and Andrews, H. L.: Studies on modification of the morphine abstinence syndrome by drugs. J. Pharmacol. & Exper. Therap., 77: 17-23, 1943.
57. Isbell, H.: The effect of morphine addiction on blood, plasma, and "extra-cellular" fluid volume in man. Pub. Health Rep., 62: 1499-1512, 1947.
58. Isbell, H.: Methods and results of studying experimental human addiction to the newer synthetic analgesics. Ann. New York Acad. Sc., 51: 108-123, 1948.
59. Isbell, H.: The newer analgesic drugs; their use and abuse. Ann. Int. Med., 29: 1003-1012, 1948.
60. Isbell, H.: The addiction liability of some derivatives of meperidine. J. Pharmacol. & Exper. Therap., 97: 183-189, 1949.
61. Isbell, H.: Manifestations and treatment of addiction to narcotic drugs and barbiturates. M. Clin. North America. (In press.)
62. Isbell, H., Wikler, A., Eddy, N. B., Wilson, J. L., and Moran, C. L.: Tolerance and addiction liability of 6-dimethylamino-4-4-diphenylheptanone-3 (methadon). J. Am. M. A., 135: 888-894, 1947.
63. Isbell, H., and Eisenman, A. J.: The addiction liability of some drugs of the methadon series. J. Pharmacol. & Exper. Therap., 93: 305-312, 1948.
64. Isbell, H., Wikler, A., Eisenman, A. J., Daingerfield, M., and Frank, K.: Liability of addiction to 6-dimethylamino-4-4-diphenyl-heptanone-3 (methadon, "amidone", or "10630") in man. Arch. Int. Med., 82: 363-302, 1948.
65. Isbell, H., and Vogel, V. H.: The addiction liability of methadon (amidone, dolophine, "10630") and its use in the treatment of the morphine abstinence syndrome. Am. J. Psychiat., 105: 909-914, 1949.
66. Isbell, H.: Unpublished data.
67. Kells, P.: Pyribenzamine as an adjunct in the control of morphine withdrawal syndrome. South. M. J., 41: 134-139, 1948.
68. Kirchhof, A. C., and David, N. A.: Clinical trial of a new synthetic heptanone analgesic (Dolophine). I. Preliminary report. West. J. Surg., 55: 183-186, 1947.
69. Kirchhof, A. C., and David, N. A.: Clinical experience with methadon (Dolophine). Anesthesiology, 9: 585-593, 1948.
70. Kolb, L.: Pleasure and deterioration from narcotic addiction. Ment. Hyg., 9: 699-724, 1925.

71. KOLB, L.: Clinical contributions to drug addiction. The struggle for cure and the conscious reasons for relapse. J. Nerv. & Ment. Dis., 66: 29-43, 1927.
72. KOLB, L.: Drug addiction: A study of some medical cases. Arch. Neurol. & Psychiat., 20: 171-183, 1928.
73. KOLB, L.: The treatment of opiate addiction with special reference to withdrawal therapy. Hospital News, 3: 26-34, 1936.
74. KOLB, L.: The United States Public Health Service Hospitals. Am. J. Juris., 2: 100-108, 1939.
75. KOLB, L.: The narcotic addict: his treatment. Federal Probation, 3: 19-23, 1939.
76. KOLB, L.: Drug addiction as a public health problem. Scient. Monthly, 49: 391-400, 1939.
77. KOLB, L., AND HEIMBURGER, C. K.: Clinical studies of drug addiction. III. A critical review of the withdrawal treatments with method for evaluating abstinence symptoms. Am. J. Psychiat., 94: 759-799, 1938.
78. KOLB, L., AND OSBENPORT, W. F.: The treatment of drug addicts at the Lexington Hospital. South. M. J. 31: 914-922, 1938.
79. KRUSE, P. DE.: God's own medicine. Reader's Digest, pp. 15-18, (June) 1946.
80. LINDESMITH, A. R.: Opiate Addiction. Principia Press, Bloomington, Ind., 1947.
81. MASON, T. H., AND HAMBY, W. B.: Relief of morphine addiction by prefrontal lobotomy. J. Am. M. A., 136: 1039-1040, 1948.
82. NOTH, P. H., HECHT, H. H., AND YONKMAN, F. F.: Demerol: A new synthetic analgesic, spasmolytic, and sedative agent: Clinical observations. Ann. Int. Med., 21: 17-34, 1944.
