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Drugs as Reinforcers in Monkey and Man

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SINCE the 1920s rhesus monkeys have been used for investigations of physiological dependence on narcotic analgesic drugs. The similarity of these nonhuman primates to man in their response to single and repeated administration of narcotic analgesics lends credence to their use in investigations of mechanisms of tolerance and physiological dependence. The similarity between man and monkey in response to narcotic analgesics has led to the development of procedures in which the monkey is used to evaluate the capacity of new drugs to produce physiological dependence of the morphine type. The goal of this research has been to find a drug which retains the analgesic properties of morphine but lacks its capacity to produce physiological dependence. Thus there is an extensive history of primate use in investigations of the basic mechanisms of physiological dependence and tolerance as well as in attempts to develop methods for predicting the capacity of a drug to produce physiological dependence of the morphine type in man.

The use of primates in such pharmacological research has set the stage for the use of animals in the study of the behavioral aspects of drug abuse. One goal of this symposium has been to critically examine the relevance of the data generated by the laboratory study of drug-taking behavior of animals to the societal problem of drug abuse.

There are three obvious ways in which an animal model of drug-taking behavior may be relevant to an analysis of the problem of drug abuse in man: 1) as a means of predicting a new drug's "abuse potential"; 2) as a means of assessing pharmacological and environmental factors which might diminish drug-taking behavior and therefore have possible therapeutic application; and 3) as a means of investigating the basic biobehavioral mechanisms underlying drug-taking behavior.

There are a number of practical and ethical advantages in using animals in the study of drug abuse, including the range of experimental manipulations ethically possible and the experimental rigor which can be imposed. On the other hand, we must establish the validity of animal models if we wish to extrapolate conclusions based upon data from animals in the laboratory to man in his natural environment. In this paper I will review some research from my laboratory to illustrate some of the assumptions and problems inherent in attempting to validate an animal model of drug abuse.

I. Drug Reinforcement Studies as a Means of Predicting Abuse Potential

One of the major areas in which the study of drugs as reinforcers appears to have practical application is in the prediction of a new drug's abuse potential. Pharmaceutical companies, for both ethical and economic reasons, are extremely interested in being able to predict whether a drug has significant abuse potential before it is marketed. Governmental agencies charged with the responsibility of drug control also look to the laboratory for guidance. In November of 1974 The World Health Organization sponsored a 6-day meeting entitled, "Scientific Group on Progress in Methodology of Evaluation of Dependence-

liability of Drugs," to review and evaluate methods for the assessment of a drug's abuse potential. A report of this meeting is forthcoming so I will not go into a detailed evaluation of the methods currently used to predict abuse potential. Rather I will examine some of the assumptions in studies of drugs as reinforcers to predict human drug-taking behavior. Further, I will present some data from our attempts to measure directly the reinforcing effects of drugs in man as a means of validating the animal model.

Let us first examine some assumptions underlying the use of preclinical studies of drugs as reinforcers in seeking new drugs with high therapeutic efficacy and low abuse potential. The first assumption is that certain drugs have as an inherent pharmacological property the capacity to serve as positive reinforcers and that other drugs are either neutral or have the pharmacological property of serving as negative reinforcers. If we are using animals we must also assume that the drug will produce the same behavioral activity in man. In the present context we are primarily concerned with the assumption that drugs which serve as reinforcers in animals will also do so in man. Finally, we must assume that a drug's abuse potential in man is based upon its ability to act as a positive reinforcer.

One way to evaluate the animal model is to test drugs with known abuse potential in man. Recent reviews of studies of drugs as reinforcers indicate that certain drugs with high abuse potential in man (*e.g.*, cocaine, amphetamine, opiates, and barbiturates) can serve as positive reinforcers in several animal species under a variety of conditions (12, 14). Other drugs known to have little abuse potential in man (*e.g.*, phenothiazines, certain narcotic antagonists) do not act as positive reinforcers but can act as negative reinforcers (3, 7).

