OPIATE ADDICTION IN THE MONKEY

I. METHODS OF STUDY

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It has been previously pointed out by Tatum, Seevers and Collins (1) that a condition closely portraying human addiction could be arrived at in the monkey (Macaca mulatta), and its superiority to other laboratory animals as a test object for the study of the problems related to addiction has been amply confirmed (2, 3, 4, 5). It is obvious, of course, that no animal experiments will entirely answer the question as to whether a given drug will appeal to the human individual in terms of "euphoria" such as to demand a repetitious experience, regardless of its ability to produce tolerance or signs on withdrawal.

It was hoped that the monkey, because of its higher cortical development, might be at least capable of associating the injection of the drug with the subsequent relief of the distressing symptoms of abstinence, even though it would not of its own accord evince a desire for the daily injection because of any pleasurable sensation obtained. No one has, however, stated definitely that he placed such an interpretation upon the actions of any of the animals so far reported.

The results obtained from the application of delayed reaction tests on various infrahuman primates (6, 7) indicate that the brain of these animals is only developed to a point that the "mental set" (not memory) for any particular problem is about two or three minutes. According to Harlow (8), it is not illogical to look upon addiction as the establishment of a delayed conditioned response and it may involve much the same cortical mechanisms as the delayed response to other situations. By analogy, then, positive "desire responses" might not be expected unless the uncondi-

tioned stimulus (cortical state or condition leading to the elimination of abstinence symptoms, i.e., drug action) were presented within a relatively short time interval subsequent to the presentation of the conditioned stimulus (needle plus person injecting and "total situation"). On this basis, the following conditions would have to be met: 1. The establishment of a positive association between the needle and the relief of symptoms. 2. The monkey must inhibit the natural association of the needle to (*a*) the disturbance of being caught and (*b*) the pain of the injection. 3. The relief of the symptoms must occur within two or three minutes.

Relief from the distress of withdrawal is not obtained for ten or fifteen minutes after the subcutaneous administration of morphine or dilaudid. Furthermore, the injection is as a rule somewhat painful and the monkey is a very "high-strung" animal. The situation is, therefore, far from ideal for the establishment of such an association pattern with these two drugs. Heroine, on the other hand, is less painful on injection and acts rapidly, the effect coming on in three to five minutes. Animals addicted to heroine actually behave as if they desire the drug, particularly during a prolonged withdrawal. One animal, addicted for fifteen months, would sit on the table, or lie quietly on her back without restraint, to receive the injection of 6 cc. of 1 per cent heroine hydrochloride without wincing, and would chatter and call throughout the procedure. No especial effort had been made to tame this animal who originally was the wildest of the group. Others will follow the attendant about in the pen, clutching at his clothing, and will return time and time again even though repelled. It may be argued, of course, that peaceful submission to the injection is fundamentally different from the establishment of a positive desire for the drug. In the final analysis, however, it should be agreed that the former is a preliminary step in the achievement of such a response. It is a common observation that all of the animals are more docile and easily handled during the height of abstinence from other addicting opiates. This occurs at the forty-eight- to seventy-two-hour period, and may result from the fact that they are so exhausted that they do not

feel like offering resistance. It has been suggested that, if the drugs were injected intravenously, where a minimum of pain and rapid onset of action are obtained, the necessary association could be more easily established.

Since the monkey, as a laboratory animal, offers the nearest approach to the study of addiction in man, and since the nature of the study differs from ordinary laboratory procedures, it was felt that a brief presentation of methods of study, care, and the signs of addiction and withdrawal based upon observations of 34 monkeys addicted for periods of four months to two years, would be of value to other workers in the field.

HOUSING, CARE AND HANDLING

The reader is referred to the excellent monograph by Hartman and Straus (9) for information concerning the general care of the Rhesus monkey. An ideal method of housing monkeys for a study of this type is to allow them free run of two large pens; a large room within the warmed animal quarters connecting with an outdoor pen by a small runway closed at either end with doors hinged at the top, and easily opened or closed by the animals.

The appetite of the monkey during addiction is as capricious as that of the human addict. It is difficult to maintain weight when on large doses unless a variable diet, adequate in every respect, is provided. During withdrawal, the monkey, like the human addict, is particularly fond of sweets and will eat sugar when other foods are refused.

Since fear will obscure, for a period at least, some of the signs of abstinence, it is important that this element be eliminated as much as possible. The monkey appears to have a fear of nets and gloves, probably acquired at the time of capture, and tends to remain wild if they are used.

Subcutaneous injections over the chest or on the extremities are made daily about 4:00 p.m. It has been found that the afternoon is preferable to the morning for the daily injection because of the fact that early signs of abstinence begin to be manifest fifteen to eighteen hours, or earlier, after the last dose. If injections are made in the morning, these early signs will occur during

the night and be overlooked. If a study of tolerance is the main objective, the morning injection is to be preferred.

