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CHAPTER I

CURRENT THEORY AND TREATMENT OF ADDICTIONS

Addiction, whether to opiates or alcohol, is a severe problem. Each person who becomes an addict subtracts one effective citizen from the population and at the same time adds a moral or criminal problem to the community.

The severity of the problem of alcoholism is shown by the fact that it is America's fourth ranking disease. Only cancer, tuberculosis, and heart disease present greater problems (23, p. 102). More specifically, of the 60 to 65 million Americans who drink, at least 4 million may be classified as alcoholics (26, p. 434).

Opiate addiction claims fewer victims than alcoholism, but the addiction produced is even more resistant to treatment. A recent increase in opiate addiction among the younger age groups (36, p. 8) and an "unbelievable growth in

the drug traffic in the United States" (36, p. 3) have made this a problem of increasing national concern.

Inadequacy of Current Treatments of Addiction

The inefficiency of current treatments for addiction is shown by the fact that many alcoholics and almost all opiate addicts who undergo treatment for their addiction promptly relapse (i.e., return to the use of drugs) after discharge from treatment. Since this tendency to relapse, this compulsion toward use of the drugs is a *sine qua non* of addiction (5, p. 98; 18, p. 47; 37, p. 3-4), it is obvious that the goal of treatment was not achieved. The term "drugs" is used in a generic sense to refer to all chemical agents which bring about compulsive behavior toward their use. Alcohol, therefore, is also referred to as a drug.

It would seem that psychotherapy might be effective in removing this compulsion, but, despite much propaganda to the contrary, it is not. The prognosis for treatment of either alcoholism or opiate addiction by psychotherapy is similar. "The curbing or controlling of alcoholic compulsions or cravings by psychiatric treatment alone is notoriously unsuccessful" (23, p. 104). Wikler of the U.S. Public Health Service Hospital at Lexington, Kentucky states that

"the efficacy of psychotherapy in the treatment of opiate addiction is limited" (37, p. 59).

Treatment of Opiate Addiction

There is no very satisfactory treatment today for opiate addiction. Even the most advanced treatment provided by the two USPHS Hospitals offers but little hope for the addict. "Dr. Kenneth W. Chapman, Assistant Chief of the Public Health Service, has been quoted as conceding that only 15 per cent of the patients treated at federal narcotics hospitals have been permanently cured" (36, p. 112). Wikler says, "The most optimistic estimates from reliable sources is that of probable 'benefit' or 'cure' in about 35 per cent of patients" (37, p. 59). Lindesmith notes a similar viewpoint held by addicts. He says,

> There is a belief prevalent among addicts that it is a misnomer to speak of a "cure" for addiction. They remark, "once a junker, always a junker". . . . There are . . . no reliable statistics on relapse among American drug addicts, and an estimate can be made only by indirect means. A careful study of about 800 German addicts led to the following findings: 81.6 per cent of the cures were followed by relapse within a year, 93.9 per cent within three years, and 96.7 per cent within five years. . . . [Since] relapse can take place after more than five years of abstention . . . even the remaining 3.3 per cent noted above could scarcely be regarded as cured, in the sense that the impulse to relapse had been permanently eradicated (18, p. 47-49).

Treatment of Alcoholism

Prognosis for the treatment of alcoholism is somewhat brighter than for opiate addiction, although it is still not good. There are at least three methods of treatment which affect the relapse rate in a clear-cut fashion. These methods are based on motivational devices to "counterbalance" the desire to drink.

One of the more successful treatments is based on the "conditioned reflex," or "conditioned aversion" method. One course (of four to eight treatments) sufficed to obtain a 44 per cent abstinence rate with 4,468 cases during a period covering 13 years. This treatment, however, is not widely used (23, p. 115).

Another fairly successful treatment depends upon a relatively recent drug discovery. Daily doses of this drug (Antabuse) are given but have no effect on the alcoholic unless alcohol is consumed. One ounce of alcohol, however, produces a drastic effect in the Antabuse-treated patient. His face becomes flushed, his heart pounds, he may become nauseated, vomit, become dizzy, suffer headache, fatigue, dyspnea, and paraesthesias (23, p. 113). It would seem that two motivational devices exist in the Antabuse treatment.

First, there is the knowledge of the effect of combining Antabuse and alcohol, and secondly, there is some "conditioned aversion" produced during initial trials which are used to determine the dosage of Antabuse to be given.

Finally, there is the supportive effect supplied by Alcoholics Anonymous through the activities of non-drinking alcoholics and their group norms. This, of course, is not a "cure" for alcoholism. Members of Alcoholics Anonymous who are not drinking still refer to themselves as "alcoholics," for they know the compulsion to drink still exists and relapse lies only one drink away (19).

Theories of Addiction

The phenomena of addiction to various drugs present a grave challenge to many fields of science. Certain aspects of the problem lie within the fields of the physiologist, biochemist, pharmacologist, physician, psychiatrist, psychologist, and sociologist. Many theories of opiate addiction (18, 37) and alcoholism (14) have resulted from these different approaches to the problem. To date, however, no theory of addiction is completely satisfactory. Blumer, in the preface to Opiate addiction states that,

> Two ideas stand out among the numerous mythical and

> fantastic notions which lay people entertain on the subject of drug addiction. It is thought, on the one hand, that the addict is weak-willed, morally deficient, and unwilling to meet personal responsibilities; on the other, that he is caught in the toils of a mysterious organic craving of chemical proportions, which renders him helpless. These ideas, with their curious inconsistencies are reflected in the current police practices of apprehension of addicts, and in the reliance on both punishment and medication as methods of cure.
>
> These two notions, with only slight modification, have hitherto largely dominated scientific studies of drug addiction. Considerable research has been posited on the underlying assumption that addicts are aberrant individuals and must be understood in terms of aberration. Such research, as a consequence, has sought to isolate the human characteristics setting off addicts from non-addicts; statistical studies being made to ascertain in what traits and to what degree addicts differ from non-addicts. Addicts are investigated clinically for the presence of peculiar psychological deficiencies.
>
> The bulk of the remainder of the scientific studies of addiction has centered on inquiry into the pharmacological character and operation of drugs, usually with the hope of discovering some neutralizer or harmless substitute for the drug under investigation. Obviously the study of the addict in terms of peculiarities or deviant traits and the study of the physiological functioning of drugs correspond to the two popular notions mentioned above.
>
> The inadequacy of lay opinion and scientific belief alike under the influence of these two ideas is, I assume, quite apparent. Neither idea alone, nor the two combined, has led to a fruitful understanding of drug addiction (18, p. vii-viii).

Psychological Theories and Emotional Dependence

Most psychological theories are based on an attempt to account for the emotional dependence of the addict on his drug. Wikler defines emotional dependence as meaning

"simply that the addict reports that, or behaves as if he feels discontented, anxious or unhappy unless he is under the influence of an opiate" (37, p. 4). Alcoholics show a similar kind of behavior. They must have drinks for fatigue, nerves, worries, troubles, and depression (19, p. 32).

Infantile theory of emotional dependence. Psychiatrists tend to see emotional dependence as a "fixation or regression to the oral stage of emotional development" (23, p. 59).

> Addicts . . . depend, as the baby once did, on the incorporation by mouth or skin of substances which make them feel both physically satiated and emotionally restored. But they are not aware that they yearn to be babies again. Only as they whine and boast and challenge are their disappointed and babyish souls revealed (4, p. 57).

Abnormal personality structure. A number of studies of the personalities of opiate addicts have been made (37, p. 4). Starting with the assumption of an abnormal personality structure in addicts, abnormalities may be found in as many as 91 per cent of the subjects (18). It is worth noting, however, that these studies do not find significant personality deviations (other than addiction) in some of the addicts (15, 18, 37).

Addiction by "pleasure." The compulsive behavior of

the addict, it is sometimes alleged, must result from the pleasure (euphoria) obtained from use of the drug. This hypothesis is enticing, but suffers numerous embarrassments, e.g., (a) other drugs such as amphetamine (benzedrine) produce euphoria (16), as may cortisone (25), but no compulsive behavior is developed toward these drugs, (b) if euphoria is the essence of addiction, then animals should also show compulsive behavior toward opiates and relapse at the first opportunity, but there is no evidence in the current literature that they do so. Spragg's chimpanzee experiments (30), for instance, showed the animals would work for an injection only when suffering withdrawal distress. Once withdrawn from the drug, they were indifferent toward it. An essential characteristic of addiction was missing in these animals. They did not relapse or show the compulsion which is characteristic of human addiction. (c) The euphoric effect of morphine is sometimes absent (16, 18, 37), and (d) Lasanga et al. (16) report that nonaddicts, who did not know they were receiving morphine were prone to report the effects as "unpleasant," yet morphine is an addictive drug.

Escape from anxiety. Some investigators (e.g. 26, p. 447), conclude that drugs are used to avoid stresses and

strains of life which upset the subject. Usually it is also assumed that this is an inherent personality trait which existed prior to addiction. Since this escape-from-anxiety hypothesis is just the reverse way of stating the fact of emotional dependence, it obviously fits the behavior of the addict.

Deficiencies of the psychological theories. As Wikler (37) points out, these theories are little more than restatements of the definition of emotional dependence.

> Furthermore, the anxiety-euphoria "explanation" of addiction might be used equally well to "explain" all human behavior, since this formulation is essentially synonymous with the pain-pleasure principles. It therefore does not explain drug addiction (37, p. 5).

Lindesmith (18) notes that studies of the personalities of addicts are poorly controlled and use data obtained from subjects after the development of addiction. Other authors suggest that, in the case of the alcoholic, personality distortions may be a result of addiction rather than a cause.

> It is a tragic fact that, independent of the original level of adjustment prior to alcohol addiction, once a person is addicted to alcohol, all cultural, educational, moral and physical dissimilarities become liquified, as it were, and then disappear in the "universal" solvent of alcohol (23, p. 34).

The alcoholic's resemblance to the man he was or to

> the woman she was, is vanishing. A few years of this completely uncontrolled kind of drinking, and the behavior it inevitably produces, and there will be a different person presented to an unsympathetic, uncomprehending world (19, p. 48).

Quite obviously, the same argument may be applied to opiate addiction, i.e., the personality traits found in opiate addicts may be the result of addiction and its problems, rather than a cause of addiction. Yost (40, p. 3), for instance, states that, "even originally normal persons who have taken drugs over too long a period are likely to develop neurotic or even psychopathic characteristics." Further, the personality studies always report a small percentage of subjects as normal people who have been accidentally addicted (15, 18, 36, 37, 40). How, then, does the process of addiction "work" on these normal people if a personality defect is a sine qua non of addiction?

Finally, the psychological theories so far proposed tend to ignore the physiological aspects of addiction in order to explain emotional dependence. This omission, of course, greatly weakens their argument.

Biochemical Theories

The biochemical approach to the problem of addiction has proven irresistable to many researchers. It is seemingly

straightforward and compelling in its simplicity. The addicting drugs (i.e., drugs which produce compulsive behavior toward their use), it is alleged, must change the metabolic processes of the user in some subtle manner so that a "biochemical need" is created which is experienced by the addict in terms of "craving" the drug. Much research has been based upon this hypothesis.

