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Barbiturate addiction

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INTRODUCTION

The use of hypnotics is relatively recent in the history of medical therapeutics. According to Sollmann (1), bromides have been used as hypnotics since 1864. This was followed by chloral hydrate, which was introduced by Leibrich in 1869; paraldehyde by Cervello in 1882; and sulfonal by Bauman and Kast in 1888. Finally barbital (diethyl barbituric acid), the first of the barbituric acid series, was introduced as "veronal" by Fisher and von Mering in 1903. Krantz (2) states that veronal was the sole barbiturate used to any extent in America until "luminal" (phenobarbital) made its appearance shortly before World War I. Since that time approximately 60 derivatives have been used in therapeutics, and approximately 17 have maintained a high degree of popularity.

It is interesting to note the tremendous increase in the production of these barbituric acid derivatives during the past few years. The following table presents in pound equivalents the amounts, as given by various authors, of barbiturates produced in the United States.

TABLE 1

Recent production of barbiturates
in the United States

Year	Am't. in lb.	Source
1933	168,000	Isbell (3)
1936	213,000	Hambourger (4)
1939	426,000	McNally (5)
1945	550,000	Gramblett (6)
1948	672,000	Isbell (7)
1950	688,000	Fazekas (8)

From this data it can be seen that the production in 1950 represents an increase of 410 per cent over that in 1933. Stated in other terms, 672,000 lb. is roughly equivalent to 3,057,730,000 capsules or tablets of 0.1 gm. (1½ gr.) each, or approximately 24 doses for each person in the United States (Isbell, 7).

Statistics show that this amount is far out of proportion to the amount needed for therapeutic purposes (9). Isbell (7) states that acute barbiturate intoxication accounts for the greatest proportion of cases of acute poisoning admitted to general hospitals; that more deaths are causes by barbiturates

than any other poison; and that barbiturates are now the most popular agents in suicidal attempts. According to Fazekas (8), one in each two thousand hospital admissions in 1950 was for barbiturate intoxication.

Similar information relative to the incidence of chronic barbiturate intoxication is difficult to obtain from the literature. One author, Hambourger (10), reviewed the combined admissions of thirteen hospitals from 1928 to 1937 and reported an incidence of one in 15,000 admissions. Isbell (3) states: "The relative neglect of chronic barbiturate intoxication in the medical literature has probably been due to the erroneous impression, which has been widely held in both the U. S. and England, that abstinence symptoms did not follow abrupt withdrawal of barbiturates from chronically intoxicated persons. These drugs were, therefore, not believed to be addicting". In view of these statements it seems doubtful that Hambourger's figure represented the actual incidence.

Isbell (3) offers the following facts as evidence that chronic intoxication with barbiturates is increasing: the increase in number of barbiturate addicts among the morphine addicts admitted to Lexington Hospital; the increased requests on management of this

condition; the increasing number of tips investigated by the Bureau of Narcotics which turn out to be barbiturate addictions; and the increasing number of prescriptions, being found by the Federal and State Food and Drug Administrations, which have been refilled hundreds of times. Saunders (11) states: "There is no mistake that barbiturate addiction is fast becoming one of our country's greatest problems. It is growing by leaps and bounds, and no doubt is now more difficult to deal with than addiction to any other drug, narcotics included".

THE CONTROVERSY CONCERNING ADDICTION AS APPLIED TO BARBITURATES

The definition of addiction varies with different authors. Pharmacologists stress in their definition the appearance of a characteristic illness following withdrawal; psychiatrists stress the psychodynamics which underlie the addiction; and social workers stress the relationship to society and crime. A comprehensive definition of drug addiction must take into account all these various points of view. Isbell (12) defines addiction as, "a condition of chronic intoxication, which is usually based on a personality disorder and which causes serious harm to the individual, society, or to both". Vogel (13) adds that drug addiction embraces tolerance, physical dependence and habituation, and defines these terms as follows: "Tolerance is a diminishing effect on repetition of the same dose of the drug, or conversely, a necessity to increase the dose to obtain an effect equivalent to the original dose when the drug is administered repeatedly over a long period of time. Physical dependence refers to an altered physiological state, brought about by the repeated administration of the drug over a long period of time, which necessitates continued use of the drug to

prevent the appearance of the characteristic illness which is termed as abstinence syndrome. Habituation refers to emotional or psychologic dependence on the drug--the substitution of the drug for other types of behavior. Habituation is closely related to a drug's euphoric effect i. e., relief of pain or emotional discomfort".