This data indicates that those drugs which serve as postive reinforcers in animals are drugs which have been abused by man (12, 14). Further, drugs such as phenothiazines and narcotic antagonists which function as negative reinforcers in animals do not appear to be abused by man. In a general sense, it seems the assumptions cited are justified and that preclinical studies of drugs as reinforcers can be used to predict whether a drug will be abused by man. Yet, through the appropriate behavioral manipulations, it may be possible to make any behaviorally active drug serve as a positive reinforcer. We are limiting our predictions, however, to drugs which can serve as positive reinforcers in a broad range of experimental conditions. This is done for practical reasons since we believe that drugs of major concern are those that serve as reinforcers under a wide variety of environmental conditions in organisms with a wide variety of past histories. If a drug can serve as a reinforcer only under restricted environmental conditions in organisms with very esoteric behavioral or pharmacological past experience, one would infer that its abuse by man would be limited.

Under new federal drug laws in the United States (The Comprehensive Drug Act of 1971) psychotropic drugs are categorized into five schedules. Schedule I includes those drugs with high abuse potential which are currently not used in medical practice (*e.g.*, heroin, LSD). Drugs in Schedule I are restricted in their availability to licensed researchers. Schedules II through V include drugs which are currently used in medical practice. Differentiation of Schedules II through V is based upon the conception that drugs differ in their relative abuse potential. Drugs in Schedule II are presumed to have higher abuse potential than those in the lower Schedules. The correct scheduling of drugs is important because of the greater restrictions imposed upon drugs in the higher schedules. Drugs in Schedule II, for example, are controlled in their production quota by the federal government. The economic advantage to a pharmaceutical house of having a new drug scheduled in Schedule III as opposed to Schedule II is

considerable. Governmental agencies responsible for scheduling new drugs are therefore faced with important decisions. The possible consequences of scheduling a drug with high abuse potential into a lower schedule are obvious. Yet, placing a drug in a higher schedule than necessary may impede its appropriate use in patients. For these reasons, governmental agencies are looking to laboratory scientists to provide scientific support for scheduling new drugs in terms of their relative abuse potential. Procedures for comparing drugs in terms of their relative reinforcing effects might be useful in predicting its relative abuse potential. This assumes that drugs which serve as positive reinforcers vary in their efficacy as reinforcers and that this variance is correlated with their abuse potential. There is very little evidence at the present time to justify this assumption. At least, in part, this lack of data is due to the problem of measuring a drug's reinforcing effects independently of its other behavioral actions. (This issue has been discussed in previous papers in this symposium.) Let us assume for the moment that drugs do vary in their reinforcing effects and that we have procedures for reliably ranking drugs on this basis. One may still ask how important are the efficacy differences between drug reinforcers in determining the relative abuse potential of new drugs. As many presentations in this symposia have shown, the schedule of reinforcement is probably a more important determinant of the persistence and frequency of drug-reinforced behavior than the nature of the reinforcer. Thus, it seems unlikely that small differences in reinforcing efficacy would accurately predict the relative abuse liability of drugs in man. Clearly, nonpharmacological variables can have as much influence on the strength of drug reinforced behavior as differences in inherent properties of the drugs. On the other hand, there may be significant differences in the toxicity produced by drugs with equal reinforcing effects. Clearly this has practical importance and points to the need to study not only the drug-taking behavior, but as well, the biological and behavioral consequences produced by the drug.

One further assumption is that a drug's ability to act as a positive reinforcer is not linked in some manner to its therapeutic efficacy. The same problem has been faced by those attempting to develop an analgesic comparable to morphine but devoid of its capacity to produce physiological dependence. Only continued drug development and testing will allow us to evaluate this assumption.

A serious problem in attempting to validate animal models is the measurement of abuse of a new drug in man. Obtaining valid and reliable estimates of a drug's actual abuse in society is an enormous methodological problem. The precision possible in animal studies far exceeds that currently possible in measures of human drug abuse. Further, it is both unacceptable and inefficient to market a drug and wait for policemen and physicians to determine its frequency of abuse. One partial solution to this problem is to compare the results of animal studies of a drug with experimental investigations of the drug in man. Experimental investigations of the abuse potential of a new drug in human subjects rules out possible species differences in response to the drug and provides at least partial validation of predictions from animal studies.