Various authors have, from time to time, indicated a number of biochemical processes, e.g., blood sugar level (33), vitamins (23, p. 63), and endocrines (23, p. 103), but none of these processes has been shown to be more than one of several factors in the situation (37, p. 3-9).

It is true, however, that each of the addicting drugs produces certain characteristic physiological effects and there is some similarity among these effects. The addicting drugs are depressants which reduce various drives such as anxiety, pains, aches, etc. Perhaps more important is the fact that distressing symptoms appear when the depressant drug is no longer administered, and these symptoms are relieved by readministration of the drug. This effect will be discussed more fully in Chapter II.

Effects of alcohol. There is a large amount of information on the effects of alcohol (14). Among other

things, it is a depressant drug which reduces anxiety, fear, tension, resentment, discomfort, and pain (3, 12, 23). It also initiated physiological changes which are eventually expressed as the "hangover." It should be noted, however, that severity of the hangover varies considerably, from the very slight malaise of the occasional drinker through the severe distress of the heavy drinker to the physical near-collapse of the chronic alcoholic.

Effects of opiates. The effects of opiates and their synthetic analogues are complex. Despite some stimulating aspects, these drugs are generally considered to be depressant drugs. They reduce anxiety, fear, tension, pains, aches, hunger, and sexual urges (18, 37). They also initiate physiological changes which are observed as tolerance to the drug, physical dependence upon the drug, and finally, the abstinence syndrome, or as it is sometimes called, the withdrawal syndrome (18, 37).

Tolerance to the drug is noted after repeated dosages of the same amount of opiates. This is an apparent loss of effect of the drug so that the dosage must be increased to obtain the original effects of the drug (18, 37).

A tolerant subject requires the drug to maintain a stable, relatively "normal" state. Cessation of

administration of the opiate shows that, despite the apparent lack of effect, the drug is "doing something." Omission of the drug precipitates a physiological upset (18, 37). This requirement of the drug to maintain relative normalcy is termed physical dependence upon the drug.

The physiological upset which occurs when opiates are withdrawn from a tolerant subject is called the abstinence syndrome or withdrawal syndrome. This upset is both extensive and severe in the case of a subject who has become tolerant to fairly large amounts of opiates.

> These [physiological symptoms] consist of yawning, lacrimation, rhinorrhea, mydriasis, gooseflesh (piloerection), tremors, muscle twitches (particularly in the lower extremities), restlessness, hot and cold flashes, nausea, vomiting, diarrhea, anorexia, weight loss, ejaculations in men and orgasms in women, elevation of body temperature, cardiac and respiratory rates and blood pressure, leucocytosis, hemoconcentration, elevation of blood sugar and a precipitous drop in circulating eosinophile count. In addition, the subject often exhibits a rather typical facies, suggestive of an individual with an acute febrile infectious disease. Often the patient "curls up" in the lateral recumbent position with a blanket drawn over his head, preferably on a hard, cold surface such as the floor. . . . [other "purposive"] changes refer to such behavior as appears to be directed toward obtaining the drug. It is expressed verbally in terms of "craving" and demanding drugs. Also, the subject may exhibit patterns of behavior which are highly individualized--threatening suicide, or violence, assuming bizarre postures and exaggerating his distress in dramatic ways (37, p. 36-7).

The severity of the withdrawal syndrome which

develops is related to previous dosage, duration of addiction, and degree of tolerance which had been developed. It reaches a maximum between 48 and 72 hours after abstinence was begun and then subsides gradually over a period of about a week. By this time the subject has made a "biologically adequate" recovery, although his weight, caloric intake, sleep, temperature, and some hematological changes may not reach control levels for several months (9, 37, p. 37). The severity of the syndrome also varies "within limits" in different individuals (37, p. 36).

Withdrawal and addiction. Lindesmith (18) has been impressed with the importance of the withdrawal experience in the genesis of relapse among addicts. He says there is a linguistic factor which allows only man living in society to become an addict (18, p. 89). By his definition, animals may not become addicts (18, p. 63). Spragg (30) also believes the withdrawal syndrome to be important in the genesis of addiction, but disagrees with Lindesmith about the possibility of animals becoming addicted to opiates.

Physical dependence and addiction. Physical dependence has been considered by some researchers to be the essence of opiate addiction (30), and it has even been considered by a few (e.g. 35) to be the essence of alcoholism.

However, the equation of physical dependence with opiate addiction came into use as a matter of convenience (30). Pharmacological and physiological research workers needed some measure which could be used as a criterion of addiction. It was convenient to use physical dependence, since abrupt cessation of drug administration to a tolerant animal precipitated measurable physiological disturbances.

Deficiencies of the biochemical theories. The inadequacy of physical dependence as a general explanatory principle has been recognized and detailed by several authors (18, 30, 37). Unfortunately, however, it has been uncritically accepted as the equivalent of addiction by some authors (e.g. 8).

There are a number of facts of addiction which physical dependence cannot explain. Addicts, for example, regularly relapse after they are no longer physically dependent upon their drug. Hospital patients, on the other hand, may become physically dependent upon opiates, be withdrawn, suffer a classical withdrawal syndrome and yet never relapse (18, 37). Animals also become physically dependent upon opiates, but there is no evidence in the current literature that after they are withdrawn they will relapse.

The long search for a possible mechanism by which an

assumed "biochemical alteration" takes place has unearthed a very large amount of information (14, 37). Yet, the original purpose of the research remains unfulfilled. In fact, there are today few leads which promise solution to the problem of addiction by means of this attack.

The "biochemical need" hypothesis is hard pressed to account for all the phenomena of addiction. The chemical dissimilarities of the various addicting drugs make a common biochemical mechanism seem implausible or, at best, highly unlikely. Therefore, the biochemical approach usually produces a specific theory for each of the various classes of addicting drugs. Also, current biochemical theories cannot explain the failure of hospital patients or animals to relapse. These difficulties make the basic assumption of a "subtle biochemical alteration" seem a less attractive approach to the problem of addiction than it does upon first consideration.

Summary

Even the more popular hypotheses of addiction fail to explain more than a restricted fragment of the phenomenon of addiction. Still, as Wikler points out, "the evidence indicates that there is a measure of truth in all these

viewpoints. Their relative importance, however, needs to be delineated further" (37, p. 9).

More extensive reviews of addiction theories are given by Wikler (37) and Lindesmith (18) for opiate addiction, while Jellinek (14) gives an exhaustive review of theories of alcoholism.

CHAPTER II

THE DEVELOPMENT OF A CONDITIONED RESPONSE TOWARD ADDICTIVE DRUGS

A general theory of addiction should not only apply equally well to any of the addicting drugs but should also integrate the physiological actions of the drug with the psychological reactions of the subject. Such a possibility exists in the form of a learning theory. It is possible, in fact, to show an exact parallel between laboratory escape training and the first stages of addiction.

Definition of Escape Training

Escape training is a method of forming a conditioned response. The escape training situation requires an aversive stimulus which can be terminated as a result of some action on the part of the subject. The action which terminates the aversive stimulus situation is sometimes called an "instrumental act." This act of escape is learned by the process of conditioning so that later presentations of the

aversive stimulus activate the conditioned response (instrumental act) which has led to escape in the past.

In the psychological laboratory, the aversive stimulus situation is usually created with electric shock which is applied through a floor grid to the feet of the experimental animal. The animal finds, at first by chance, that a particular action, e.g., pushing a bar, allows escape from the aversive stimulus. This instrumental act is rapidly learned, i.e., becomes conditioned, so that the aversive stimulus quickly evokes the conditioned response of escape. For example, an animal which is well conditioned quickly pushes the bar which turns off shock applied to a floor grid.

Concept of the Aversive Stimulus

An aversive stimulus situation (or noxious stimulus situation) may be defined as one which the subject actively attempts to avoid or terminate.

Electric shock is the aversive stimulus most frequently used in the psychological laboratory because it is easily produced, measured, and controlled. The very simplicity of this procedure, however, may lead the psychologist to err in his thinking about the concept of the aversive stimulus. An error becomes operative when he limits his

conception of the aversive stimulus to one which he can apply to the subject. This is an unnecessary limitation based upon the origin of the aversive stimulus. The origin of the aversive stimulus, however, makes little or no immediate difference to the subject. A more important aspect of the situation is the fact that the organism attempts to avoid or terminate the sensation produced by the aversive stimulus.

Stimulation of the pulp of a tooth with an electric current will give rise to the sensation of pain. This aversive stimulus may be used to promote learning of an escape or avoidance response. Yet, this same sensation may occur without the electric current. The tooth may produce the same sensation of pain "spontaneously." A response which efficiently terminated this sensation would be learned just as it was when the pain arose from stimulation by an electric current. This is true even though the origin of the sensation was within the body rather than the result of a stimulus being applied <u>to</u> the subject from the outside.

An excellent illustration of this viewpoint is the stimulus complex labeled "hunger." It is a "spontaneously" occurring aversive stimulus situation. Also, it may be terminated or avoided by an appropriate response on the part

of the subject. Further, the response used in terminating this naturally-occurring aversive stimulus complex is rapidly learned by the subject.

In summary, an aversive stimulus need not necessarily be applied to the subject from the outside. It may simply occur as the result of metabolic or other bodily processes. Any response which terminates or avoids the aversive stimulus will tend to be learned, regardless of the origin of the aversive stimulus.

Addiction as Escape Training

Demonstration of a parallel between laboratory escape training and addiction requires identification of an aversive stimulus situation which occurs in connection with the use of the addicting drug and the means of escaping the aversive stimulus situation which, in this case, must be that of obtaining and using the addicting drug. This instrumental act will then produce a conditioned response toward using the drug. If this process of escape training can be demonstrated, then it should be obvious that each instrumental act of escape will strengthen the act of taking the drug. Also, since the aversive stimulus follows use of the drug, a cyclical pattern of behavior is established with each cycle

strengthening the conditioned response of using the drug.

Opiate Addiction as Escape Training

There seems little doubt that the symptoms comprising the withdrawal syndrome can be considered an aversive stimulus situation. Wikler (37, p. 36), for instance, refers to the morphine abstinence syndrome as "unqualifiedly distressing."

The instrumental act which allows escape from this aversive stimulus is obtaining and taking an injection of opiates. "When abstinence symptoms . . . set in . . . those terrible symptoms are banished as if by magic by a sufficiently large dose of morphine" (18, p. 73). "The physical suffering is accompanied by a mental anguish deriving from the addict's knowledge that all of his pains could be quickly cured with the administration of one 'shot'" (36, p. 115).

If we can believe that the withdrawal syndrome is an aversive stimulus situation and that an injection of morphine efficiently relieves these symptoms, then it follows that this is a conditioning situation and that the act of obtaining and taking the drug should be learned as a conditioned response by the process of escape training.