83. PARTINGTON, J. E.: The comparative mental efficiency of a drug addict group. J. Appl. Psychol., 24: 48-57, 1940.
84. PESCOR, M. J.: The Kolb classification of drug addicts. Pub. Health Rep. Supp., 155: 1-10, 1939.
85. PESCOR, M. J.: Prognosis in drug addiction. Am. J. Psychiat., 97: 1419-1431, 1941.
86. PESCOR, M. J.: Physician drug addicts. Dis. Nerv. System, 3: 2-3, 1942.
87. PESCOR, M. J.: A statistical analysis of the clinical records of hospitalized drug addicts. Pub. Health Rep. Supp., 163: 1-30, 1943.
88. PESCOR, M. J.: Follow-up study of treated narcotic drug addicts. Pub. Health Rep. Supp., 170: 1-17, 1943.
89. PFEIFFER, A. Z.: Psychosis during withdrawal of morphine. Arch. Neurol. & Psychiat., 58: 231-236, 1947.
90. PFEIFFER, A. Z., AND RUBLE, D. C.: Chronic psychoses and addiction to morphine. Arch. Neurol. & Psychiat. 56: 665-672, 1946.
91. PHATAK, N. M., MALONEY, J., AND DAVID, N.: Use of hyperglycemic response for estimating addiction potentials of analgesic compounds. Federation Proc., 7: 240, 1948.
92. PIERCE, I. H., AND PLANT, O. H.: Studies in chronic morphine poisoning in dogs. II. Changes in blood cells and hemoglobin during addiction and withdrawal. J. Pharmacol. & Exper. Therap., 33: 350-370, 1928.
93. POLONIO, P.: Pethidine addiction. Lancet, 1: 899-894, 1947.
94. POPPEN, J. L.: Prefrontal lobotomy for intractable pain. Lahey Clin. Bull., 4: 205-207, 1946.
95. RADO, S.: The psychoanalysis of pharmacothymia (drug addiction). Psychoanalyt. Quart., 2: 1-23, 1933.
96. REINHARD, J. D.: The narcotic addict before the court. Federal Probation, 3/4: 21-25, 1939.
97. REINHARD, J. D.: The role of the probation officer in the treatment of drug addiction. Federal Probation, 6/3: 15-21, 1942.
98. REINHARD, J. D.: Narcotic drug addiction; a symptom of human maladjustment. Dis. Nerv. System, 4: 275-281, 1943.
99. REINHARD, J. D.: Addiction: some theoretical considerations as to its nature, cause, prevention, and treatment. Am. J. Psychiat., 103: 721-730, 1947.
100. ROJAS, NERIO, AND BELBEY, J.: Toxic habituation and dolantin. Semana med., 27: 616-618, 1941.
101. SAKEL, M.: Neue Behandlung der Morphinsucht. Deutsche med. Wchnschr., 56: 1777-1778, 1930.
102. SAKEL, M.: Theorie der Sucht. Ztschr. f. d. ges. Neurol. u. Psychiat., 139: 639-646, 1930.
103. SCARFF, J. E.: Unilateral prefrontal lobotomy for relief of intractable pain and termination of narcotic addiction. Surg., Gynec. & Obst., 89: 285-293, 1949.
104. SCHLAN, L. S., AND UENA, K.: Some effects of myanesin in psychiatric patients. J. Am. M. A., 140: 673-673, 1949.
105. SCOTT, C. C., AND CHEN, K. K.: The action of 1,1-diphenyl-1-(dimethylaminoiso propyl)-butanone-3, a potent analgesic agent. J. Pharmacol. & Exper. Therap., 87: 68-71, 1946.
106. SCOTT, C. C., CHEN, K. K., KOELLREUTT, K. G., ROBBINS, E. B., AND ISRAEL, F. W.: Further observations on the pharmacology of 'dolophine' (methadone, Lilly). J. Pharmacol. & Exper. Therap., 91: 147-156, 1947.
107. SEEVERS, M. H.: Animal experimentation in studying addiction to the new synthetics. Ann. New York Acad. Sc., 51: 98-108, 1948.