Although drug-taking behavior has been extensively studied in animals, this direct approach to the problem of predicting abuse potential has rarely been utilized in man. With a few exceptions, the assessment of abuse potential has been based upon subjective judgments of institutionalized ex-addict subjects; these subjects are given a drug and then asked whether they like it and whether it resembles any drug they have every abused. In some instances mood scales purporting to measure a drug's ability to produce euphoria are used, on the assumption that a drug's euphorogenic properties are the basis of its abuse. Be-

cause of the differences in the design of studies with ex-addicts, the results are difficult to compare with the direct measures of reinforcing efficacy used in animal studies. In an attempt to minimize such problems, we conducted three experiments to investigate reinforcing efficacy of opiate drugs given orally to human subjects. There were two purposes; first, to investigate various strategies for measuring the reinforcing effects of drugs in man; and secondly, to compare the results obtained in man with those obtained in animals. The drugs were codeine, methadone, and pentazocine. Unpublished observations from my laboratory had shown that codeine, pentazocine, and methadone all could serve as positive reinforcers in rhesus monkeys. Each drug maintained responding under a 20-response fixed-ratio schedule across a wide range of doses. Physiological dependence upon methadone or codeine was not a necessary antecedent condition for these drugs to serve as positive reinforcers.

The abuse potential of codeine and methadone is well established. When methadone is administered intravenously many addicts prefer its effects to those of natural morphine-like drugs (8). It can also suppress opiate withdrawal. Codeine is also effective in the treatment of the opiate withdrawal syndrome. Further it is commonly used by heroin addicts when heroin is not available. Pentazocine is a weak opiate antagonist with analgesic activity of about one-third the potency of morphine (16). At the time our studies were being planned, the abuse potential of pentazocine was controversial. In studies at the National Institute of Mental Health Addiction Research Center, pentazocine was found to have low abuse potential in ex-heroin addict volunteers (4). On the other hand, there were scattered reports of its abuse in the medical literature.

Codeine (experiments 1 and 2) and methadone (experiments 2 and 3) were expected to function as positive reinforcers in man. Pentazocine would be predicted to function as a positive reinforcer on the basis of our research in animals, but not on the basis of human data.

The first experiment was carried out on an in-patient detoxification ward for heroin abusers in conjunction with Dr. Jerome Jaffe. Detoxification from heroin was accomplished by giving gradually decreasing doses of methadone over a period of 6 days. At the end of this detoxification period, subjects were told that for the next 4 days they could report to the nurses' stand every 4 hr to receive an experimental drug which "might make them more comfortable." In addition, they were given all pertinent information regarding the possible toxic consequences of the medication. The 17 subjects were divided randomly into three groups: group I received placebo capsules (N=6); group II received 50 mg pentazocine capsules (N=5); and group III received 50 mg codeine capsules (N=6). All capsules were identical in appearance but were kept in coded bottles for identification. Furthermore, the dispensing nurse did not know what the drugs were; she was instructed simply to give the subject the medication from their coded bottle and to record the time it was dispensed. Nurses and other ward personnel were discouraged from talking about the experiment.

The average number of times subjects requested medication over the four day period is shown in table 1. As would be expected, the frequency of requests for placebo rapidly declined. In contrast, the average number of daily requests for codeine or pentazocine remained close to the maximum (6) over the entire 4-day period. Therefore, both codeine and pentazocine were sufficiently reinforcing to maintain almost maximal frequency of medication requests.