Much controversial material is present in the literature relative to whether or not the barbiturates fulfill all these criteria of addiction. According to Young (14), cases of both acute veronal poisoning and "habit" were reported as early as 1904 by Laudenheimer; however, no additional information which would qualify these cases of "habit" as addiction was given. In 1927 Pickworth et al. (14), stated that from their own studies and from a review of the literature, they had no doubt that the continued use of the barbiturates led to the formation of a definite addiction. It is evident, however, that they did not subscribe to the pharmacological definition of addiction in view of further stating that tolerance was not established by long continued dosage, and that sudden discontinuence of the drug was not followed by withdrawal symptoms. Hambourger (10), in reviewing the reports of 85 patients admitted for

barbiturate addiction to 13 hospitals during the period from 1928 to 1937, found that only one was reported to have had withdrawal symptoms. He concluded that this was in agreement with the generally accepted opinionthat barbiturates did not produce withdrawal symptoms in the sense that such symptoms occurred in opiate addicts. In 1934 Gillespie (15) presented the following as evidence against the likelihood of addiction to barbiturates: "In most instances the barbiturates produce nothing resembling euphoria of alcohol or morphine, and withdrawal of the barbiturates is not accompanied by the distressing subjective results and the objective manifestations that accompany withdrawal of alcohol or morphine". Weiss (16), in 1936, also stated that hypnotics did not lead to addiction, and believed that the nervous manifestations in chronic intoxication were a result of accumulation of the drug and the toxic effect on the structure of the nerve cells. Tatum (17), in 1939, insisted that repeated and continued use of bar- induced a condition of habituation or psychic dependence, but not a true addiction as exemplified by the use of morphine. He points out that mental disturbances occur during the period of drug taking, and adds that they are obviously due to the positive action

of the drugs rather than to the cessation of drug taking or abstinence phenomena. Archdall (18), 1940, also felt that the condition arising after the prolonged use of barbiturates was an habituation and not a true addiction. This opinion was also expressed by Curran (19) in 1944, Goldstein (20) in 1947, Hammes (21) in 1948, and Keller (22) in 1948. Many textbooks in medicine and pharmacology also share this view: Krantz and Carr (2) state that there is a limited tolerance developed in man but no physical dependence or syndrome of withdrawal occurs. Cecil (23) states: "The discontinuance of the use of barbiturates does not result in physiologic manifestations of addiction". Neither Goodman and Gilman (24), nor Harrison (25), mentions anything concerning convulsions or other symptoms of withdrawal.

Prior to 1948, those writers (more especially writers in the U.S.) who presented evidence of barbiturate addiction to the full extent of it's definition, were in the minority. As early as 1914 the German writer von Muralt (26) clearly described the barbiturate withdrawal syndrome of convulsions and psychosis following withdrawal of barbiturates from chronically intoxicated persons. According to Isbell (7), a large number of such papers have appeared in the German lit-

erature. In 1928 Work (27) recognized the physical symptoms of chronic intoxication with veronal, and described a mental state of "confusion and uncertainty" in such a patient. He considered the diagnosis to be that of addiction to veronal. Ginker (28) and Fox (29), in 1927 and 1929, demonstrated conclusively that siezures in epileptic patients not only increased in number when phenobarbital was stopped, but became much more frequent than they had been prior to medication. Palmer (30,31), 1932, used large amounts of sodium amytal therapeutically in narcoanalysis, and noted symptoms of withdrawal including convulsions, at the time of terminating the narcosis. He called these symptoms "complications", and noted that they could be avoided by slow reduction in the dosage of the sedative. In 1938 Schmidt (30) described what he considered to be withdrawal symptoms in his series of 11 human cases who had been taking phenobarbital for six or more years, and considered them to fit into the category of true addicts. In 1942 Kalinowski (33) reported seven cases of non-epileptic patients who had convulsions four days after withdrawal of soluble barbital. They had been accustomed to this sedative for one to two years, and none of them had seizures prior to or after this occurrence.

He further stated that seizures occur after withdrawal of the various barbiturates, paraldehyde and other hypnotics of the aliphatic group, and that they are seen only after prolonged medication, never after acute intoxication. He felt that the increase of seizures in epileptic persons following sudden discontinuance of phenobarbital was explainable by the same mechanism. He also noted the development of a psychosis resembling delerium tremens following the withdrawal of the barbital in his seven cases.

Since Kalinowski's article in 1942, numerous papers have appeared in the literature describing similar convulsions and/or psychoses (both in the majority of instances) following the withdrawal of barbiturates in cases of chronic intoxication: Brownstein et al. (34), Osgood (35), Hewitt (36), Isbell (3, 12, 37), Fechner (38), Alexander (39), Saunders (11), and Morgan (40). Isbell (7) further substantiated these reports in his recent carefully controlled experimental work with human subjects (page 14), and concluded that chronic intoxication with barbiturates represents a true addiction--no matter how addiction is defined.