108. SIMMEL, E.: Um Problem von Zwang und Sucht. Ber. ueber d. v. aerztl. Kongr. f. Psychotherapie, 1930.
109. SMITH, M. I.: The pharmacology of drug addiction. Ann. Rev. Physiol., 4: 500-526, 1942.
110. STRAUS, E.: Zur Pathogenese des chronischen Morphinismus. Monatschr. f. Psychiat. u. Neurol., 46: 1-20, 1919.
111. SWAIN, J. M.: The central nervous system in morphinism. Am. J. Psychiat., 102: 378-384, 1945.
112. TATUM, A. L., SEEVERS, M. H., AND COLLINS, K. H.: Morphine addiction and its physiological interpretation based on experimental evidences. J. Pharmacol. & Exper. Therap., 36: 447-475, 1929.
113. TATUM, A. L., AND SEEVERS, M. H.: Theories of drug addiction. Physiol. Rev. 40: 107-121, 1931.
114. THEISEN, C. H.: Morphine addiction and withdrawal: effect of calcium therapy on symptoms and tissue hydration. J. Pharmacol. & Exper. Therap., 66: 36, 1939.
115. UENA, K.: Antagonistic effect of N-allylnormorphine upon morphine. J. Pharmacol. & Exper. Therap., 79: 27, 1943.
116. VOGEL, V. H.: Treatment of the narcotic addict by the U. S. Public Health Service. Federal Probation, 12/2: 45-50, 1948.

117. Voegtl., V. H., Isbell, H., and Chapman, K. W.: Present status of narcotic addiction: With particular reference to medical indications and comparative addiction liability of the newer and older analgesic drugs. J. Am. M. A., 128: 1019-1026, 1945.
118. Watts, J. W., and Freeman, W.: The frontal lobes. Proc. Research Nerv. & Ment. Dis., 27: 715-723, 1948.
119. Wieder, H.: Addiction to meperidine hydrochloride. J. Am. M. A., 122: 1066-1069, 1946.
120. Wieder, H.: Objective evaluation of insulin therapy of the morphine abstinence syndrome. J. Nerv. & Ment. Dis., 110: 26-35, 1949.
121. Wikler, A.: Treatment of drug addiction. Conference on therapy, Cornell University Medical College. New York State J. Med., 44: 1-6, 1944.
122. Wikler, A.: Effects of morphine, nembutal, ether, and eserine on two neuron and multineuron reflexes in the cat. Proc. Soc. Exper. Biol. & Med., 58: 193-196, 1945.
123. Wikler, A.: Effects of a cycle of morphine addiction on conditioned responses and experimental neuroses in dogs. Federation Proc., 5: 213, 1946.
124. Wikler, A.: Reactions of chronic decorticated dogs during a cycle of addiction to methadon. Federation Proc., 7: 265, 1948.
125. Wikler, A.: Recent progress in research on the neurophysiologic basis of morphine addiction. Am. J. Psychiat., 105: 329-338, 1948.
126. Wikler, A., and Massermann, J.: Effects of morphine on learned adaptive responses and experimental neuroses. Arch. Neurol. & Psychiat., 50: 401-404, 1943.
127. Wikler, A., and Frank, K.: Hindlimb reflexes of chronic spinal dogs during cycles of addiction to morphine and methadon. J. Pharmacol. & Exper. Therap., 4: 383-400, 1948.
128. Williams, E. G.: Blood concentration in morphine addicts. J. Pharmacol. & Exper. Therap., 67: 200-208, 1939.
129. Williams, E. G.: Personal communication.
130. Williams, E. G., and Ohnell, F. W.: A cycle of morphine addiction. Part I. Biological investigations. Pub. Health Rep., 61: 1-25, 1946.
131. Wolff, P. O.: The treatment of drug addicts. A critical survey. Bull. Health Organ., League of Nations, 12: 455-625, 1945-46.
132. Woods, L. A., Wyngaarden, J. B., and Seevers, M. H.: Addiction potentialities of 1,1-diphenyl-1-(3-dimethylaminopropyl)-butanone-2 hydrochloride (Amidone) in the monkey. Proc. Soc. Exper. Biol. & Med., 66: 113-114, 1947.

PART II. BARBITURATES

133. Alexander, L.: Deaths from poisoning. Incidence in Massachusetts. J. Criminal Psychopath., 3: 109-111, 1941.
134. American Medical Association, Bureau of Legal Medicine and Legislation. Regulation of the sale of barbiturates by statute, J. Am. M. A. 114: 2029-2036, 1940.