Alcohol Addiction as Escape Training

The fact that escape training appears to play a role in opiate addiction leads to a search for a similar mechanism in alcohol addiction. In the consumption of alcohol, the physiological changes which are expressed as a "hangover" are conceived to constitute the aversive stimulus. It should be noted also that sub-acute "hangover-type" physiological changes occur following the consumption of even small amounts of alcohol, although a fully developed hangover may not occur. The instrumental act which permits the aversive stimulus to be escaped is obtaining and taking an alcoholic drink. The use of an alcoholic drink to escape a hangover is commonly expressed as "It takes a hair of the dog that bit you to cure you."

> Hangovers . . . make themselves felt, in the peculiarly horrible form known to alcoholics, on every awakening from sleep, and whenever possible are immediately wiped out by drinks. Since these awakenings may take place at any hour of the day or night, such drinking cannot be called strictly morning drinking, although to the alcoholic it is "as if" morning (19, p. 52).

> Anyone who has experienced [a really severe hangover] will find little difficulty in understanding why the alcoholic resorts to a "hair of the dog that bit him" to help him withstand the onslaught, after he learns that it will invariably do just that (19, p. 36).

Again, if we can believe that the "hangover" is an

aversive stimulus situation and that an alcoholic drink efficiently relieves the symptoms of the hangover, then it follows that this is a conditioning situation and the act of obtaining and taking an alcoholic drink should be learned as a conditioned response by the process of escape training. Some evidence and opinion support this position.

> It has been postulated that in heavy drinkers, abstinence from alcohol can cause symptoms that are alleviated by drinking alcoholic beverages. Relief from these symptoms could motivate the desire for alcohol (20, p. 52).

Lemert, discussing a study by Jellinek, observes that, "The 'morning drink' was reported as an early feature of the drinking of 91 per cent of one group of alcoholics whose histories were recorded by questionnaires" (17, p. 371).

> Within one to three years subsequent to acquiring the "morning drink" habit, the alcoholics manifested true addictive behavior by going on "benders" during which they stayed drunk for days at a time, with no thought for their responsibilities. . . . These are clearly the earmarks of compulsive drinking (17, p. 373).

The parallelism between laboratory escape training and escape training with opiates and alcohol may be clarified by this comparison:

Type of Training	Aversive Stimulus	Instrumental Act of Escape (Conditioned Response)
Laboratory	Electric shock	Pushing a bar; jumping barrier
Opiate	Withdrawal distress	Obtaining a "fix"
Alcohol	Hangover	Taking an alcoholic drink (morning drink; hair of the dog)

Supporting this view of addiction is the observation that the incidence of opiate addiction is positively correlated with the severity of withdrawal symptoms produced by the various opiate drugs (27). The fact that hospital patients may receive opiates without becoming addicts can be explained in terms of this analysis. No instrumental act was performed by the patient. He never learned that withdrawal distress could be escaped by some action on his part and therefore never became conditioned (addicted) to the drug.

Summary

An integrated approach to the problem of addiction has been formulated from well-established conditioning principles and the known physiological responses produced to opiates and alcohol.

According to the analysis presented in this chapter,

there is an exact parallel between laboratory escape training and the first stages of addiction.

CHAPTER III

DEVELOPMENT OF EMOTIONAL DEPENDENCE ON ADDICTIVE DRUGS

It is an observed fact that addicts seem to use their drug to escape the worries and anxieties which are part of everyday living. Alcoholics, for example, say they drink because of a "tired feeling," "nerves," worries, troubles, or depression (3, 19, 23). Opiate addicts show similar behavior; they tend to

> become hypochondriacs. . . . they will say they are suffering from many complaints, such as "weak" kidneys, sore throat, and miscellaneous pains and ailments. . . . the addict recalls that when he was using narcotics he was not troubled by them. The inclination to relapse takes the form of a rational decision. The individual concludes that he is "no good" off the drug, and might as well go back to it (18, p. 128).

According to the analysis given in Chapter II, when an addict uses drugs he is performing a conditioned response. The problem presented by emotional dependence is to show how this conditioned response of using drugs may be activated by other distressing stimuli.

Emotional Dependence in Opiate Addiction

The first usage of opiates as an instrumental act is undoubtedly to escape the aversive stimulus situation of the withdrawal syndrome. However, opiates not only provide an escape from withdrawal symptoms but also reduce anxiety, tension, worries, pain, hunger, and sexual urges (23, p. 330; 37, p. 18). After the subject has made the instrumental act of escape, he says he feels "fixed." This term denotes a state of well-being, of relief from the drives of anxiety, tension, worries, pain, hunger, and sexual urges (37, p. 17).

The "fixed" state, however, gradually changes toward the withdrawal state. "Restlessness" begins to appear and becomes marked by the end of about eight hours of abstinence from opiates (18, p. 26). The withdrawal symptoms become progressively worse until a peak of distress is reached sometime between 48 and 72 hours after the last dose of opiate (37, p. 37).

Since the aversive stimulus situation gradually builds up, the instrumental act will begin to appear earlier and earlier so that really severe withdrawal symptoms are no longer experienced. Thus, the character of the instrumental act changes from an escape response to an avoidance response.

More and more the instrumental act will be performed to signs indicating withdrawal distress is approaching.

> During the initial stages of withdrawal, every slight stomach cramp, which Dequincey described as the "gnawing of some imprisoned reptile" is endowed with some of the significance and painful attributes of all the stomach cramps the user knows there are to follow. The suffering becomes all the more unendurable because the means of relief are so simple (18, p. 83).

The state of being "fixed" is characterized by an absence of the drive stimuli from anxiety, tension, worries, pain, hunger, and sexual urges. Therefore, the <u>return</u> of these drive stimuli is a sign the "fix" is wearing off and withdrawal distress is approaching. The identification of these "signs" with the withdrawal distress is easy because of the "considerable resemblance between the changes which characterize the morphine abstinence syndrome and those which are characterized as 'anxiety'" (37, p. 7).

There may be some stimulus generalization so that these similar stimuli tend to elicit the conditioned response (CR) directly. There is reason to believe, however, that these stimuli produced by the returning drives also become able to activate the conditioned response by means of the classical conditioning procedure. The stimuli from these drives come to be for the user a "sign," (i.e., a

conditioned stimulus or CS) that withdrawal distress (the unconditioned stimulus or US) is approaching. A classical conditioning situation occurs because the US (withdrawal distress) and CS (anxiety, etc.) are both terminated by the same instrumental act (conditioned response). Eventually, as occurs in classical conditioning, the CS comes to evoke the CR as an avoidance response.

These drive stimuli which serve as a CS for the addict occur inevitably as part of the process of everyday life. It would seem, then, that the observation that addicts "can't stand normal stresses and strains" is, in a sense, justified. Any anxiety, pains, tensions, depressions, etc., will tend to activate the CR of obtaining a "fix."

> Having become accustomed to the drug and having learned to interpret all the vicissitudes of life in terms of withdrawal symptoms, the chronic user continues to identify his difficulties with withdrawal distress even after his supply is cut off (18, p. 124).

Emotional Dependence in Alcohol Addiction

The development of emotional dependence in the alcohol addict may be explained in the same manner as in opiate addiction. Alcohol terminates the aversive stimulus of the "hangover" (and sub-acute physiological changes), but it, like opiates, does more than this. Alcohol also reduces

anxiety, fear, tension, resentment, discomforts, and pain (3, 11, 12, 23). As in opiate use, drive stimuli are terminated (or greatly reduced) at the same time as an aversive stimulus is reduced. Again, the classical conditioning paradigm is appropriate to the situation. The CS (drive stimuli from anxiety, etc.) eventually comes to evoke the CR as an avoidance response.

This conditioning process is facilitated by the remarkable resemblance between the CS and the US. "[The] postalcoholic state contains many manifestations similar to those found in anxiety tension states" (23, p. 209). "The day after considerable drinking [the] patient is tremulous, restless, apprehensive and sleepless. His mood is irritable and depressed" (23, p. 209). "Abrupt withdrawal of alcohol . . . is . . . described by patients as 'cold turkey.' The patients nearly always display irritability, restlessness, fatigue, difficulty in sleeping, apprehension and feelings of guilt"(23, p. 199).

The similarity between the anxiety, tension, fear, etc., that occur in everyday living and the postalcoholic state may allow some stimulus generalization so these drive stimuli may activate the CR directly. However, these drive stimuli also become effective in activating the CR by means

of the classical conditioning procedure.

The stimuli which comprise the CS, i.e., tension, anxiety, fear, discomfort, depression, fatigue, etc., occur inevitably as part of the process of everyday life. As in the case of the opiate addict, it would seem that the observation that alcoholics "can't stand the normal stresses and strains of life" is, in a sense, justified. These stimuli act as CS so the alcoholic's CR of taking an alcoholic drink is activated. "There is an A.A. [Alcoholics Anonymous] saying that an alcoholic plus a resentment equals a drunk, as surely as two and two equal four" (19, p. 161).

Summary

The observed behavior of addicts suggests that they use their drug to escape the worries and anxieties which are part of everyday living. This behavior has been termed emotional dependence on their drug.

According to the analysis presented in this chapter and in the preceding chapter, emotional dependence is the observed behavior of a well-conditioned addict. In such a person, the habit strength (in the learning sense) is so great that the "worries and anxieties" of everyday living, acting as conditioned stimuli, are sufficient to activate a

conditioned avoidance response. This avoidance response is the action of taking the addictive drug to "escape their worries and anxieties."

CHAPTER IV

ANALYSIS OF THE PROBLEM OF RELAPSE

Relapse is the crucial problem of addiction. If addicts did not relapse, then addiction would present only a very minor medical problem. Yet, many alcoholics and almost all opiate addicts return to the use of their drug after a "cure." The use of drugs by an addict is, according to the analysis given in Chapters II and III, a conditioned response. The problem posed by the phenomenon of relapse, therefore, is to show persistence of the CR and why the addict has great difficulty in resisting the CR, even though he is not physically dependent upon the drug.

Persistence of the Conditioned Response

The avoidance response produced in the laboratory by electric shock training is often extremely difficult to extinguish (32, p. 449). In part, this resistance to extinction is due to similarity between the acquisition and extinction phases. A well conditioned animal always makes the

response to the CS and thus the animal cannot discover that the US is not being presented during the extinction phase. The CS is presented and the subject promptly performs the CR. The difference between acquisition and extinction, therefore, is manifested only upon a failure of the animal to respond to the CS.

According to Mowrer (21), the avoidance response obtained in the laboratory to electric shock is mediated by anxiety. Anxiety supplies the drive stimuli for the laboratory avoidance response. Therefore, if extinction of the response has occurred, the CS must no longer produce enough anxiety drive stimuli to activate the conditioned response. Yet, the anxiety mediated response is extremely difficult to extinguish, and the more traumatic the aversive stimulus, the greater the difficulty in extinguishing the response (32, p. 450).

The CR of the addict, however, is connected not only to anxiety, but to several other drives as well. Some of the addiction-connected drives occur as part of the biological functioning of the normal, healthy individual (e.g., hunger and sex drives), while other addiction-connected drives may occur as part of everyday living (e.g., anxiety, pain, depression).