In a second experiment, an attempt was made to determine the reinforcing efficacy of orally administered methadone, codeine, pentazocine, and placebo in out-patient addicts (13). A total of 120 names of males within the age range of 21 to 50 years were randomly selected from the waiting list for

TABLE 1

Average number of medication requests for placebo, codeine (50 mg) and pentazocine (50 mg) in hospitalized exheroin users

Medication Group	Days			
	1	2	3	4
Placebo N = 6	5.0	3.5	1.8	1.5
Codeine N = 6	5.3	5.0	4.6	5.3
Pentazocine N = 5	5.6	4.8	5.2	5.0

enrollment in the State of Illinois Drug Abuse Rehabilitation Program. Letters were sent to these potential subjects asking them to volunteer for a medical experiment. The letter assured them that their status in the treatment program was not contingent in any way on participation in this experiment. In addition, the letter informed them that they would receive medication for 5 consecutive days which might help them with their drug dependence problem. Ninety-four people responded to the letter and of these 6 were judged medically unsuitable because of the existence of a chronic disease condition necessitating treatment. From the 88 subjects selected 19 subjects were assigned to the methadone group, and 23 subjects were assigned to each of the other three treatment groups.

Doses of 50 mg of codeine, 50 mg of pentazocine, and 5 mg of methadone were placed in identical gelatin capsules. Placebo capsules contained 50 mg of dextrose. Eight capsules of each medication were placed in each of 10 individual plastic bottles which were labelled with code numbers and days 1 through 10. After a physical examination, those people accepted into the experiment were randomly assigned to one of the four medication groups. They were told that they should report to the clinic between the hours of 9 and 11 A.M., and that they would receive $2.00 per day to defray expenses. They were initially told that medication would be available for 5 consecutive days. When subjects reported to the clinic on days 2 through 5 they were asked to return the bottle given to them on the previous day, including any capsules which had not been ingested. To receive more medication they had to complete a 30-min paper and pencil test, provide a urine specimen, and be interviewed regarding the medication's effects. After completion of these tasks, subjects received their medication bottle containing eight capsules and were requested to take their first capsule in the presence of the dispensing nurse. They were instructed to take one or two capsules every 4 to 6 hr thereafter if they felt the medication was doing them any good. After the 5-day period, all subjects who had continued coming to the clinic were informed that the experiment would last an additional 5 days with no change in design except that they would no longer be payed $2.00 per day.

At the beginning of this experiment, the number of capsules taken was to be used as the measure of reinforcing efficacy of the different medications. It became apparent quickly that this was not a sensitive measure, since with few exceptions all subjects who returned to the clinic reported having taken all the medication. The frequency of subjects reporting to the clinic for medication, however, did seem to be a sensitive measure. The percentage of subjects reporting to the clinic over the 10-day period for each of the medication groups is shown in table 2. In the first 5 days, subjects receiving methadone and codeine showed a greater frequency of clinic attendance than those receiving pentazocine or placebo. In the second 5 day period, these differences were even more marked. However, there were no differences between the methadone and codeine group. Overall, all groups showed a marked attrition rate with only about one-third of the group assigned to methadone or codeine continuing to attend the clinic. Note that many subjects, including some in the placebo group, reported a decreased heroin use which they attributed to the dispensed medication.

The results seem to indicate that methadone (40 mg) and codeine (400 mg) were more reinforcing than pentazocine (400

TABLE 2

Frequency of clinic attendance (in percentage) for subjects receiving codeine (400 mg), methadone (40 mg), pentazocine (400 mg) or placebo

Drug Group	Days									
	With monetary reinforcement					Without monetary reinforcement				
	1	2	3	4	5	6	7	8	9	10
Codeine (N = 23)	100	78	74	70	57	61	52	44	48	35
Methadone (N = 19)	100	84	63	58	68	47	21	37	32	32
Pentazocine (N = 23)	100	65	44	48	39	22	18	22	18	13
Placebo (N = 23)	100	61	57	53	49	26	22	26	13	18