135. Anonymous: Barbiturates leading cause of fatal accidental poisoning. Statist. Bull. Metrop. Life Insur. Co., 29: 7, 1948.
136. Ashworth, W. C.: Injurious effect of veronal and related drugs, and suggestion for more restricted use. South. M. J., 22: 813-817, 1929.
137. Ashworth, W. C.: The injurious effect of veronal and related drugs and a suggestion for their more restricted use. South. Med. & Surg., 98: 502-504, 1936.
138. Blakemore, H. W.: Sleeping Pills ("Goof Pills"). Louisville Times, March 1, 2, 3, and 4, 1940.
139. Bonhoeffer, K.: Alkohol-, Alkaloid- und andere Vergiftungspsychosen. Ztschr. f. ärztl. Fortbild., 8: 415-423, 1911.
140. Braker, M. A. B., and Finkelnburg, J. W.: Action of barbiturates on the cerebral cortex. Arch. Neurol. & Psychiat., 53: 51-56, 1945.
141. Brownstein, S. R., and Pacella, B. L.: Convulsions following abrupt withdrawal of barbiturate; clinical and electroencephalographic studies. Psychiat. J., 17: 113-122, 1943.
142. Bucher, Karl-Heinz: Phanodormsucht mit psychischen Störungen. Inaugural-Dissertation zur Erlangung der Doktorwürde der hohen medizinischen Fakultät der Friedrich Alexanders-Universität, Erlangen. K. Dörries, Erlangen, 1937.
143. Bürow, H. v.: Beobachtungen an einem Phanodormdelir, Nervenarzt., 8: 362-366, 1935.
144. Cady, L. D.: Barbiturates should be sold only on prescription. J. Missouri M. A., 36: 485-487, 1939.
145. Camp, W. J. R.: The barbiturate problem. Laboratory Digest, April, 1948.
146. Carlisle, N., and Carlisle, M.: Thrill pills can ruin you. Collier's, 123: 20, 1949.
147. Carravala, R. E.: Barbiturismo cronico experimental. La Semana Medica, 2: 304-309, 1936.
148. Carravala, R. E.: Barbiturismo cronico experimental. Rev. Assoc. Med., 59: 1623-1630, 1936.
149. Curran, F. J.: The symptoms and treatment of barbiturate intoxication and psychosis. Am. J. Psychiat., 95: 73-81, 1939.
150. Curran, F. J.: Current views on neuropsychiatric effects of barbiturates and bromides. J. Nerv. & Ment. Dis., 100: 143-160, 1944.
151. Diethelm, O.: The bromide treatment for epilepsy in the dispensary. Arch. Neurol. & Psychiat., 21: 664-676, 1929.
152. Dörries, H., and Langelüddeke, A.: Weitere Beobachtungen über Phanodormpsychosen und Phanodormsucht. Ztschr. Neurol., 154: 668-672, 1936.
153. Duncking, H. S.: Convulsions following withdrawal of sedative medication. Internat. Clinics, 3: 264-304, 1945.
154. Federal Security Agency, U. S. Pub. Health Serv., National Office of Vital Statistics. Accident fatalities in the United States, 1946. Vital Statistics Special Reports, National Summaries, 29: 238, 1949.

185. Fincher, R. P.: A review of the present status of barbiturate regulation. J. Am. Pharm. A., Scientific Ed., 35: 198–204, 1946.
186. Gillespie, R. D.: On the alleged dangers of the barbiturates. Lancet, 1: 337–345, 1934.
187. Goldstein, S. W.: Barbiturates: A blessing and a menace. J. Am. Pharm. A., Scientific Ed., 36: 9–13, 1947.
188. Goldstein, S. W.: Barbiturates—Are they narcotics? J. Am. Pharm. A., Scientific Ed., 36: 97–100, 1947.
189. Gruber, C. M., and Ketter, G. F.: A study of the development of tolerance and cross tolerance to barbiturates in experimental animals. J. Pharm. & Exper. Therap., 86: 186–196, 1946.
190. Hambourger, W. E.: A study of the promiscuous use of the barbiturates: their use in suicides. J. Am. M. A., 112: 1240–1243, 1939.