The extinction of anxiety drive stimuli which are aroused by a laboratory CS may be accomplished with a relatively large number of extinction trials (32, p. 499). However, some addiction-connected drive stimuli (e.g., hunger and sex drive stimuli) cannot be extinguished, while other drive stimuli (e.g., anxiety and pain drive stimuli) cannot be entirely avoided. The tendency to perform the CR, then, must exist as long as the habit and the drive stimuli persist, that is, continuously in varying degrees from day to day.

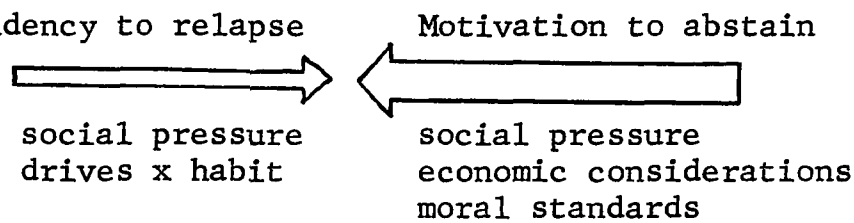
Difficulty of the Addict in Resisting the CR

The conditioned drive stimuli and the habit strength (once established) both exist independently of any physiological effect of the drug. It follows, then, that the tendency to respond with the instrumental act of taking the drug must also exist independently of the drug effects. Addiction-connected drive stimuli operate upon the habit strength built up over a long period of conditioning to produce a continuously-present and autonomous tendency to perform the CR.

> The effectiveness of the desire to slip back to opiate consumption . . . depends upon its persistence and subtlety rather than its intensity. As Cocteau

> exclaimed, "The patience of the poppy! He who has smoked will smoke again. Opium can afford to wait" (18, p. 129).

To remain abstinent, the drug user must maintain a continuously active motivation to abstain. The larger arrow on the right of the following diagram indicates that the motivation to abstain is stronger than the tendency to relapse.



This diagram, which does not purport to include all possible reasons for abstaining or pressures to relapse, does, nevertheless, indicate that drive stimuli act upon acquired habit strength to increase the tendency to take a drink (or "fix") and that this tendency may be opposed by other considerations. This diagram, in theory, would represent the condition of a "heavy drinker" who could control his drinking. There is motivation to drink but it can be overcome by other motivation. As the process of conditioning continues, however, the habit strength of the CR becomes greater and greater. The tendency to make the CR, therefore, becomes greater and greater. The tendency to make the CR

increases as the conditioning process continues, while the motivation to abstain may remain about the same. When these two response tendencies are about equal, there are at least two other factors which become important in the resolution of the abstinence-relapse conflict situation.

Although the motivation to abstain has been pictured as a constant force, it is not really constant. This abstinence motivation must fluctuate some with various changes that occur in the subject's life. Prior to the time when the response tendencies were approaching equality, fluctuation in abstinence motivation was a minor factor in the abstinence-relapse situation because the abstinence motivation was relatively strong. However, when these two response tendencies approach approximate equality, the margin of safety becomes dangerously low. Should the motivation to abstain falter by a slight amount now, relapse will probably follow. It is at this point that the "heavy drinker" changes over to the "alcoholic" who can no longer control his drinking.

The other important factor occurs as a result of a conflict between the two response tendencies. Strecker and Chambers report that alcoholics who attempt to quit describe the attempts as very distressing, unhappy ordeals. "Analysis

of their states of mind reveals that there is a continuous conflict" (33, p. 92). One of the resultants of this conflict is anxiety, and the drive stimuli from anxiety have been attached by previous conditioning to performance of the CR. Therefore, a conflict between abstinence and relapse produces additional drive stimuli which increase the tendency to relapse.

Even if the emotional states produced by the conflict are not originally connected to performing the CR, they will be after a few trials. Under the conditions described above, relapse is highly probable. When relapse occurs, the conflict is, to a large extent, resolved and the conflict-produced emotional states are reduced. It is obvious that this represents a second-order conditioning situation. Emotional states which are produced by the conflict situation will, therefore, become able to activate the CR of taking the drug. These additional drive stimuli have become effective, by this second-order conditioning process, in initiating the performance of the CR. Since some learning theorists, e.g., Hull (13), believe that the tendency to respond is a multiplicative function of the strength of the habit and the drive stimuli acting upon it, an addition to either drive or habit strength produces an increase in the

tendency to perform the CR.

Emotional responses to different conflict situations may possibly differ, but if the emotional responses produced by a given conflict situation are similar to those produced by the abstinence-relapse conflict, then the drive stimuli will activate the CR. In other words, an argument or frustration not originally connected with drinking or taking a "fix" may, in the well conditioned addict, precipitate a relapse.

Summary

By the process of classical conditioning, including higher order conditioning, a number of drive stimuli have become CS for producing the CR of taking the addictive drug. These drive stimuli are summarized in the lists below. The difference between the lists is due, in part, to a difference in the physiological effects produced by opiates and alcohol. The specific labels attached by various investigators to the drives which these drugs reduce also tend to vary somewhat. The terms listed below are those which occur in the literature on opiate addiction (23, p. 330; 37, p. 18) and alcoholism (3, 11, 12, 23), plus the general category of "conflict-produced emotional states."

Opiate addiction	Alcohol addiction
anxiety	anxiety
tension	fear
worries	tension
pain	resentment
hunger	discomfort
sexual urges	pain
conflict-produced emotional states	conflict-produced emotional states

These lists are not intended to be comprehensive, but rather to be illustrative of the range of stimuli which may activate the CR during relapse and therefore produce the behavior which is observed as "emotional dependence upon the drug."

CHAPTER V

EXPERIMENTS I AND II: ADDICTION

Selection of the Problem

The analysis of addiction discussed in the preceding chapters is much too broad to be tested within a reasonable research program. Experimental investigation has, therefore, been limited to opiate addiction. Morphine was the opiate drug used in the following experiments.

It has been demonstrated that chimpanzees (30) and rats (7) will learn a new response when rewarded with morphine. However, the author has been unable to find a single instance of an animal exhibiting "craving" or making any action to obtain opiates once it was no longer physically dependent upon the drug.

The fact that relapse has never previously been demonstrated in animals may be due to several factors: (a) there is a relatively long time interval, measured in minutes (18, p. 27; 30, p. 126), between performance of the

instrumental act and the physiological changes constituting an escape (except in intravenous injections), and (b) the inconsistency of the instrumental act required of the animals increases an already difficult conditioning situation, e.g., Spragg's chimpanzees (30) were required to perform a variety of actions for an injection of morphine.

The difficulties of conditioning animals with morphine may be minimized by keeping the instrumental act consistently the same from trial to trial and by arranging the learning situation so the physiological changes constituting an escape occur in temporal contiguity with the instrumental act. One method might be injection of morphine directly into the blood stream of an animal in withdrawal, following performance of the instrumental act. This approach, however, was not feasible because of limited experimental facilities. The only subjects available for this experiment were albino rats of the Sprague-Dawley strain. The instrumental act, therefore, had to be an action within the capabilities of the rat but an action not normally performed. In addition, this action had to result in a morphine intake.

An oral intake of morphine solution was chosen as the instrumental act. This act could be kept consistent from trial to trial and would occur over a period of time.

Despite a delayed action of the morphine, present drinking actions would occur during the physiological changes resulting from prior drinking, and thus, drinking the solution would be reinforced. A few drinking responses at the start of the trial, however, would not be reinforced.

Morphine solution is effective orally, but has (to humans, at least) a distinctly bitter taste. Rats offered a choice between water and a 0.5 mg/cc. morphine solution will drink large quantities of water but only 1 or 2 cc. from the morphine solution. This action seemed well suited to the requirements of an instrumental act, but one problem remained. If the animals did not normally make the instrumental response (the small amount actually consumed is negligible), why should they be expected to do so when suffering withdrawal symptoms?

This problem was solved by arranging the learning situation so that the animal in withdrawal also had a high thirst drive and only morphine solution was offered for the animal to drink during the training trial. Possible effect of thirst on the experimental results is evaluated in a second, control experiment.

Experiment I

Apparatus and Subjects

Twelve female Sprague-Dawley strain albino rats weighing between 150 and 190 grams each were caged individually in a temperature-controlled room (72° F.). A small excess of food was available at all times.

Procedure

Days 1-25: production of initial withdrawal symptoms. To produce a motivated state in the animals (i.e., a withdrawal state), preliminary injections of morphine hydrochloride were given for 25 days and then stopped. The injections started at 20 mg/kg and increased 5 mg/kg/day.

Days 26-29: initial preference test. Initial preference for the morphine solution was measured by a preference test given during the 96 hour withdrawal period on days 26 to 29. The preference test consisted of simultaneous presentation of two 100 ml animal drinking tubes to each animal. The animal had a choice between tap water in one tube and tap water containing 0.5 mg/cc. morphine hydrochloride in the other tube. Even though withdrawal distress presumably was increasing during this period, the small amount of morphine consumed (1 to 2 cc.) was not enough to reduce the

withdrawal symptoms appreciably. Therefore, it seems reasonable to assume that the rats did not learn the escape response of drinking the morphine solution during this period. Following the initial preference test, the rats were randomly assigned, six to an experimental group and six to a control group.

Days 30-65: training trials: experimental animals. Withdrawal distress reaches a peak between 48 and 96 hours (or about three days) after the last dose of morphine (18, 23, 36). Therefore, access to the morphine solution, which serves the dual function of reducing withdrawal distress and setting the stage for another round of distress, should occur about every three days. Consequently, every three days (presumably when the distress had reached a maximum) the experimental group was presented with only the morphine solution. To insure that the rats would drink enough of the morphine solution to accomplish a "pharmaceutical escape" (and thus reduce their withdrawal distress), all fluids were removed for 24 hours prior to the presentation of the morphine solution. One complete training trial covered three days, and consisted of 24 hours with no liquids (symbolized O), 24 hours with morphine solution only (M), and 24 hours with water only (W). A series of training trials would be

symbolized in this manner: O, M, W, O, M, W, O, M, W, etc. A total of ten escape training trials were given to the experimental animals.

Days 30-65: training trials: control animals. The control group received ten similar training trials, except W was substituted for M in the cycles: O, W, W, O, W, W, O, W, W, etc. In order that possible group differences could not be attributed to a difference in morphine intake, control rats and experimental rats were arbitrarily paired. On the day following the drinking of the morphine solution by the experimental rats, the control rats were injected with the same amount of morphine which the paired experimental rat drank. If experimental animal number one drank 20 cc. M containing 10 mg. of morphine, then control animal number one was injected with 10 mg. of morphine. It should be noted that no instrumental act was made by the control animals, so even though they "escaped" their withdrawal symptoms, no escape training was received.

Days 66-114: complete abstinence. After the tenth training trial (and second preference test) the animals were removed from all sources of morphine except for a preference test given after two weeks of abstinence and a similar test given after 35 more days of abstinence.

Preference tests. Preference tests between water and the 0.5 mg/cc. morphine solution were given to both groups after the fifth training trial, after the tenth training trial, after two weeks of complete abstinence, and finally after 35 more days of complete abstinence. The preference tests covered a period of 24 hours and were given at the point in the training cycles when the next presentation of M would have occurred, e.g., the preference test given after the fifth training cycle was given during the 24 hour period when presentation of M for the sixth training trial would otherwise have occurred.