mg) or placebo, since they were able to maintain higher frequencies of clinic attendance. Obviously, however, for over 60% of the group assigned to methadone or codeine, these drugs were not reinforcing enough to maintain clinic attendance. Clearly the conclusions drawn from this experiment are limited to the dosages of the drugs employed. The dosage of codeine and pentazocine selected were based upon analgesic potencies. The dosage of methadone was selected on the basis of its ability to suppress signs of opiate withdrawal. It is interesting to compare the results of this study with the first in the series where subjects had been detoxified from heroin and were hospitalized. In that study, both the pentazocine group and the codeine group requested medication at almost every opportunity. The different results obtained in these two experiments may have been due to the differences in the amount of behavior required to obtain the test drug and availability of other drug reinforcers. In the hospitalized subjects, medication was contingent upon a short walk to the nurses' stand. Further, no other drugs were available in the hospital environment. In contrast, subjects in the second study had to come to the hospital, be interviewed, leave a urine specimen, and take a 30-min test. For most subjects the total time for completing this chain of behaviors would be well over an hour. Further, heroin was available on the streets. The data from the second experiment show that codeine was sufficiently reinforcing to maintain clinic attendance for about 35% of the subjects despite the response cost. On the other hand, subjects assigned to pentazocine failed to report to the clinic with any greater frequency than those given placebo. Pentazocine seems to be a weak reinforcer capable of maintaining limited amounts of behavior in an environment where other drug reinforcers were not available. When the behavioral requirements for obtaining drug were higher and other drug reinforcers were available, the weak reinforcing actions of pentzocine were not sufficient to maintain behavior. There is, however, another interpretation for this data. The hospitalized subjects had been detoxified from heroin and were no longer receiving methadone when they were allowed to take pentazocine. In contrast, the subjects in the second experiment were physiologically dependent upon heroin as substantiated by the presence of free morphine in their urine. It has been shown that intravenous pentazocine is a positive reinforcer for lever-pressing behavior in rhesus monkeys who were not dependent on opiates but a negative reinforcer in opiate-dependent rhesus monkeys (5). Possibly the differences in reinforcing efficacy of pentazocine in the two experiments are attributable to the presence or absence of physiological dependence. However, the hospitalized subjects had only been off opiates for 1 day when pentazocine was offered and therefore should not be considered totally free of opiate physical dependence. The issue is a complicated one

since long-term increased sensitivity to opiate antagonists has been shown in post-dependent monkeys (6). Clearly the only way to resolve this question experimentally would be to use human subjects with no previous opiate drug experience. Under current government guidelines for drug investigations, this would not be allowed. This highlights a very important problem in the development of procedures for assessing the abuse liability of a drug; how do we obtain the necessary data in man to validate our preclinical measures of abuse potential. It may be pharmacologically inappropriate to use only human subjects with previous drug experience but one cannot use subjects who have not abused opiates.

Another interesting and unexpected finding in experiment 2 was the relatively large attrition rate in the subjects assigned to methadone. Although these subjects reported to the clinic much more frequently than subjects assigned to placebo, more than 60% of the group were lost over the 10-day period. Data from methadone maintenance clinics suggested that methadone, at a dose of 40 mg, would maintain a high frequency of clinic attendance. Further, because of its greater efficacy in suppressing the opiate withdrawal syndrome, we had expected methadone to maintain a significantly higher clinic attendance level than codeine; however, both groups had comparable clinic attendance. Although there are high drop-out rates in methadone maintenance programs, these seldom occur in the first 10 days of treatment. In methadone maintenance therapy, the patient is given the whole daily dose of methadone at one time; however, in our experiment, methadone was given in divided doses and subjects were encouraged to take 5 to 10 mg of methadone every 4 to 6 hr because we had hoped the number of capsules taken as the measure of the reinforcing efficacy of the different drugs. We decided, therefore, to investigate the reinforcing efficacy of methadone given as one 40-mg capsule. In the third experiment, the same general procedure was used as in experiment 2. Of 26 male subjects between the ages of 21 and 50 years obtained from the patient waiting list of the State of Illinois Drug Rehabilitation Program, 14 were randomly assigned to the methadone group and 12 to the placebo group. They were told that they could report to the clinic every morning for 5 mornings in order to receive an experimental medication that might help them with their heroin problem. As in experiment 2, they had to participate in an interview, submit a urine sample and complete a 30-min paper and pencil test. Subjects were required to take one capsule immediately upon reporting to the clinic before starting the assigned tasks. For the methadone group this capsule contained 40 mg of the drug. All subjects received seven additional capsules to take home. For both groups all the take home capsules were placebo. Thus, the only difference between the two groups was in the medication received in the clinic. As in the previous out-patient experiments, subjects were given $2.00 daily to defray their travel expenses. On the 5th day the subjects were told that the experiment was to be continued for another 5 days, however, they would no longer be payed for coming to the clinic.