EXPERIMENTAL WORK ON THE ADDICTING PROPERTIES OF BARBITURATES

In 1926 Hoff and Kauders (41) administered sodium barbital in increasing doses to two dogs for periods of one and two months, respectively. Beginning witn a dose of 100 mgm. per kilogram of body weight, they raised the dose 100 mgm. per kilogram each week until death occurred. They observed that the animals became progressively more irritable and were ataxic and incoordinate. They were fairly normal when aroused from sleep but after twenty-four hours of abstinence were wild and attempted to bite. Both animals exhibited clonic convulsions during the latter part of the experiment and one animal, on tne day before death, had an almost continuous clonic shaking of the extremities exaggerated by sensory stimuli. In 1931 Seevers and Tatum (42) conducted a similar experiment. They gave each of six dogs 100 mgm. per kilogram of sodium barbital, through a total period of three and one half years. They also noted that within a period of two to six months characteristic physical signs appeared, and that they were best seen twenty four hours following the last dose of the drug. They state: "Muscle tremors, incoordinate gait, and a type of intention tremor seen when the

animal atempts to take food, are the predominant signs. These signs disappear after the daily dose is given. If the dog is allowed to go 48 hours without any barbital, nervous irritability increases, the tremors become more severe, motor unrest with continuous ataxic movement is seen, and convulsions are seen frequently". They concluded that sodium barbital causes physiological dependence.

Other authors have reached an opposite conclusion. Stanton (43), in 1936, tested rats for abstinence irritability, with doses of phenobarbital and pentobarbital up to 30 per cent minimum lethal dose daily for seven weeks. His largest dose of sodium pentothal was 36 mgm. per kilogram of body weight. He failed to find an increase in abstinence irritability, and therefore concluded that these drugs do not have an addicting liability. Swanson (44), in 1937, did a similar experiment with dogs and monkeys. He gave 40 mgm. per kilogram of body weight of sodium amytal three times a week, for three to six months. Swanson's animals showed no abnormal symptoms when the drug was discontinued, and he, therefore, also concluded that sodium amytal did not have addicting properties.

A possible explanation of the above differences

becomes apparent when the factors related to the severity of the withdrawal effects are considered. According to Alexander (39), these factors are: the size of the dose, the time interval between doses, and the duration of administration of the drug. Swanson gave the drug three times a week, and observed no objective signs of withdrawal effect; Seevers and Tatum gave 50 per cent more, and gave it daily, and observed signs in two to six months. Stanton gave doses roughly equivalent to those of Seevers and Tatum, and also gave the drug daily, but discontinued administration at the end of seven weeks. These facts appear to be in agreement with the clinical observation of Isbell (37); that for signs and symptoms of abstinence to occur, a minimum dosage of 0.8 gm. must be taken daily over a minimum period of two months.

Several investigators have demonstrated experimentally that tolerance to the barbiturates does occur. Masuda et al.(45) administered anesthetic doses of various barbiturates daily to rabbits and observed that the sleeping time showed a distinct decrease in the case of phenobarbital, pernoston and amytal both in the individual animals and in the average. These authors concluded that the rabbits had acquired tolerance to these

drugs. The acquired tolerance was of short duration, about three days for pentobarbital and four to five days for pernoston and amytal. Carmichael et al. (46) also noted a decrease in the hypnotic effect of nembutal within four weeks of repeated administration to guinea pigs. Seevers and Tatum (42) also noted that a certain degree of tolerance was established in their dogs, as evidenced by the shortening of sleeping time, but concluded that it was in no way comparable to that occuring with morphine. Brodie et al. (47) noted that after a large dose of thiopental, human subjects awoke at plasma levels that were considerably higher than those occurring after smaller doses. He concluded that tolerance was probably a tissue adaptation to the effects of the drug. He found that this tolerance was not persistent in that it was no longer evident after one week.

In 1950 Isbell et al. (7) reported the results of their experimental investigation concerning chronic barbiturate intoxication on five human subjects. Isbell felt that many of the papers on chronic barbiturate intoxication and on the effects of their withdrawal, were unsatisfactory because many were cases of mixed addiction (morphine and alcohol), and that it was therefore impossible to tell which symptoms were

due to the withdrawal of barbiturates and which were not. Moreover, he felt that the physical and mental conditions of the patients before their addiction were not known and it was difficult to determine whether the development of convulsions and psychoses was dependent on an underlying psychotic or epileptic diathesis. In order to obtain clear-cut information, he carried out an experimental investigation on five men who had been morphine addicts. These men were volunteers who were serving sentences for violation of the Narcotic Act. None had significant physical defects and all had normal electroencephalograms. The subjects received five doses each day of either secobarbital, pentobarbital, or amobarbital sufficiently large to induce continuous mild to severe intoxication for periods varying from 92 to 144 days. The initial dose of 0.4 gm. per day was gradually increased so that at the end of three weeks they were being given approximately 1.3 gm. each per day. This dosage was maintained 30 to 50 days, following which a small increase to 1.6-1.8 gm. was made, and this dosage was maintained to the end of the experiment. The symptoms of chronic intoxication included impairment of mental ability, confusion, regression, increased emotional instability, nystagmus,