Environment change during period of complete abstinence. To minimize possible extinction of cues associated with making the CR, the animals were removed from the individual cages, which had wire mesh bottoms, and placed in one large cage with a litter pan during the periods of complete abstinence. The rats were kept in the large cage during the time between the preference test following the tenth training trial and the preference test two weeks later and during the time from this preference test to the test given 35 days later. They were replaced in the individual cages for the preference tests given during the abstinence period. Food and water were available ad libitum during the periods of

complete abstinence.

Experiment II

There is a possibility in Experiment I that any differences between the experimental and control groups might be ascribable to the association of the distinctive taste of morphine solution with reduction in thirst drive stimuli. It is necessary, then, to perform a comparable experiment in which the distinctive taste will be separate from the morphine.

If the results of Experiment I are due to the association of the (presumed) bitter taste of the morphine solution with the reduction of thirst drive stimuli, then similar learning should occur to an equally rejected quinine solution or alum solution.

Apparatus and Subjects

Eighteen male Sprague-Dawley rats weighing between 140 and 150 grams each served as subjects. Preliminary to the experiment, 20 additional male Sprague-Dawley rats were used to equate a quinine solution and an alum solution with the 0.5 mg/cc. morphine solution. The apparatus and location of Experiment I were used.

Procedure

Because the supply of morphine hydrochloride had been exhausted during Experiment I, morphine sulphate was used in Experiment II. There is no reason to believe there is any essential difference in the addictive liability or taste of the two forms of morphine. The preliminary injections and initial preference test were the same as Experiment I. The 17 rats which survived the preliminary injections were randomly assigned, six to an experimental group, six to a quinine group, and five to an alum group.

Quinine equation with morphine. Five naive male Sprague-Dawley rats were placed in a large cage with a tube of 0.5 mg/cc. M and another tube containing 0.01 mg/cc. quinine solution (Q). Much more Q than M was consumed. The concentration of the Q was increased and the tube positions changed daily until the rats drank more M than Q. This change occurred abruptly between Q concentrations 0.5 mg/cc. and 0.6 mg/cc. These animals were then discarded.

To test the equation, five more naive rats were placed in the cage with a choice between 0.5 mg/cc. M or 0.5 mg/cc. Q. Approximately equal amounts were drunk from the two tubes. Only a small amount more Q than M was consumed.

The equation was accepted as sufficiently close for the experiment. These five rats were also discarded.

Alum equation with morphine. Using the procedure given for equating Q and M, ammonium alum (A) was equated with the 0.5 mg/cc. M when a concentration of 0.04 mg/cc. was reached.

Training cycles. The morphine group repeated the training cycles of the morphine group of Experiment I. The quinine group repeated the same cycles except these rats received a quinine solution to drink instead of a morphine solution. Similarly, the alum group received the alum solution to drink during the same cycles.

Equation of morphine intake among groups. So that possible group differences could not be explained on the basis of the amount of morphine received by the groups, injections were given to the Q and A groups on the day following the presentation of their test solutions. As a matter of convenience, the rats in the Q and A groups were injected with the same amounts as the control group of Experiment I. These groups (Q and A) actually received slightly more morphine than the experimental group in Experiment II.

Results of Experiments I and II

During the course of making the numerous injections required by the procedure, a number of interesting symptoms were observed to follow the intraperitoneal injection of large amounts of morphine to the tolerant rat:

1. Immediate postinjection contraction of the abdominal muscles. This state is due, in part, to the rapidity of the injection and is not specific to morphine. It lasts about 30 to 60 seconds.

2. The heavily morphinized animal presents the appearance of exopthalmia.

3. Hyperkinesis of rapid, darting character appears 10 to 15 minutes postinjection.

4. The animal gnaws on sticks, bars of cage, faces, own paws or tail in an indiscriminate manner.

5. "Posturing" occurs so the animal tends to remain unmoving in odd postures until moved or startled.

6. There is an abnormally high muscle tension so the animal seems fairly rigid when supported at the midsection with head, tail and feet in a horizontal plane.

7. A characteristic positioning of the front and hind legs close to the body occurs when the animal is suspended by its tail. The normal animal extends its legs when held in this position.

8. There is an exaggerated startle response so that group, self-stimulated, running responses may occur. One animal reacts to the sounds produced by another, thus producing sounds which cause the remainder to run, etc.

9. Approximately an hour after injection the animal feels much warmer than normal when picked up by the experimenter. This seems to be the result of an increased skin temperature.

10. The animals tend to pull hair out from those skin areas which are accessible to them. Spragg (30) noted a similar phenomenon in chimpanzees.

A summary of the quantitative results of Experiment I is given in Table 1. Because of skewed distributions and because experimental and control rats were paired on the basis of amount of morphine received during the experiment, Wilcoxon's (38) paired replicate T test was used to obtain the indicated significances. Table 1 also gives the sum of ranks and mean rank for each group.

The mean amount of morphine solution consumed by the experimental rats during their escape trials is approximately 100 mg/kg per trial for each rat. This amount is large enough to maintain a good physical dependence (and thus withdrawal symptoms) from trial to trial. There is, however, a steady decline from the first trial to the tenth trial. Approximately 145 mg/kg was consumed on the first trial, whereas the mean consumption on trials 8, 9, and 10 is approximately 90 mg/kg. The decline from the initial levels of intake is presumably due to the fact that the total amount of morphine the animals obtained from drinking the morphine

Table 1

Significance of Rank Differences of Preference Test Scores of Experiment I

Preference tests		n	Sum of Ranks	Mean Rank	Difference in Sums of Ranks	p
Training tests	E	6	21.5	3.6		
1	C	6	56.5	9.4	35	.05
	E	6	21.0	3.5		
2	C	6	57.0	9.5	36	.05
Abstinence tests	E	6	25.5	4.3		
1	C	6	52.5	8.8	27	.05
	E	5	19.0	3.8		
2	C	4	26.0	6.5	7	NS[a]

[a]Even a maximum difference between groups of this size may occur readily by chance alone.

solution was not enough to maintain the level of physical dependence which was established by the initial injections. Presumably, there is also some loss of physical dependence between trials.

During the preference test following two weeks' abstinence, the two rats which drank the most M (more than 110 mg/kg apiece) were the only rats which behaved differently just after the M tube was presented. They darted rapidly about the cage and then returned immediately to consume small amounts of the morphine solution.

Three rats died prior to the fourth preference test of Experiment I. The small number remaining in the two groups made a test of significance between the scores of the groups on the fourth preference test meaningless. Even a maximum difference between groups of this size has so large a probability of occurring by chance alone that a dependable conclusion about the group differences on this test cannot be reached.

Table 2 gives the sum of ranks, mean rank, and significances of the differences among the groups of Experiment II. The over-all probabilities were computed by the Kruskal-Wallis H test (34). Individual comparisons were computed by Wilcoxon's unpaired replicate T test (38). One rat in the A group died prior to the fourth preference test. The intake of test solution by the M group was significantly greater than the intake of test solution by either the Q or A groups during all training tests but was not significantly different

Table 2

Significance of Rank Difference of Preference Test Scores of Experiment II

Preference tests		n	Sum of Ranks	Mean Rank	p of these Hypotheses:[a]		
					E=Q=A	E=Q	E=A
Training tests	M	6	28.0	4.7			
	Q	6	71.5	11.9			
1	A	5	53.5	10.7	.05	.05	.05
	M	6	21.0	3.5			
	Q	6	79.0	13.2			
2	A	5	53.0	10.6	.005	.01	.01
Abstinence tests	M	6	35.0	7.0			
	Q	6	69.0	11.5			
1	A	5	49.0	9.8	NS	NS	NS
	M	6	36.0	6.0			
	Q	5	50.0	10.0			
2	A	4	34.0	8.5	NS	NS	NS

[a]All differences between Q and A groups are nonsignificant.

in the abstinence tests. Although the M group drank more test solution than the A and Q groups, the total liquid intake was about the same due to an increased consumption of water by the A and Q groups during the W phase of the training cycle.

Discussion

As may be seen from Tables 1 and 2, the mean ranks of the groups which received escape training are lower (indicating greater morphine intake) than their comparison control groups in all cases, although all of these differences are not statistically significant. These differences may not be attributed to any morphine-induced biochemical or physiological changes alone, since all control groups received as much (or more) morphine as the experimental groups.

The consistently low consumption of Q and A in all the preference tests of Experiment II refutes the possibility that association of taste with reduction of thirst drive stimuli may explain the results of Experiment I.

There is a significant difference ($p = .05$) between the morphine groups of Experiments I and II on the first preference test. Any of several differences between the two experiments may account for this difference in results (e.g.,

sex of animals, difference in stage of withdrawal symptom development at the start of the experiment, etc.).

The significant difference between the experimental and control groups after two weeks abstinence, as shown by the third preference test of Table 1, is considered especially noteworthy. Wikler (37) reports that in humans the withdrawal syndrome subsides gradually to a very low level after about one week of abstinence. Stanton (31) gives graphs showing that rats given four weeks of injections which are then stopped, struggle at high levels when restrained. This struggling gradually subsides to preinjection levels after 10 to 12 days of abstinence. Thus, the withdrawal syndrome appears to diminish asymptotically and reach a very low level in a 7 to 12 day period. Therefore, it seems that the physiological state of the animal must asymptotically approach a normal adjustment during the same period. The significant difference between the groups of Experiment I after 14 days abstinence must, then, have been obtained after the withdrawal syndrome had reached a very low level. Since these animals drank the morphine solution when their physical dependence was negligible, this action may be considered a relapse. Five of the six experimental animals exceeded the maximum amount drunk by the control

animals, two by a very large amount (110 mg/kg during the 24 hour period). These rats consumed an appreciable amount (their first injection was only 20 mg/kg) of the normally refused alkaloid when they had the option of drinking plain water and when their physical dependence upon morphine was certainly of an extremely low magnitude. Even after 35 more days of abstinence in Experiment I, one rat drank 42 mg/kg and another drank 32 mg/kg. These results and the results of the third preference test (after two weeks abstinence) appear to be a relapse by these animals to the use of morphine.

The results of these experiments are not inconsistent with the proposed analysis of the phenomena of addiction. There is, however, a large individual variation in the response of the animals to this procedure. There is also variation in response to morphine by human subjects (37). Since the response to morphine is largely the pharmacological effect of the drug on the physiological functioning of the subject, the individual variation in response to morphine may be dependent upon physiological variation between individuals.

One highly important source of physiological variation between individuals lies in the functioning of the

endocrine system (12). Adrenal activity has already attracted the interest of some investigators of the problem of addiction (23). This possibility seemed worthy of investigation.

Two lines of evidence pointed to activity of the pituitary-adrenal axis as an important factor in individual variation in the response to morphine. First, severity of the withdrawal symptoms seems to be correlated with activity of the pituitary-adrenal axis (37), and it has been shown that Cortisone and ACTH "do not alleviate morphine abstinence changes; in fact these agents may intensify them" (37, p. 37). If Cortisone and ACTH do intensify the withdrawal symptoms, then within the normal range of endocrine activity, animals with the most active pituitary-adrenal system might suffer the greatest withdrawal symptoms. According to the analysis presented previously, withdrawal symptoms provide the motivation for learning, and, consequently, these animals should learn better. Addictive liability might, therefore, be correlated with activity of the pituitary-adrenal system.