191. Hoge, S. F.: A case of prolonged use of a barbiturate. Am. Med., 40: 235–238, 1934.
192. Isbell, H., Altschul, S., Kornetsky, C. H., Eisenman, A. J., Flanary, H. G., and Fraser, H. F.: Chronic barbiturate intoxication: An experimental study. Arch. Neurol. & Psychiat. (In press.)
193. Kalinowsky, L. B.: Convulsions in nonepileptic patients on withdrawal of barbiturates, alcohol and other drugs. Arch. Neurol. & Psychiat., 48: 946, 1942.
194. Kornetsky, C. H.: Psychological effects of chronic barbiturate addiction. (In preparation.)
195. Laignel-Lavastine, and d'Heucqueville, G.: Barbiturisme chronique d'asile, barbiturisme aigu d'hôpital et toxicomanie barbiturique, La Clinique, 33: 3–5, 1938.
196. Lowy, O.: A comparative study of the habitual use of barbiturates and coal-tar derivatives as furnished by reports from various hospitals throughout the United States. Canad. M. A. J., 31: 638–641, 1934.
197. Meerloo, A. M.: Slaapmiddelbezicht en slaapmiddelvergiftiging. Nederl. tijdschr. v. geneesk., 81: 669–672, 1937.
198. Meyer, H. J.: Über chronisches Schlafmittelmissbrauch und Phanodormpsychosen. Psychiat-Neurol. Wchnschr., 4: 273–281, 1939.
199. Morasch, F. P.: The abuse of sedative drugs in the practice of medicine. M. Clin. of North America, pp. 879–893 (July) 1946.
200. Mork, W.: The influence of age and sex on the repeated administration of sodium pentobarbital to albino rats. J. Pharmacol. & Exper. Therap., 59: 66–85, 1937.
201. Moore, M., and Gray, M. G.: Drugs as a factor in the production of mental diseases. J. Criminal Psychopath., 2: 371–396, 1941.
202. Mott, F. W., Woodrough, D. L., and Pekkworth, F. A.: The pathological effects of hypnotic drugs upon the central nervous system of animals. British J. Exper. Path., 7: 236–246, 1926.
203. Muralt, L. v.: Ein Fall von akuter Psychose bei chronischer Trional-Veronal-Vergiftung. Ztschr. f. d. ges. Neurol. u. Psychiat., 22: 122–123, 1914.
204. Mourgue-Fourmier, J. C., Aubry, E. G., and Arrighetti, G.: Syndrome parkinsonien et troubles mentaux dans un d'intoxication chronique par le véronal. Disparition complète des symptomes nerveux et mentaux par la suppression de l'hypnotique. Bull. Mem. de la Soc. Med. des Hopitaux de Paris, 47: 1748–1753, 1931.
205. McNally, W. D.: The use and abuse of barbiturates. J. Michigan State M. Soc., 41: 635–643, 1942.
206. Newman, H. W.: Variability in tolerance to depressant drugs. Stanford M. Bull., 5: 12–14, 1947.
207. Osgood, C. W.: Convulsive seizures following barbiturate withdrawal. J. Am. M. A., 133: 104–106, 1947.
208. Palmer, H. D.: Six years experience with narcosis therapy in psychiatry. Am. J. Psychiat., 94: 37–57, 1937.
209. Poehlisch, K.: Über psychische Reaktionsformen bei Arzneimittelvergiftungen. Monatschr. f. Psychiat. u. Neurol., 69: 209–267, 1928.
210. Poehlisch, K., and Faber, F.: Schlafmittelmissbrauch. Georg Thieme, Leipzig, 1934.
211. Polanyi, P.: Prolonged sedation with sodium barbital. Psychiat. J., 11: 213–222, 1937.
212. Pruitt, R. S.: Medicolegal aspects of the sale and use of barbiturates. J. Missouri M. Assn., 44: 419–423, 1947.
213. Ramsey, H., and Haag, H. B.: The synergism between the barbiturates and ethyl alcohol. J. Pharmacol. & Exper. Therap., 80: 312–322, 1940.