dysarthria, ataxia and depression of the superficial abdominal reflexes. The clinical manifestations were similar to those of chronic alcoholism. The effect of a certain dose varied significantly in the same person from day to day, and this variation was partly related to changes in food intake. Withdrawal symptoms occurred in all instances. During the first 12 to 16 hours after the last dose of barbiturate had been given the condition of all five patients appeared to improve; confusion became less and neurological manifestations almost disappeared. After this they began to complain of vague anxiety and of increasing weakness. They slept poorly, ate little and had a coarse tremor of the face and hands. Within 24 to 36 hours after the last dose of the drug had been given, anxiety became severe and weakness was so great that the patients could hardly stand or walk. They felt faint and preferred to remain in bed. The tremor increased, and in four instances fasciculation of isolated muscle groups was seen. Four of the subjects vomited. The patients were mentally clear and well orientated and showed no evidence of hallucinations at this time. Four of the patients had convulsions of the grand mal type, lasting about three minutes, at various times within 30

to 115 hours following withdrawal. Four of the patients developed a psychosis which began four to five days following withdrawal, and which was from three to ten days in duration. These withdrawal psychoses resembled alcoholic delirium tremens and were characterized by anxiety, agitation, insomnia, confusion, disorientation, delusions, and auditory and visual hallucinations. These investigators also demonstrated that some tolerance had developed during the period of chronic intoxication by abruptly returning the patients, within 60 to 90 days following withdrawal, to the same dose of barbiturates they had been receiving at the end of the experiment. These patients became markedly more intoxicated than they had at any time during the period of chronic administration in which they had attained this same dosage level gradually.

THE QUESTION OF IRREVERSIBLE CENTRAL NERVOUS SYSTEM DAMAGE IN CHRONIC BARBITURATE INTOXICATION

Not all investigators are in agreement as to whether or not irreversible central nervous system damage occurs in chronic barbiturate intoxication.

Mott, Woodhouse and Pickworth (45) in 1926, poisoned cats and monkeys with doses of 150 to 600 mgm. of various barbiturates daily for periods of one to six weeks. The animals were then killed and examined histologically using various staining techniques. They found numerous masses of peculiar mucinoid material, 5 to 60 micra in diameter, distributed throughout the central nervous system. They also observed chromatolysis, loss of Nissl substance and signs of cell degeneration in the nerve cells of the cerebellum, midbrain and spinal cord. This cell degeneration was accompanied by the appearance of numbers of phagocytic cells which appeared to digest the nerve cells. Polson (46) found these mucinoid deposits in normal rabbits which had not received barbiturates, with the same frequency, and therefore questioned the significance of Mott's findings.

Hoff and Kauders (41, page 11) also observed the macroscopic and microscopic central nervous system changes in their experiment with dogs. Macroscopically,

they found that the brains showed dilated blood vessels and perivascular blood. Microscopically, venous congestion was seen throughout, and there were elective areas of injury to ganglion cells, namely, those of the inferior olivary nuclei, the cells around the aqueduct of Sylvius, the infundibular region and the oculomotor nuclei. The cells in these areas showed destruction of Nissl bodies, vacuole formation, and tigrolysis. The protoplasm of the ganglion cells was shrunken, atrophic and basophilic. In a few areas there was swelling of the ganglion cells with obliteration of their structure. Seevers and Tatum (42, page 11) described similar findings in their series. In 1934, Vanderhorst (47) injected a series of cats with barbituric acid compounds. The brains of these animals showed degenerative changes in the ganglion cells also, and no mucinoid material was seen. In 1951 Jervis and Joyce (48) described a case which terminated fatally following prolonged use of large quantities of an opiate and barbiturate together. At autopsy definite pathological changes were found in the brain and spinal cord. They state: "Bilateral necrosis of the basal ganglia was found. In addition, small necrotic foci were present throughout the cerebral hemispheres and the cerebellum. These

changes are considered to result from anoxia which is brought about through damage of the blood vessels and by direct action on the nervous parenchyma". Hassin (49), and DeGrout (50) have described similar pathological changes in patients who have succumbed to overdosage with phenobarbital or barbital. It is interesting to note the similarity in the pathology described in these cases of acute intoxication, to that described in the above cases of chronic intoxication in experimental animals.