Another line of evidence comes from conditioning experiments. Avoidance conditioning seems to be facilitated by activity of the pituitary-adrenal system. Hypophysectomy, for instance, makes the acquisition of conditioned avoidance

responses extremely difficult (1, 2). On the other hand, "emotional" animals condition better than apathetic animals (29), and "emotionality" has been correlated with hypertrophy of the thyroid, adrenal, and pituitary glands (39). Injection of ACTH during conditioning of an avoidance response in rats significantly prolonged the subsequent extinction rate (22).

It seems, therefore, that activity of the pituitary-adrenal system may facilitate the acquisition of an avoidance response and may be correlated with more severe withdrawal symptoms. Either of these phenomena would, according to the proposed analysis of the problem, enhance the addictive liability of the subject. To test this possibility, post mortem extirpation of the adrenal and pituitary glands of the experimental animals (those receiving escape training) was performed. It was not possible to perform a biochemical assay on these organs, but activity of the endocrines is correlated with their weight. This is a crude measure but no alternative was available. The weights of the endocrines were expressed as a per cent of the body weight of the animal. Rank order correlations between the adrenal index (wt. as percent of body wt.) and the amount of morphine solution consumed on each preference test were then computed. Similar

correlations between the pituitary index and consumption of morphine were computed. The results are given in Table 3.

Table 3

Correlations between Endocrine Indices and Preference Test Scores of Escape Trained Animals[a]

Preference tests	Experiment I		Experiment II	
	Pituitary	Adrenal	Pituitary	Adrenal
Training tests				
1	.00	+.50	--[b]	--[b]
2	-.32	+.67	+.24	+.64
Abstinence tests				
1	-.32	+.67	-.27	+.53
2	+.10	+.80	--[b]	--[b]
Correlation of % pituitary with % adrenal	+.50		+.31	

[a]None of these correlations are statistically significant.

[b]If no animal exceeded 15 cc. on a given test, it was assumed that the small dispersion and group size did not justify computing a correlation.

From inspection of the table it is apparent that there is little consistent correlation between the pituitary

index and morphine consumption during the preference tests. The adrenal index, however, is consistently positive, except for the two instances not computed. Although none of the correlations in Table 3 are statistically significant, the trend of the adrenal index and morphine consumption is in the direction that would be expected from the preceding analysis.

CHAPTER VI

EXPERIMENT III: VARIATION OF WITHDRAWAL

Introduction

Experiments I and II support the hypothesis that the withdrawal syndrome is a motivating state of affairs. It follows, then, that a change in the withdrawal symptoms would constitute a change in the motivation of the subject. From experimental variation of the withdrawal syndrome, a variation in learning the instrumental act by the subjects might be expected, which in this case would be reflected by scores on the preference tests. The major hypothesis of this experiment is that a variation in learning the instrumental act, as reflected in test scores, may result from manipulation of the withdrawal syndrome. A minor hypothesis, partially confirmed by Experiments I and II, is that there is a correlation between the adrenal index and liability to addiction.

Manipulation of the withdrawal syndrome is a formidable task, for the physiological reactions to opiates are

complex. Tolerance, physical dependence, and withdrawal symptoms all tend to vary in an interdependent way. It has been postulated (10, 37) that these manifestations are merely different aspects of the same process and that one assumption can account for these different observations. The desired pharmacological actions of opiates depend upon their depressant effects upon the central nervous system. If it is assumed that the normal biochemical processes of the nerve cells can, over a period of time, counteract the depressant effect by reorganization of the cell metabolism to produce a "hyperirritability," then the observed phenomena of tolerance, physical dependence, and withdrawal symptoms are easily explained. Tolerance is the balance achieved between "hyperirritability" and the depressant effects of opiates. Physical dependence is the necessity for maintaining this balance to prevent expression of the "hyperirritability." Expression of the "hyperirritability" is observed as the phenomena of withdrawal symptoms.

> Repeated, regular administration of morphine is associated with the development of "masked" hyperirritability of certain internuncial neuron systems throughout the neuraxis, and possibly with increased metabolic requirements of skeletal muscle. When morphine is withheld, these changes become manifest and autonomic and pituitary-adrenal homeostatic mechanisms become mobilized. . . . Within limits, the

> intensity of this artificially induced need varies with the dosage and duration of morphine administration . . . . as tolerance develops, progressively larger doses must be used [to obtain the original effects of morphine] . . . . A "vicious cycle" is therefore induced, during the course of which the pharmacogenic need for the drug becomes intensified progressively (37, p. 46).

It can be seen from the above discussion that withdrawal symptoms cannot be varied alone. Variations in tolerance, physical dependence, and withdrawal effects probably occur together. The greater the tolerance and physical dependence, the greater are the withdrawal symptoms. Yet, withdrawal symptoms can be produced only at some cost to the tolerance and physical dependence of the subject, unless a very large dosage of morphine is used to terminate the withdrawal syndrome. It is likely that the procedure of Experiment III changes tolerance, physical dependence, and withdrawal effects simultaneously. This concomitance is inherent in the unitary nature of these three phenomena and does not invalidate the argument that variation in withdrawal symptoms represents a variation in motivation of the subject.

Apparatus and Subjects

Thirty-nine female Sprague-Dawley rats weighing between 185 and 250 grams each served as subjects. The apparatus and location of Experiments I and II were used.

Initial Procedure

A pre-experimental preference test was administered prior to the preliminary injections. Starting at 20 mg/kg and increasing 5 mg/kg/day, all animals were given daily intraperitoneal injections of morphine hydrochloride for 29 days. On the 29th day, the animals received 160 mg/kg. Nine animals died during the preliminary injections. The remaining 30 animals were randomly assigned, ten to group I and twenty to group II. Group I received the same treatment that the experimental groups of Experiments I and II received. In this group (I), the withdrawal motivation was allowed to develop to a relatively high level every three days and at this time M was presented.

The other group of 20 animals (II) received identical treatment except that, in an attempt to cause diminution of the withdrawal syndrome, the 20 animals of this group were given subcutaneous injections of a very small amount (2 mg.) of morphine at three different times during the training cycle. Injections were given approximately 6 1/2 hours and 1 1/2 hours prior to presentation of M and the remaining injection was given approximately 8 hours after the removal of M. The two injections given prior to the presentation of M were designed to reduce the withdrawal motivation.

The third injection was given during the W period to reduce the presumed withdrawal distress. This would minimize any possible negative reinforcement of drinking water which might occur from association of withdrawal distress with W.

Preference tests. The preference tests of this experiment were identical in procedure and timing with the preference tests of the previous experiments, except fifteen training trials were given all groups and therefore an additional preference test was given after the fifteenth training trial.

Results of the first preference test. Comparison of the two treatment groups (Group I and Group II) showed the difference in total morphine intake (oral plus injected) to be nonsignificant for the two groups; however, the injected group (Group II) drank significantly more M than the non-injected group ($p = .05$). This was unexpected and contrary to the original assumptions. Re-evaluation of the procedure in terms of these results made it seem possible that the small injections given to the injected group were reversing the tendency toward loss of tolerance and physical dependence which would normally occur during the periods between the M training trials and that this was more important than the possible diminution of withdrawal symptoms. Accordingly,

the procedure was modified for half the injected group.

Modified Procedure

Animals which drank less than 20 cc. of M on half their training trials prior to a given preference test were omitted from the statistical computations for that particular test but continued in the experiment. M consumption on the training trials tended toward a bimodal distribution. Very few animals drank only slightly more than 20 cc. If they exceeded this figure, most did so by a relatively large amount. It was assumed that only the plus 20 cc. group was receiving enough morphine to maintain physical dependence (and thus withdrawal symptoms) from trial to trial. Thus, only the plus 20 cc. group was receiving escape training.

Due to failure of some animals to consume 20 cc. on half their trials and to deaths, the number of animals in each group was reduced. Fifteen animals in the group receiving injections met these criteria. Seven were transferred to a new group, group IIb. Group I continued to receive the standard, non-injected escape treatment. Group IIa (remainder of group II) continued to receive injections on the schedule indicated previously. Group IIb was put on a modified injection schedule to make the distribution of

injections more uniform over the time between M trials. The injection which, on the old schedule, was made just prior to presentation of the M was removed and placed half-way between the other two injections. Thus, the longest time interval between injections in the new group (IIb) was only 17 hours (excluding the time M was available), whereas there was a 34 hour interval between injections in the original schedule. If the injections were acting to reverse the tendency toward loss of tolerance and physical dependence, then it seemed possible that the new schedule might be more effective in preventing this loss than the original schedule.

Results

Table 4 gives the sum of ranks, mean rank, and significance of the obtained differences among the groups of Experiment III. All differences among the groups in total amount of morphine received (oral plus injected) were statistically nonsignificant. All differences between the injected groups (IIa and IIb) were also nonsignificant, although the sum of ranks was lower for group IIb on all preference tests. The significance levels were all computed with the Kruskal-Wallis H test (34).

The difference between the combined injected groups

Table 4

Significance of Rank Differences of Preference Test Scores of Experiment III

Preference tests		n	Sum of Ranks	Mean Rank	p of this hypothesis: injected = noninjected [a]
Training tests	I	8	122.0	15.3	
1	II	14	131.0	9.4	.05
	I	8	144.0	18.0	
	IIa	8	72.5	9.1	
2	IIb	7	59.5	8.5	.005
	I	8	131.5	16.4	
	IIa	8	85.0	10.6	
3	IIb	7	59.5	8.5	.05
Abstinence tests	I	8	123.5	15.4	
	IIa	8	87.5	10.9	
1	IIb	7	65.0	9.4	.08
	I	8	101.0	12.6	
	IIa	8	108.5	13.6	
2	IIb	7	66.5	9.5	NS

[a] All differences between groups IIa and IIb are nonsignificant.

(IIa and IIb) and the non-injected group approached significance on the first abstinence test (p = .08). The only two animals which showed a definite relapse were in group IIb (see Table 8 in appendix). One animal consumed 57 cc. M, the equivalent of 98 mg/kg, and the other 74 cc. M, the equivalent of 160 mg/kg. Even after 29 more days of abstinence, one animal in group IIb drank 71 mg/kg.

One animal's behavior differed sufficiently during separation and marking of the animals prior to the initial injections that a note was made that it seemed to suffer "emotional diarrhea." This is the animal which consumed the largest amount of M on the first abstinence test. Four animals were rated as extremely depressed by the first injection (20 mg/kg) during the preliminary injections. These animals did not survive the preliminary injection period.

Correlations between the adrenal index and morphine consumption were computed and are given in Table 5.

Discussion

The ultimately small number in each treatment group made it difficult to secure statistically reliable differences and correlations among the groups. It was possible to demonstrate, however, that injection of a small amount of

Table 5

Correlation of Adrenal Index and Preference Test Scores[a]

	Training tests			Abstinence tests	
Group	1	2	3	1	2
I	+.41	--[b]	-.12	--[b]	--[b]
IIa	+.49	+.55	+.11	--[b]	--[b]
IIb	+.27	+.03	+.62	+.56	+.30

[a]None of these correlations are statistically significant.