The percentage of subjects reporting over the course of the 10 days for the methadone and placebo groups is shown in table 3. The frequency of clinic attendance was higher for the subjects given 40 mg of methadone than those given placebo capsules. However, in experiment 3, the methadone group showed an attrition rate of over 50% during the 10 days. Whether methadone was given as a single 40 mg capsule or in divided dosages made no difference in the frequency of clinic attendance. Other nonpharmacological variables must be responsible for the greater clinic attendance seen in methadone maintenance programs.

These three experiments illustrate some

TABLE 3

Frequency of clinic attendance (in percentage) for subjects receiving methadone (40 mg) or placebo

Drug Group	Days									
	With monetary reinforcement					Without monetary reinforcement				
	1	2	3	4	5	6	7	8	9	10
Methadone (N = 14)	100	93	71	64	71	50	43	50	36	36
Placebo (N = 12)	100	73	50	42	50	33	25	17	17	17

of the problems in attempting to directly determine the abuse potential of drugs in man. Environmental variables such as the behavioral requirements and the concurrent availability of other drugs may markedly alter assessment of the abuse potential of a drug. (For a discussion of these variables in animal research, see (8a).) Other variables such as physiological dependence may be critical in determining whether drug-taking behavior will be maintained. Although all of these variables can be assessed in animals, we are extremely limited in the experiments we can perform in man. There is, therefore, no simple solution to the problem of validating our preclinical procedures for predicting a drug's abuse potential in man.

II. Assessment of Possible Therapeutic Manipulations

There are two major approaches in the treatment of drug abuse; psychotherapeutic and pharmacological. To date preclinical research has contributed almost exclusively to the assessment of pharmacological manipulations which might have some therapeutic efficacy in the treatment of drug abusers. It is obvious from this symposium, however, that there is developing an increased effort in the assessment of psychological variables which may have important implications for therapy.

Several approaches have been suggested as possible means of treating heroin abusers. One such approach involves the immunization of people against the actions of a drug (17). In this section, I will briefly review some research in the development of a procedure for immunizing monkeys against the reinforcing actions of heroin (1). Hopefully, this will illustrate the general problems of attempting to assess a totally new procedure for its possible therapeutic efficacy.

This research was based upon data showing that rabbits given injections of morphine-protein conjugates develop antibodies which would bind free opiate. The antigen, which was developed by my colleagues, was morphine-6-hemisuccinyl-bovine serum albumin (M-6-HS-BSA). Antiserum obtained from rabbits immunized with M-6-HS-BSA had about the same affinity for morphine and heroin but progressively less affinity for opioids of decreasing chemical similarity (18).

Our first studies indicated that these antibodies could prevent morphine's inhibition of electrically stimulated contractions of the guinea pig ileum. The antibody induced reversal of the inhibition of muscle contraction produced by 120 nM morphine was comparable with the reversal observed after the addition of 10 nM naloxone (19). To test more directly whether immunization might be useful in treatment of heroin abuse, we next determined whether it would alter a monkey's heroin-reinforced behavior. In this experiment a rhesus monkey was trained to press a lever under a 10-response fixed ratio schedule of intravenous heroin or cocaine injection. Only one of the two drugs was available in each 2-hr daily session. Each session began with the illumination of a stimulus light located over the correct lever for that day. Separate levers and stimulus lights were associated with the two drugs. The dose of cocaine was adjusted so that the number of cocaine injections delivered under fixed-ratio schedule were the same as the number of 6

μg/kg heroin injections. The final dose of cocaine was 100 μg/kg. Since cocaine is not bound in significant amounts by antibodies developed to M-6-HS-BSA these sessions acted as a control for nonspecific changes in drug-taking behavior produced by the immunization procedure.