214. Raffel, W. v.: Beobachtungen bei plötzlichem Luminalentzug. Psychiat-Neurol. Wchnschr., 41: 484–485, 1940.
215. Ravine, W.: Chronic barbital poisoning. J. Med., 15: 269, 1934.
216. Robinson, G. W.: Addiction to barbituric acid derivatives. J. Missouri M. A., 34: 374–378, 1937.
217. Robinson, G. W.: Observations on addiction to barbituric acid derivatives. J. Missouri M. A., 36: 490–493, 1939.
218. Sands, I. J.: Barbital (veronal) intoxication. J. Am. M. A., 81: 1519–1521, 1923.
219. Sargant, W., Halstead, H., Slater, P., and Glen, M.: Effects of alcohol and sodium amytal on intelligence-test score. Lancet, 1: 617–618, 1945.
220. Schmidt, G.: Erscheinungen bei Luminalentzug. Münch. Med. Wchnschr., 85: 1944–1946, 1938.
221. Schneider, K.: Ein Veronaldelirium. Gerichtl. Med., 72: 87–99, 1915.
222. Schubert, H.: Zur Frage des Schlafmittelmissbrauches. Med. Welt, (Jan. 9) 1937, pp. 47–50.
223. Schuler, T. L.: Tissue changes in chronic intoxication of barbitals. California & West. Med., 50: 256–258, 1939.
224. Schütz, F.: Mechanism of drug addiction and drug tolerance. Nature, 148: 735, 1941.
225. Schütz, F.: An effect of barbiturates on serum cholinesterase. J. Physiol. 102: 250–256, 1943.
226. Seevers, M. H., and Tatum, A. L.: Chronic experimental barbital poisoning. J. Pharmacol. & Exper. Therap., 42: 217–231, 1931.
227. Seaton, E. J.: Addiction and tolerance to barbiturates? The effects of daily administration and abrupt withdrawal of phenobarbital-sodium and pentobarbital-sodium in the albino rat. J. Pharmacol. & Exper. Therap., 97: 245–253, 1936.
228. Stone, C. W.: Some undesirable effects from the prolonged use of various barbiturates. Ohio State M. J., 32: 208–212, 1936.
229. Stone, W. J.: 1,250,000,000 doses a year. Hygiea, 20: 662–663, 1942.

201. SWANK, R. L., AND FOLEY, J. M.: Respiratory, electroencephalographic, and blood gas changes in progressive barbiturate narcosis in dogs. J. Pharmacol. & Exper. Therap., 91: 331-366, 1948.
202. SWANK, R. L., AND WATSON, C. W.: Effects of barbiturates and ether on spontaneous electrical activity of dog brain. J. Neurophysiol., 12: 137-160, 1949.
203. SWANK, R. L.: Synchronization of spontaneous electrical activity of cerebrum by barbiturate narcosis. J. Neurophysiol., 12: 161-173, 1949.
204. SWANSON, E. E., WEAVER, M. W., AND CHEN, K. K.: Repeated administration of amytal. Am. J. M. Sc., 193: 246-251, 1937.
205. TATUM, A. L.: The present status of the barbiturate problem. Physiol. Rev., 19: 473-495, 1939.
206. TATUM, A. L.: The pharmacology of the barbiturates. Ann. Rev. Physiol., 2: 339-370, 1940.
207. TILLOTSON, K. J.: The abuse of drugs in certain psychopathic states—with reports of a few cases. New England J. Med., 209: 990-993, 1939.
208. TRICHTER, J.: Control over the distribution of barbiturates and their public health importance. J. Quart. Bull. A. Food and Drug Officials, 9: 127-140, 1945.
209. WAGNER, C. P.: Barbiturate addiction. A report of the study made by the Society's committee on drug addiction. Connecticut M. J., 6: 124-125, 1942.
210. WEISS, S.: The clinical use and dangers of hypnotics. J. Am. M. A., 107: 2104-2109, 1936.
211. WERKLE, W.: Waco was a barbiturate hot-spot. Hygeia, 23: 432-433, 1945.
212. WIKLER, A., AND ALTSCHUL, S.: Drug Addiction. Handbook on Neurology, 1st Ed., Edited by A. B. Baker. (In press.)
213. WILCOX, W.: British Med. Assn. Meeting, Sec. of Psychiatry, and Sec. of Therapeutics and Pharmacology. Discussion on the uses and dangers of hypnotic drugs other than alkaloids. Proc. Roy. Soc. Med., 27: 689-698, 1934.
214. WORK, P.: Barbital (veronal) addiction. Arch. Neurol. & Psychiat., 19: 294-298, 1928.