[b]If no animal exceeded 15 cc. on a given test, it was assumed the small dispersion and group size did not justify computing a correlation.

morphine (which did not change the total morphine intake significantly) could significantly improve learning of the instrumental act by the injected animals as shown by the various preference tests (see Table 4). The difference between the injected and non-injected groups even approached significance on the first abstinence test ($p = .08$). It seems likely that the injections acted to reverse the tendency toward loss of tolerance and physical dependence so the

motivation of the animals was maintained from trial to trial.

Comparison of the results of the two abstinence tests shows that some animals relapse on both tests. A few, however, relapse on only one test. An uncontrolled factor which may be responsible for this variation is the stage of the four-day estrous cycle the rat was in at the time of presentation of M. Sexual drive, according to the proposed analysis, might activate the CR, so that motivation to relapse would presumably vary somewhat with the phase of the estrous cycle of the rats.

Valid generalizations from one case may possibly be made, but at best they are always questionable. Nevertheless, it is interesting that the one animal out of 39 which was behaving so differently that a notation was made ("emotional diarrhea") also turned out to be the animal (one out of 22) that consumed the most M on a relapse test. This is consistent with the proposed analysis which indicates emotional drive stimuli may operate the CR during relapse.

The correlation of adrenal index and test scores is in the expected direction but again is not statistically significant. However, the fact that such positive correlations have been obtained on three separate experiments lends support to a belief in their validity.

Summary

Small amounts of morphine injected at various intervals significantly improved learning of the instrumental act by the injected animals, even though the total morphine intake of these animals was not significantly increased over the intake of the non-injected animals. Apparently, the injections acted to maintain the motivation of the animals from trial to trial.

There seems to be a correlation between the adrenal index and liability to addiction by morphine, although the strength of this conclusion depends upon the consistency of appearance of small positive correlations rather than on the statistical significance of any of them.

CHAPTER VII

GENERAL DISCUSSION

Completed Research

Results from our three experiments tend to support the assumption that withdrawal distress is a motivating state of affairs and that a means of escaping this distress is learned as an instrumental act. Experiments I and II emphasize the performance of an instrumental act as a crucial factor in the development of addiction. Rats which could instrumentally escape their distress by drinking a morphine solution learned to perform this action even though it was originally avoided. Other rats which received the same amount of morphine without performing an instrumental act showed no evidence of a change in behavior toward the morphine solution.

The apparent paradox of hospital patients who receive opiates without becoming addicted is no paradox when viewed in the context of instrumental conditioning. No instrumental act is performed by the patient. He never learns that some

action on his part would result in escape from his distress (withdrawal distress), and, therefore, he never becomes addicted (conditioned) to using the drug.

Interpretation of the results of Experiment III is less clear. However, the injection of small amounts of morphine appears to have significantly improved learning of the instrumental act by the injected animals, even though the total intake of morphine by these animals was not significantly increased over the intake by non-injected animals. Apparently, the injections acted to maintain the motivation of the animals from trial to trial. If this interpretation is correct, then Experiment III was successful in varying the aversive stimulus situation and this resulted in a variation of conditioning.

The injected animals (Groups IIa and IIb combined) which were believed to be more highly motivated than the non-injected animals (Group I), drank the most M during the training preference tests and also showed a higher relapse rate (consumption of 15 cc. or more M on an abstinence preference test) although this latter difference was not statistically significant.

Suggestive but inconclusive evidence on individual variation in susceptibility to addiction parallels the

observation of individual variation in response to laboratory conditioning experiments. Emotional subjects tend to condition more easily in standard conditioning situations and they also seem to show greater liability to addiction than the more apathetic subjects. Hirsh (11, p. 100) states that the "high strung" run greater risks of becoming alcoholics.

Since relapse is an essential aspect of human addiction, one of the most interesting results obtained from these experiments is the demonstration of relapse by animals. A search of the literature revealed no instance of animal relapse, and opinion has been divided on whether or not an animal may become an addict (18, 30). Examination of the data on the amount of morphine consumed (see Tables 6, 7, and 8 in the Appendix) shows a few rather outstanding examples of heavy consumption on the abstinence tests. These would seem to be instances of relapse. It is believed that relapse by some of the animals in this project is the first demonstration of this phenomenon in animals.

It is undeniable, however, that most of the animals did <u>not</u> relapse. Our apparent inability to produce addiction in so many of the experimental animals undoubtedly affected our statistical tests for relapse because relapse can hardly occur if addiction has not been produced. Obviously, the

problem needs further study to determine those conditions under which addiction can be produced most reliably and the conditions under which relapse is most likely to occur.

Addiction in humans tends to extend over long periods of time with relapses occurring years after a period of abstinence was begun. Yet, examination of the data on the amount of morphine consumed during the abstinence tests (see Tables 6, 7, and 8) shows a decreasing preference for the M during abstinence. This index of preference is, of course, strongly dependent upon the retention of a learned instrumental act. For rats, this act is difficult to retain without extinction occurring during the abstinence periods. Obviously, this is much less true for man. How, then, may we account for this difference in behavior?

Several major differences between man and rat combine to facilitate the retention of the instrumental act by man. First, man has a greatly superior learning ability which is aided by his superior instrument of learning (i.e., language) which serves to unify his experiences and make possible goal-oriented behavior which can span time intervals.

> Various animals have been studied in "delayed reaction" experiments in which the animal must wait for a period of time between perception of a goal object and actual discovery and attainment of it.

> Summarizing studies on chimpanzees, Yerkes and Nissen noted their dependence on spatial cues. When the experimenter eliminated the possibility of using spatial cues, delayed response became extremely difficult or impossible for most chimpanzees. . . . Yerkes concluded that the difficulty was traceable to the fact that the chimpanzee lacked a "symbol or representative process" comparable to human words. A chimpanzee cannot say to himself, "The reward is under the green box," and remember this days or weeks later, as a human subject can (28, p. 466).

In the present series of experiments spatial cues are minimized by random presentation of the drinking tubes. Retention of the instrumental act in this case, depends upon association of the taste of the M with escape from withdrawal distress. Nevertheless, the principle is the same for both cases, i.e., language facilitates retention of an association over a period of time.

From another viewpoint, language is still more vital in the process of addiction. Lindesmith (18) has already pointed out that there is a linguistic factor involved in restructuring of the ego ("definition of oneself as an addict") which occurs in human addiction. This restructured ego acts to maintain the attitudes and relationships developed during the process of addiction.

Secondly, man can use a much more effective instrumental response (injecting morphine directly into a vein) which permits a more effective (more rapid) escape and thus

is much more reinforcing for the instrumental act. Finally, the animals in these experiments received only a few learning trials, whereas the human addict may have had thousands of training trials by the time he reaches a treatment center, so he has developed a tremendous habit strength.

Results of this research program are not inconsistent with the proposed analysis of the problem of addiction. It is considered advantageous that this general theory of addiction is based upon the known physiological responses to the addicting drugs and that it provides a rationale for many otherwise discrete phenomena of addiction.

Future Experimentation

The technique used in this research program is highly time-consuming and not very efficient. It is conceivable that a shorter and more precise technique might be evolved which would allow animals to operate a device (i.e., perform an experimental act) which would deliver a small amount of morphine solution directly into a vein. It is expected that an animal in withdrawal distress would rapidly learn to operate the morphine-delivering device and that this action would become a conditioned response, just as an animal in a Skinner box learns to escape hunger stimuli by pushing a bar.

It has been demonstrated (6) that strains of emotional and non-emotional rats (i.e., by the criteria employed) may be selectively bred. This fact might be used to investigate further the possible differences between emotional and non-emotional subjects with respect to susceptibility to addiction. A further possibility lies in the difference between strains of animals. Wild rats, for instance, have adrenal glands three to four times larger than laboratory rats (24) and are more emotional than laboratory strains of rats (32, p. 311). We would expect, then, that the wild rat might be more susceptible to addiction than the laboratory rat.

Finally, a similar investigation should be made in the area of alcohol addiction.

A Theoretical Interpretation of Some of the Facts of Addiction

Detailed application of the proposed general theory of addiction to all the facts of addiction would seem to be somewhat premature, considering the fact that experimental investigation has been limited to a few aspects of morphine addiction. It is, nevertheless, interesting to attempt to apply the theory to a few of the more notable facts of

addiction and thus obtain a preliminary estimate of the "goodness of fit" between theory and fact.

Cultural differences in alcoholism. Evidence indicates a difference in the alcoholism rates of different cultures (3). This difference is usually ascribed to differences in the social norms of the culture. Diethelm, for example, reports a study of alcoholism in New York's Chinatown. The study of this ethnic group is interesting because "the incidence of chronic alcoholism is low and alcoholism as a social problem is relatively unimportant" (3, p. 225).

> The children . . . soon learned a set of attitudes that attended the practice [of drinking]. While drinking was socially sanctioned, becoming drunk was not. The individual who lost control of himself under the influence of liquor was ridiculed and, if he persisted in his defection, ostracized. His continued lack of moderation was regarded not only as a personal shortcoming, but as a deficiency of the family as a whole. . . . in Kwangtung this very often meant the entire village (3, p. 186).

It would seem that an essential difference between cultures having a high incidence of alcoholism and those cultures having a low incidence of alcoholism might lie in social norms which fall into two general categories. First, social norms which act to enhance or diminish the probability of escape training would be important. Secondly, those social norms which act to provide motivation for temperance

or abstinence versus indulgence would act to affect the alcoholism rate.

Individual variation in susceptibility to alcoholism. Hypoglycemia, or low blood sugar, results in feelings of anxiety and apprehension. It might be expected, then, that within the normal variation of blood sugar level, those subjects at the lower extreme of the normal range would also experience more anxiety and apprehension. Since these stimuli form part of the CS for taking an alcoholic drink, it seems reasonable that those subjects who suffer from hypoglycemia might condition more easily. A concomitance of hypoglycemia and alcoholism has been reported in the literature and the desire for a drink has been correlated with drops in the blood sugar level (33). These subjects are apparently responding to the drive stimuli produced by the hypoglycemia and those drive stimuli are experienced as anxiety and apprehension, which according to the proposed analysis, are part of the CS which may operate the CR of taking an alcoholic drink.

"Craving." A tendency to perform the CR of taking an alcoholic drink or a "fix" would probably be verbalized by the addict in terms which have been labeled "craving." Wikler (37) notes that craving intensifies and withdrawal-

like symptoms occur in some post-addicts whenever availability of narcotics increases. He refers to this as a "pharmacogenic need" which has been "reactivated." An alternative explanation might be that there are perceptual or ideational stimuli associated with the increased availability of narcotics and these stimuli act as CS to increase the motivation to relapse. When this motivation to relapse is in conflict with his motivation to abstain, or with the restrictions imposed by the situation, then this conflict situation produces an emotional state capable of producing responses which resemble withdrawal symptoms. These response-produced stimuli may serve as additional CS for producing the CR, thus increasing the conflict situation in a positive feedback cycle.