Krop et al. (51), in 1946, administered approximately one-half the lethal dose of seconal, pentobarbital, the barbital of sigmodal, and phenobarbital to cats and dogs. No evidence of central nervous system damage was found in any of the dogs. Similarly, no evidence of nerve tissue damage was found in those cats which received compounds free of the bromallyl group, namely, seconal, pentobarbital and phenobarbital. Of the 102 cats which received barbital of sigmodal (amyl-beta-bromallyl barbituric acid), 8 per cent were found to have demonstrable histological damage to the central nervous system.

Although no histological studies were possible on the subjects of Isbell's experiment, they showed

complete recovery with no clinical evidence of central nervous system damage following the completion of the experiment. During the course of the experiment these patients were maintained on the highest dosage of barbiturate which each respective subject would tolerate. This dosage ranged from 1.3 to 1.8 gm. per day, which is equivalent to approximately 18 to 25 mgm. per kilogram of body weight. This is slightly higher than the dosage maintained by the average barbiturate addict, which, according to Isbell (37), is approximately 1.25 gm. per day. It is noted that in those cases cited above which demonstrated central nervous system damage, the daily dose of the barbiturate used far exceeded (400 to 700 per cent in the cases involving experimental animals) that of Isbell's subjects. The similarity between the pathology described in these animals and that described in the cases of overwhelming intoxication in humans is also noted.

In view of these facts, it seems logical to conclude that some irreversible central nervous system damage may occur in some humans receiving overwhelming dosages of barbiturates, and in most experimental animals receiving correspondingly high dosages; but that in all probability, the dosage level of chronic intoxication

as seen in the barbiturate addict produces no such irreversible central nervous system damage.

ETIOLOGY

Most recent authors agree that the persons likely to become addicted to barbiturates are those with psychoneuroses or character disorders. Isbell (12) emphasizes that addiction to any drug represents not a disease, but a symptom of a psychiactric disorder. He believes: that the psychiactric conditions which are responsible for most types of drug addiction are psychoneuroses of various types, particularly neuroses associated with anxiety and tension and the so-called character disorders (psychopathic personalities); that conflicts centering around excessive dependence are very common in these individuals; and that major psychoses apparently play no role in the genesis of drug addiction.

Saunders (11) feels that people with character disorders are most frequently introduced to the barbiturates by associates for the purpose of intoxication. Isbell (3, 7, 12) insists that the psychoneurotic patients most frequently become addicted to barbiturates as a result of careless therapeutic usage of these drugs by physicians. Hambourger (10, page 6) found in his review that approximately two-thirds of the barbiturate addicts claimed that they became familiar with

the drug through physician's therapeutic administration. According to Isbell (3), these psychoneurotic patients characteristically maintain their dosage at low levels for considerable periods of time; but when they do begin to elevate the dose, they increase it rapidly, and "the drug is changed from a means of inducing sleep to a means of producing intoxication".

In many cases the chronic use of barbiturates is begun in relation to other addictions. The inability to obtain narcotics frequently causes the individual to switch to barbiturates until narcotics can be obtained. According to Saunders (11), these individuals usually continue to take both drugs. Isbell (12) states that alcoholics are likely to begin the use of barbiturates to relieve their nervousness following on a long debauch. They find that the effects are similar to those of alcohol and continue to use the drugs in order to induce intoxication and not to relieve nervousness or insomnia. Still others use barbiturates concomitantly with alcohol purposly. This produces a profound intoxication and narcosis. Mass (52) points out the danger in this practice in that death may result even though non toxic quantities of each drug are ingested. This is explained on the basis of the

synergistic effect between alcohol and the barbiturates. Pharmacological studies have shown that the lethal dose of any barbiturate is greatly reduced in the presence of alcohol levels sufficient to produce intoxication. Ramsey and Haag (53) have shown that the L.D.50 of seconal could be lowered from 140 mgm. per kilogram to 105 mgm. per kilogram in mice when the drug was administered concomitantly with alcohol. They also observed that the lethal dose of sodium pentothal was reduced by 40.9 per cent in mice which had been given three cc. per kilogram of ethyl alcohol, prior to the sodium pentothal, over those mice which received no alcohol. They further observed that in dogs picrotoxin was less efficient as an antidote to the depression produced by the combination of sodium pentobarbital and alcohol, than it was against the action of pentobarbital alone. This led them to conclude that a potentiative, rather than a simple additive, type of synergism exists between the barbiturates and alcohol. Smith et al. (54) and Grabill et al. (55), in working with intravenous alcohol and pentothal, have expressed similar conclusions. In 1951, Sandberg (56) conducted a similar experiment with mice, but used other short acting barbiturates instead of pentothal. He also concluded that a

potentiative, not a simple additive, type of synergism exists between the effect of alcohol and the short acting barbiturates; and that the degree of potentiation varies with the dose and derivative.