After responding had stabilized, saline was substituted in the sessions in which cocaine had been injected previously. Responding in these saline extinction sessions showed a gradual decrement to low levels. Alternating sessions in which lever pressing behavior was maintained by heroin showed no change in the frequency of self-injection. After the re-establishment of cocaine maintained responding, saline was substituted in the sessions in which heroin had been injected previously. Responding in these saline extinction sessions rapidly decreased whereas there was no change in the monkeys self-injection behavior during the alternating cocaine sessions. These manipulations were carried out to demonstrate the independence of the behaviors maintained by the two drugs as well as to determine how quickly extinction would take place when saline was substituted. After this portion of the study the animal was removed from the experimental regimen and immunization was started.

The progress of the immunization procedure was monitored by following serum levels of antibody. After 20 weeks, the titers of serum antibody appeared to have reached stability at a level of 77,550 pmol ml^{-1} undiluted antiserum. A catheter was then re-implanted in the left jugular vein and the animal responded again under the same schedules of heroin or cocaine injection that prevailed before immunization. Lever-pressing behavior maintained by cocaine resumed at the same frequency as before the 20-week immunization period. However, the rate of responding under the schedule of heroin injection was not above that maintained by saline. The dose of heroin was then double after every third heroin session until a dose of 100 μg/kg was reached; at this dose, responding for heroin reinforcement increased significantly. Thus, it was necessary to increase the dose of heroin 16-fold in order to overcome the antibody blockade. Note that the dose of 100 μg/kg of heroin does not maintain response rates above control levels in non-immunized animals probably due to its nonspecific depressant actions. It is likely that the antibody population had been progressively saturated as the dosage of heroin increased. A series of consecutive cocaine sessions were interposed to allow time for the free antibody titers to return. Heroin injections were again introduced at a dose of 6 μg/kg and again rate of responding was very low. In the second series of ascending heroin doses, rates of responding increased markedly when the dose reached 50 μg/kg.

To summarize, these results indicate that antibodies against opiates can be induced in monkeys. Further these antibodies can bind heroin rapidly enough to prevent it from functioning as a reinforcer even when delivered intravenously. However, this blockade can be overridden by large increases in the dose of heroin.

What are the implications of this research for human heroin abusers? It seems probable that people could be immunized against the actions of heroin. There are a variety of reasons, however, that effectively preclude such a therapeutic application. The morphine antigen was injected in a solution of Freund's adjuvant. Because of its toxicity, the use of Freund's adjuvant is not allowed in man. In rhesus monkeys under our immunization regimen, there is a marked irritation and scarring at the site of injection sufficient to produce irreversible muscle damage. It is not known whether a less traumatic procedure (*i.e.*, one using another adjuvant) would be effective in stimulating antibody production. Even if a less toxic immunization procedure were developed, there remains the possible problem of kidney damage caused by antigen-antibody complexes. Although such kidney damage was not found in the one monkey we have exposed to heroin after immunization, it remains a possible danger. Further objections to the use of

immunization procedures as a treatment for heroin abuse are illustrated in our own data. As we have shown, the blockade of heroin's actions by immunization can be overcome by increased dosages of heroin. Moreover, the antibodies are fairly specific in their binding capacity which means that other opioids could be utilized as a replacement for heroin. Thus anyone seeking the effects of opiate drugs could either increase the dosage of heroin to overcome the antibody blockade or switch to another opiate which is not bound in significant quantities by these antibodies. Finally, there remains the problem of getting heroin addicts to volunteer for immunization. From either an ethical or a pharmacological viewpoint, this form of therapy entails serious problems.