Secondary conditioning. It is an odd fact of opiate addiction that an addict who is off the drug may show what has been called a "needle yen." He may like to "play with the needle, or to prick himself with it, or to receive sterile injections" (18). Physiological saline injections may also produce relief in addicts who believe they are receiving morphine (18). Spragg (30) has noted a similar effect with chimpanzees, and this is commented upon by Miller in these words:

> Incidental observations suggested that temporary relief from withdrawal symptoms could be produced by injections of physiological saline. Such relief must have been the product of learning (32, p. 462).

In terms of our analysis, the needle and injection have previously been associated with diminution of the aversive stimulus situation and the drive stimuli of anxiety. Thus, the needle and injection have presumably acquired the power of secondary reinforcers. Because of previous association of needle, injection, and the reduction of drive stimuli, the drive stimuli of anxiety may be reduced by the needle and injection which act to reduce the stimuli of anxiety by the process of secondary reinforcement.

Injection "thrill." The so-called thrill which occurs upon intravenous injection of opiates is probably an emotional effect which occurs as a result of immediate relief from the various drive stimuli which opiates reduce. Wikler (37, p. 35) notes that "the relief of . . . [abstinence] symptoms is intensely pleasurable." Lindesmith makes a similar observation. "The satisfaction of the addict's craving for drugs may itself be called a pleasure. The relief from withdrawal distress which an injection gives may also be so designated" (18, p. 159). These views are consistent with the proposed analysis of the problem of

addiction.

The "de luxe" dose. It is routinely observed that the opiate addict will, whenever possible, increase the dosage of opiate far more rapidly than is found necessary in purely medical usage. Lindesmith says the additional amount above what is necessary for comfort has been called the "de luxe" dose. He also says, "It may be possible by resolute determination to stabilize drug consumption at a low level, but the trend towards a progressively larger dosage is probably a distinguishing characteristic of addict behavior" (18, p. 61).

It is possible that the small amount of drive stimuli which presumably remains after performing the CR may continue to activate the CR because the addict has built up a very strong habit strength. The small amount of drive stimuli and the strong, easily activated habit combine to evoke the CR and the addict then takes more of the drug, or, possibly, learns to take larger initial doses to achieve a satisfactory suppression of the drive stimuli with one dose.

CHAPTER VIII

SUMMARY

Addiction to opiates, alcohol, and other compulsion-producing drugs is a phenomenon which presents a grave challenge to several fields of science. From widely differing approaches to the problem have come a large number of ingenious theories, yet development of an adequate theory of addiction is still in the preliminary stages. Of the many proposed theories of addiction, none is generally accepted in the field today.

A review of the facts of addiction has suggested a new approach to the problem. A parsimonious integration of the facts of addiction is possible on the basis of a learning theory. According to this view, the addict has become conditioned toward use of his drug.

Escape stage. A subject suffering the distress of hangover or withdrawal takes the first step toward addiction when he learns his distress can be escaped by using more of the drug. This instrumental act (of using the drug) is

rewarded by a "pharmaceutical escape" from his distressing situation. This is a conditioning situation, specifically, instrumental escape conditioning.

Avoidance stage. The escape response rapidly becomes an avoidance response by the process of classical conditioning. Taking the drug not only allows escape from a distressing situation, but at the same time the pharmacological action of the drug reduces several other drive stimuli as well (stimuli from anxiety, pains, aches, sexual stimuli in the case of opiates, etc.). These drive stimuli become "signs" which are conditioned stimuli within a classical conditioning situation. After a number of trials, performance of the instrumental act (of taking the drug) no longer depends upon escape from distress of a hangover or withdrawal syncrome but may now be initiated in the highly conditioned subject by stimuli from anxiety, pains, aches, etc., which act as conditioned stimuli.

Emotional dependence. The conditioned stimuli of anxiety, pains, aches, etc., occur as part of normal living, and the well-conditioned subject responds by performing the instrumental act of taking the drug. This is the behavior which is labeled "emotional dependence" upon the drug.

Relapse. The conditioned drive stimuli and habit

strength (once established) both exist independently of any physiological effect of the drug. The tendency to respond with the instrumental act has, therefore, become autonomous. It seems reasonable, then, that if motivation to abstain should falter, relapse would likely occur.

Part of this theoretical framework was tested on animals using morphine as representative of the compulsion-producing drugs.

Experiment I tested the hypothesis that an instrumental act which allowed escape from withdrawal distress would be learned as a conditioned response. Withdrawal distress was produced in 12 rats by an initial series of injections which were then stopped. Six rats could escape their distress by drinking a morphine solution. The other six rats performed no instrumental act of escape but were injected with morphine equal to the amount drunk by the escape group. Despite equal morphine intake, only the escape-trained group showed a significant increase in preference for the morphine solution. Even after the physiological effects of the drug had become negligible (after 14 days abstinence), the escape group still showed a statistically significant preference for the morphine solution, i.e., they relapsed.

Experiment II, a similar experiment using quinine and

alum solutions, demonstrated that association of the distinctive taste of the solution with reduction of thirst drive stimuli could not account for the increase in preference.

Experiments I and II support the hypothesis that withdrawal distress is a motivating state of affairs. Varying the severity of the withdrawal symptoms, then, should vary the motivation of the subjects, which should be reflected in a difference in learning to prefer the morphine solution. Experiment III used three groups of rats. One group received the same escape training given in Experiment I. The other two groups received small injections of morphine at various intervals. The injected animals learned the instrumental act significantly better than the non-injected animals, even though the total amount of morphine (oral plus injected) did not differ significantly among the groups. Apparently, the injections acted to minimize loss of tolerance and physical dependence between trials so the motivation of the animals (i.e., withdrawal effects) was maintained better in the injected groups.

The results of these experiments lend some support to the proposed general theory of addiction. Relapse in animals was demonstrated for what is believed to be the first time.

The application of this analysis to a few of the more striking facts of addiction and possible techniques for future experimentation are discussed.

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APPENDIX

Table 6

Ccs. of Morphine Solution Consumed on Preference Tests of Experiment I

	Training Tests			
	1		2	
	Escape Group	Control Group	Escape Group	Control Group
	7.0	1.0	4.5	1.0
	31.0	1.0	4.5	0.5
	45.0	1.0	44.0	1.0
	34.0	1.5	61.0	1.0
	28.0	0.5	4.5	1.0
	1.5	1.0	2.0	1.0
Mn	24.5	1.0	20.5	0.9
Md	29.5	1.0	4.5	1.0

	Abstinence Tests			
	1		2	
	Escape Group	Control Group	Escape Group	Control Group
	3.5	0.5	22.0	7.5
	3.5	1.0	2.0	---[a]
	38.0	1.0	16.0	1.0
	40.0	1.5	4.0	1.0
	2.5	0.5	---[a]	---[a]
	0.5	0.5	1.0	0.5
Mn	14.7	0.8	9.0	2.5
Md	3.5	0.8	4.0	1.0

[a]These animals died prior to this test.

Table 7

Ccs. of Test Solution Consumed on Preference Tests of Experiment II

Training Tests

	1			2		
	Morphine	Quinine	Alum	Morphine	Quinine	Alum
	4.0	2.0	2.0	8.5	2.0	3.0
	6.0	0.5	0.5	11.0	0.5	0.5
	0.5	0.5	1.0	7.0	0.5	1.0
	7.0	0.5	0.5	4.0	0.5	0.5
	6.0	0.5	0.5	23.5	0.5	2.5
	5.0	0.5	___	11.0	0.5	___
Mn	4.8	0.8	0.9	10.8	0.8	1.5
Md	5.5	0.5	0.5	9.7	0.5	0.8

Abstinence Tests

	1			2		
	Morphine	Quinine	Alum	Morphine	Quinine	Alum
	4.0	1.0	0.25	2.5	0.5	0.5
	4.5	0.5	0.5	5.0	0.5	1.0
	0.5	0.5	1.0	0.5	0.5	0.5
	0.5	0.5	1.0	0.5	0.5	0.5
	3.5	0.5	1.0	0.5	0.5	---[a]
	24.5	0.5	___	2.0	---[a]	___
Mn	6.2	0.6	0.8	1.8	0.5	0.6
Md	4.8	0.5	1.0	1.25	0.5	0.75

[a]These animals died prior to this test.

Table 8

Ccs. of Morphine Solution Consumed on Preference Tests of Experiment III

	Training Tests								
	1			2			3		
	I	IIa	IIb	I	IIa	IIb	I	IIa	IIb
	20.0	16.0	2.4	12.5	12.5	2.2	10.5	22.0	10.0
	1.8	32.0	45.0	1.9	16.5	59.0	2.0	8.5	55.0
	7.0	5.0	11.0	8.0	15.0	12.5	10.0	17.0	58.0
	5.0	26.0	2.1	5.7	14.5	17.0	3.6	36.0	25.0
	1.6	4.8	20.0	4.2	6.2	20.0	4.4	10.0	15.0
	5.0	29.0	16.0	4.4	22.0	15.0	3.2	25.0	24.5
	2.0	4.0	13.0	6.0	9.0	14.0	8.0	6.8	10.0
	4.0	1.4[a]		8.0	16.0		102.0[b]	33.0	
Mn	5.8	16.7	15.6	6.3	14.0	20.0	18.0	19.8	28.2
Md	4.5	16.0	13.0	5.8	14.8	17.0	6.1	19.5	25.0

	Abstinence Tests					
	1			2		
	I	IIa	IIb	I	IIa	IIb
	3.8	15.0	3.5	2.0	7.5	2.0
	1.7	2.6	57.0	2.1	1.5	41.5
	3.4	9.0	8.7	2.5	3.8	3.9
	5.1	9.1	74.0	3.2	2.2	16.0
	4.5	2.8	4.5	3.0	1.7	8.4
	3.2	4.9	5.1	6.7	2.6	3.0
	2.8	2.9	2.7	2.5	2.4	2.0
	3.3	9.9		7.5	8.6	
Mn	3.5	7.8	22.2	3.7	3.8	11.0
Md	3.6	7.4	5.1	2.8	2.5	8.4

[a]Omitted from statistical computation for this test only (See Chapter VI, "Modified Procedure").

[b]This figure is correct. The author has no ready explanation for it.

Table 9

Total Mg. Morphine (Oral plus Injected)

Consumed during Experiment III

	Trials 1 to 5			Trials 1 to 10		
	I	IIa	IIb	I	IIa	IIb
	281	135	176	536	305	365
	90	163	185	187	371	405
	134	206	180	278	414	385
	153	163	176	314	349	351
	96	91	169	252	250	392
	222	157	177	470	340	376
	134	192	160	285	336	361
	126	34[a]	___	207	152	___
Mn	154.5	158.1	174.7	316.1	314.6	376.4

	Trials 1 to 15		
	I	IIa	IIb
	785	475	310
	291	562	639
	415	582	594
	444	523	533
	418	741	576
	651	524	573
	427	520	551
	335	402	___
Mn	470.8	541.1	539.4

[a]Omitted from statistical computation for this test only (See Chapter VI, "Modified Procedure").