SIGNS AND SYMPTOMS

According to Isbell (12), the symptoms and signs of chronic barbiturate intoxication are predominantly those of cortical depression and of cerebellar dysfunction.

Cortical depression is manifested by difficulty in thinking, inability to perform simple calculations and psychometric tests, confusion, somnolence and defective judgement. Kornetsky (57) measured the psychological changes in the subjects of Isbell's experiment during the period of chronic intoxication, and found the greatest impairment in performance of tasks involving speed, and some impairment in tasks involving copying.

The signs of cerebellar dysfunction often suggest organic disease of the nervous system such as multiple sclerosis, Parkinsonism, cerebellar brain tumor, et cetera. These signs include nystagmus, ataxia in gait and station, adiadokokinesis, choreiform movements, dysarthria, and tremors. The superficial reflexes may be absent but the deep reflexes, the corneal reflex and the pupillary reflex are seldom altered unless a severe acute intoxication is superimposed upon the chronic intoxication already present. The pulse, blood pressure

and respiratory rate are not significantly changed. Body temperature may be slightly depressed.

Chronic barbiturate intoxication also causes marked social and emotional deterioration. According to Saunders (11), the neglect of their personal appearance may be one of the early signs in these individuals. They are unable to work or care for themselves adequately. Isbell (3) has observed that their behavior resembles that of chronic alcoholics and that it appears to be influenced to some degree by their basic personality makeup and by the mood prevailing on any given day. He also noted that loss of emotional control frequently occurs and that they are likely to fight over minor matters. Others become infantile, and still others may develop paranoid ideas. Tendencies to depression are accentuated. Hallucinations and delusions are uncommon as long as the addict is continuing to take the drug.

THE WITHDRAWAL SYNDROME

Symptoms of abstinence may occur if the dosage being taken by the addict is suddenly reduced from twenty to fifty per cent or more in persons who have been using 0.8 gm. or more of any barbiturate daily for as long as two months. Symptoms may or may not occur in persons who have been ingesting 0.3 to 0.7 gm. of barbiturates daily, and they seldom occur in those who have been ingesting less than 0.3 gm. per day.(Isbell, 37). Most authorities agree that abstinence from barbiturates is more dangerous to life than is abstinence from morphine.

Saunders (11) and Isbell (7) have found that in the first 12 to 16 hours following withdrawal intoxication declines, confusion improves, and the neurological signs diminish. Following this period, weakness, anxiety, nervousness, nausea and vomiting make their appearance. The weakness becomes severe and they develop difficulty in making cardiovascular adjustment on assuming upright posture. Isbell (7) observed in the subjects of his experiment, that on standing their pulse rates rose fourty to eighty beats per minute; their systolic blood pressure fell fifteen to fifty mm. of

Hg.; and that their diastolic blood pressure increased. With this decreased pulse pressure the patients become pale, begin to perspire and may be unable to stand for more than two or three minutes.

From 12 to 30 hours after the last dose of barbiturate is taken, tremor and twitching of the various muscle groups appear. There may be uncontrollable bouts of shaking of the extremities without loss of consciousness.

Between 16 hours and 5 days (usually at about 30 hours) these patients have one or more convulsions which are typically grand mal in type. Following these convulsions the patients regain consciousness in a few minutes. They may be slightly confused for several hours but prolonged stupor as seen following convulsions due to idiopathic epilepsy, seldom occurs. Usually no more than three or four convulsions occur, but numerous minor episodes characterized by clonic twitching without loss of consciousness, or by athetoid movements of the extremities may occur before, between or after the major convulsion. Between and following the convulsions the patients continue to exhibit weakness, slight fever, disturbed vascular adjustment to change in posture, tremor anorexia and nervousness. Unless the patient

becomes psychotic, these symptoms gradually disappear, and after two or three weeks they have usually recovered completely (Saunders, 11 and Isbell 7, 12).

Definite electroencephalographic changes occur during chronic intoxication and during withdrawal. According to Cohn (58), the electroencephalogram taken during sustained barbiturate intoxication shows fast activity, superimposed on slow waves. During withdrawal, the fast activity disappears and a normal record may follow, but if a convulsion is iminent, paroxysmal bursts of high voltage slow waves appear. The electroencephalogram of grand mal convulsions due to barbiturate withdrawal is indistinguishable from that of similar convulsions due to other causes.

According to Isbell (12), a psychosis usually appears between the third and seventh day of abstinence, irregardless of whether or not convulsions have occurred. The onset of the psychosis is usually preceeded by insomnia of twenty-four to forty-eight hours duration, after which patients begin to experience hallucinations, both visual and auditory, the former being much more prominent. The patients are confused and usually disorientated in time and place, but not in person. The emotional reaction to the psychosis appears

to be influenced by the patients basic personality; some become agitated, and others become very quiet. The psychosis is likely to appear and is frequently more severe during the night. Most patients recover from the psychosis within two weeks of its onset. Improvement generally begins with a return of the ability to sleep. The hallucinations become less vivid and finally fade.