For all of these reasons, we do not consider immunization against heroin a viable treatment procedure for heroin abusers. For purposes of the present discussion, it is important to note that we were able to evaluate the feasibility and liabilities of such treatment with an animal model of drug abuse.

III. Investigations of Mechanisms Underlying Drug Reinforcement

For the past several years, we have been investigating the neurochemical bases of the actions of methamphetamine as a reinforcer (11). It is well established that many of the central nervous system effects of the amphetamines are dependent upon recently synthesized dopamine and norepinephrine. In a series of investigations we have attempted to determine whether the reinforcing actions of methamphetamine in the rhesus monkey can be antagonized by depleting the central stores of recently synthesized norepinephrine and dopamine with *alpha*-methyl-tryrosine.

Alpha-methyl-para-tyrosine (AMT), a competitive inhibitor of tyrosine hydroxylase (15), has been used to study the interactions between the behavioral effects of amphetamine and brain catecholamines. Weissman *et al.* (20) have shown that the anorexic effects of amphetamine, the rate-increasing effects of amphetamine in animals responding under a nondiscriminative avoidance procedure, and the increase in spontaneous motor activity produced by amphetamine can all be antagonized by AMT. It has also been shown that the antagonism by AMT of amphetamine-induced increases in behavior are dependent upon newly synthesized catcholamines.

To study the interaction of AMT and the actions of methamphetamine as a reinforcer, rhesus monkeys were trained to press a lever under a 10-response fixed ratio schedule of intravenous methamphetamine injection. Daily 2-hr sessions were signalled by the onset of a light over the lever. After responding by methamphetamine had stabilized, the effects of single doses of 10 and 40 mg of AMT per kg were assessed. We had previously established that these doses produced a significant depletion in catecholamines. Pretreatment with AMT caused a significant increase in rates of responding maintained by methamphetamine injections. That this increase was a function of the AMT induced depletion of catecholamines was supported by the observation that the increases in rate of responding maintained by methamphetamine was reversed by treatment with 20 mg of L-dopa per kg. At this dose, L-dopa alone had no effect on rates of responding maintained by methamphetamine. Further, the specificity of this interaction between AMT and methamphetamine reinforcement was investigated. Animals trained to lever-press under fixed ratio 10 schedule of pentobarbital injections were given the same doses of AMT. At no dose of AMT was there an increase in responding maintained by pentobarbital.

In the next phase of these investigations, 10 mg of AMT per kg was given daily 2 hr before the 2-hr session of responding under the schedule of methamphetamine injections. Responding in these sessions showed the same pattern of change as that observed when saline was substituted for methamphetamine. This similarity suggests that pretreatment with AMT was blocking the effects of methamphetamine

and thus causing extinction of lever pressing that had been maintained by the drug.

Investigations from other laboratories have provided additional support for the conception that the action of methamphetamine as a reinforcer is mediated through catecholamines (CA) and that the inhibition of CA synthesis by AMT blocks these reinforcing actions (2, 10).

In man it has been shown that AMT can block the "euphorogenic" actions of amphetamines (9). Assuming that there is some relationship between measures of euphoria and the ability of a drug to act as a reinforcer, these human data confirm the prediction that would have been made from the animal experiments. However, studies of drugs as reinforcers in man are needed because there is not *a priori* reason to equate measures of euphoria with measures of positive reinforcement. Nevertheless, this illustrates how an animal model can be used to investigate the neurochemical mechanisms underlying behavior maintained by drug injections. The correlative neurochemical changes in the brain could, of course, only be carried out in animals illustrating the greater range of experimental manipulations possible with nonhuman subjects.

Summary and Conclusions

I have presented data to illustrate and evaluate the use of animal experiments on behavior maintained by drug injection as an animal model of human drug abuse. I believe, the data justify the cautious application of such an animal model for predicting the abuse potential of a new drug, for evaluating new forms of treatment, and finally, for investigating biological and environmental variables controlling drug taking behavior. However, there are a variety of assumptions whenever we extrapolate conclusions from laboratory studies to man in his natural environment.

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