Isbell (12) has found that the abstinence syndrome varies considerably from patient to patient. He found that some patients had convulsions but escaped the psychosis; others did not have convulsions but developed a psychosis; and a few escaped both.

TREATMENT

The treatment of barbiturate addiction may be divided into three phases: the withdrawal of the drugs, rehabilitation, and psychotherapy.

According to Isbell (37), withdrawal of the drug should always be carried out in a hospital. The patient should be under constant supervision, and should not be allowed to walk about unattended. Abrupt withdrawal of barbiturates from addicted persons is contraindicated. Even sudden reduction may result in the appearance of signs of abstinence. In withdrawing the barbiturates, Isbell (37) uses the following procure. The "stabilization dosage" is first determined for the individual patient. This is the amount of one of the short acting barbiturates which constantly maintains a mild degree of intoxication in the patient. This dosage is determined by the signs of intoxication. If the patient shows transient nystagmus on lateral gaze, light dysarthria, and swaying on the Romberg test, the degree of intoxication is sufficient to prevent the appearance of manifestations of abstinence. If nystagmus is present constantly, dysarthria is marked, and if the Romberg test cannot be performed without falling, the dosage of the barbiturate is too great and should

be reduced. Isbell (37) has found that in the average case 0.2 to 0.4 gm. of pentobarbital every six hours is the adequate amount. After the stabilization dosage has been determined, the drug should be gradually withdrawn at a rate not greater than 0.1 gm. per day. When 50 per cent, and again when 25 per cent, of the stabilization dosage is reached, the reduction should be stopped and the patient maintained at this respective level for two to three days. Reduction of the dosage should also be stopped if excessive anxiety, insomnia or tremor appears during withdrawal of the barbiturate, and the amount of the drug held constant until these symptoms disappear. If possible the patients should be followed by electroencephalography. If an epileptic pattern is observed during treatment, an extra dose of pentobarbital should be given immediately and reduction of the dosage stopped until the high voltage slow waves have disappeared. Since acute barbiturate intoxication is frequently superimposed on barbiturate addiction, it should always be ascertained following their recovery from coma, whether they have been taking the drugs chronically, and if such be the case, the above regimen should be instituted. If the diagnosis is made after the major manifestation of convulsions, 0.15 to 0.25 gm.

of sodium pentobarbital should be given intravenously at once to terminate the convulsions. Complete withdrawal of barbiturates the method which has been presented usually requires two to three weeks.

Saunders (11), in addition to the gradual withdrawal of the barbiturates, begins supportive therapy as soon as these patients are admitted. Vitamins are given intravenously at first, and later intramuscularly and orally. Fluid intake and diet receives special attention. He gives all these patients 50 micrograms of vitamin B12 intramuscularly every day for at least two weeks, and from one to two gm. of Tolserol three times a day for the same length of time.

According to Isbell (37), withdrawal of the barbiturates is only the first step in treatment, and unless this is followed by an intensive period of rehabilitation therapy, the patient will almost certainly relapse to the use of barbiturates or some other drug. The duration of adequate rehabilitative therapy varies with the individual, but should be at least four to six months. During rehabilitation they should be given the opportunity to engage in useful, productive and interesting work. Whenever possible, this work should be of the type which will maintain or add to the skills which

the patient possesses. Adequate recreation must also be provided. Any organic disease should also be treated following the withdrawal phase of the treatment. If a chronic disease is not curable, treatment should be designed to bring about the greatest possible physical improvement and teach the patient to manage his disease without resorting to the chemical crutch of barbiturates or other drugs.

It is beyond the scope of this paper to present any techniques of psychotherapy which may be involved in the treatment of these patients. According to Isbell (37), the form which this therapy will take will depend on the patient's problems and on the personality, attitude, training and orientation of the therapist. It does not differ in any way from the psychotherapy of neurotic patients who have never been addicted to drugs. Some patients, such as those who have intense infantile fixations, receive little benefit from psychotherapy. Isbell (37) feels that in these cases it is best to provide only a short period of close supervision, followed by a long period of close supervision in the patient's home enviornment. Patients who have reached a greater level of emotional maturity prior to addiction should be offered intensive psychotherapy. Isbell (37)

also believes that these patients should be encouraged to participate in the alcoholics anonymous groups, since many patients appear to derive great benefit from this organization, which also provides help and encouragement to remain abstinent after discharge from the hospital.

POSSIBLE PREVENTIVE MEASURES TO DECREASE THE INCIDENCE OF BARBITURATE ADDICTION

Most states now require pharmacists to dispense the barbiturate drugs only on a physicians prescription. The barbiturates are still too easily available to the average person however, but to apply the Harrison Act to these drugs would, according to Overholser (59), make their legitimate use extremely difficult, and is probably not desirable, at least until other methods of control have been tried and have failed.

Most authorities agree that the most important factor in the chain of control is the physician himself, and next to him the pharmacist. The physician should be alert to the dangers of barbiturate addiction, and should be especially careful to prescribe only enough for the particular use and try to avoid giving the patient an opportunity to accumulate a large number of tablets or capsules. In addition the physician should mark each prescription "not to be refilled". The pharmacist should in turn, sell only on written prescription, and if a prescription is presented for refilling, he should ascertain from the physician that there is no objection.

According to Overholser (59), the present state

of thinking on the part of federal officials appears to be that the control of traffic in barbiturates is properly a state function, and that by appropriate state legislation, plus cooperation of physicians, pharmacists, and pharmaceutics manufacturers, the use of these drugs can be limited to proper medical administration.

SUMMARY AND CONCLUSIONS

Since the introduction of the first barbiturate in 1903, the production of these drugs has steadily increased and now appears to exceed greatly the amount nedded for therapeutic purposes. Evidence of such excess is manifest by the increasing incidence of both acute and chronic barbiturate intoxication.

Many authors in the past have dealt extensively with the question of acute intoxication, but few, prior to recent years, have recognized the entity of chronic intoxication as addiction. This is apparently due to the fact that withdrawal symptoms were not recognized by the earlier writers. Since 1940 reports describing convulsions and psychoses on withdrawal of the barbiturates in chronically intoxicated individuals, have appeared with increasing frequency in the U. S. literature; and consequently the question of addiction to these drugs has received more attention.

It has been demonstrated by experimental work with both laboratory animals and human subjects, that all the essential factors of the term addiction are satisfied in chronic barbiturate intoxication. Clear-cut evidence of tolerance, habituation, and abstinence

phenomena has been demonstrated by these workers; and has confirmed the clinical observations as reported by current authorities on this subject.

Irreversible central nervous system damage has been found in some humans receiving overwhelming dosages of barbiturates, and in most experimental animals receiving correspondingly high dosages; but in view of the evidence which has been presented, it can be concluded that at the dosage level which is maintained by the average barbiturate addict, no such irreversible central nervous system damage is produced.

The most important factor which predisposes to addiction to barbiturates is the presence of a personality defect. The psychiactric conditions which are usually responsible are the psychoneuroses (especially the neuroses associated with anxiety and tension), and the psychopathic personalities. These individuals are frequently introduced to the drug via the physician's prescription. Many barbiturate addicts use the drug concomitantly with alcohol; a combination which has been demonstrated to produce a potentiative type of synergism.

The signs and symptoms of barbiturate addiction are chiefly those of cortical depression as manifested by impairment of intellectual functing, poor judgment,

confusion, depression, and melancholia; and those of cerebellar dysfunction as evidenced by nystagmus, ataxia, dysarthria, hypotonia, and decrease in superficial reflexes. Social and emotional deterioration also occur.

Following abrupt withdrawal or sudden decrease in dosage of the barbiturate being taken by the addict, definite abstinence phenomena develop. These phenomena consist of anxiety, anorexia, nausea and vomiting, convulsions of grand mal type, and a psychosis which is characterized by anxiety, agitation, insomnia, confusion, disorientation for time and place but not for person, delusions, and visual and auditory hallucinations. It has been observed that these phenomena seldom occur in persons taking less than 0.3 gm. per day; may or may not develop in those taking from 0.3 to 0.8 gm. per day; and almost always appear in those taking 0.8 gm. or more per day. The average barbiturate addict uses between 0.5 and 2 gm. per day.

In the treatment of barbiturate addiction a regimen of gradual withdrawal is essential if the appearance of withdrawal symptoms is to be avoided. This augments the importance of approaching this problem as one of addiction with withdrawal effects, rather than as one

of toxicity, since the latter would imply withholding the barbiturates -- a procedure which is definitely contraindicated. Withdrawal of the drug should begin by establishing the stabalization dosage (that amount necessary to produce mild intoxication) followed by gradual reduction of this dosage by not more than 0.1 gm. per day. Upon completion of withdrawal, adequate rehabilitation and psychotherapy should be instituted.

It is important that the practitioner recognize that addiction to the barbiturates occurs, since many potential addicts are first introduced to the drug via the physician's prescription. He will, thereby, contribute towards reducing the incidence of barbiturate addiction through more careful and judicious prescribing of these drugs.

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