Our experience, similar to that of Kolb and DuMez (2), has been that injections must be made every day, including Sundays and holidays, if the best results are to be obtained and the animals maintained in an optimum condition. A forty-eight-hour withdrawal period over Sunday is deleterious to the general health. Furthermore, when large doses are attained, it has been found that tolerance is so rapidly lost over this period of forty-eight hours that the dose must be reduced to one-half or one-third of the accustomed quantity for fear of killing the animal in convulsions or depression. Three animals have been lost by failing to heed this fact. An essential part of a study of this nature is to become familiar with the individual behavior and personality of each animal in its normal state. It is a practice in this laboratory to allow a period of two or three months for such a study before the initiation of addiction.

BEHAVIOR DURING ADDICTION

The majority of monkeys lose weight during an addiction of long standing. The degree of weight loss depends upon the rapidity of onset and severity of the addiction. To a considerable extent it is probably secondary to a diminution in appetite, although this is not the sole factor. Once a new level of weight is attained, little variation is to be expected. Growth and maturation are definitely hindered in adolescent animals. In contrast to the dog, the monkey never vomits or seldom salivates after the opiates. We have seen only one animal develop the conditioned salivary reflex so commonly seen in the dog. Only recently, one animal of a different species (Macaca mordax) has developed a conditioned vomiting reflex. This is of considerable interest, since the animal was never seen to vomit after the injection. When the attendant comes into the quarters and begins to inject the other animals, this monkey will usually vomit prior to receiving the drug. It appears as if there has been established a conditioned reflex without the unconditioned stimulus, unless it can be considered that nausea is the stimulus in this case.

The recurrent constipation and diarrhea seen in the dog and man are not commonly observed in the monkey, possibly because of differences of diet.

We have observed three instances of hydrophilia after injection, as described by Kolb and DuMez for the monkey, and Tatum, Seevers and Collins for the cat. The animals will sit in the container and splash the water over themselves. One animal developed the habit of repeatedly submerging his head in the container.

Sexual activity, as in the human, subsides during administration. It is rare to observe either sexual play or masturbation. Menstrual bleeding ceases immediately on administration of the drug to recur during abstinence or protracted withdrawal, although a certain degree of cyclical reddening of the posterior parts persists if the animals are on small doses. Codeine, in one female, failed to cause a cessation of menstrual activity.

Kolb and DuMez continually refer to a condition of rigidity or spasticity of the skeletal muscles as a part of the picture of addiction to morphine. This will most certainly be observed but is, we believe, to be interpreted as a sign of abstinence rather than an accompaniment of drug action since it disappears after administration of the drug, to recur hours after the injection.

Convulsions are occasionally seen, occurring, in our experience, either as a result of drug action following the loss of tolerance during extended withdrawal, an accidental overdosage, or as a sign of abstinence. It must be recognized that convulsions of two types may be produced by the morphine derivatives and may be distinguished by their response to artificial respiration or oxygen. They may be either asphyxial in origin, occurring as a result of excessive respiratory depression, especially with heroine, or result from a direct stimulant action of the drug on the central nervous system. The latter type responds poorly to artificial respiration, in contrast to the former, but may be controlled by the barbiturates, whereas it might be fatal to administer a barbiturate in the former condition.

Generally the pupil of the monkey dilates during administration and constricts during withdrawal, a reversal of the condition often

seen in man. This reaction constitutes one of the few differences between monkey and man. Temporary indispositions are occasionally seen in addicted animals, such as mild upper respiratory infections. We have never observed the necrosis of the eartips as described by Kolb and DuMez, and doubt whether it can be attributed to a specific drug effect.

BEHAVIOR DURING WITHDRAWAL

Light and his associates (10) give the following signs and symptoms, in the order of their appearance, during a forty-eight-hour withdrawal period in man: restlessness, yawning, chilliness, hot flashes, respiratory alteration, goose flesh, rhinorrhea, "yen" sleep, lacrimation, cramps in the abdomen, back and lower extremities, vomiting, diarrhea, perspiration, muscular twitchings and rigidity, intention tremor, refusal of food and water, insomnia, diplopia, seminal emissions in the male and orgasms in the female.

The careful observer can see in the monkey, all the signs as listed above, as well as behavior, which allows an objective interpretation of the majority of the above symptoms.

The following classification of signs indicates that little difference exists between this animal and man, as far as their objective appearance during abstinence is concerned.

Classification of the signs of abstinence in the monkey

Mild (may be considered as of no significance by the untrained observer): Apprehension, continual yawning, rhinorrhea, lacrimation, hiccup, shivering, perspiration on face, chattering, quarreling and fighting.

Moderate: Intention tremor, anorexia, pilomotor activity, muscle twitchings and rigidity, holding the abdomen (cramps).

Severe: Extreme restlessness, assumption of peculiar attitudes, vomiting, severe diarrhea, erection and continued masturbation, inflammation of the eyelids and conjunctiva (insomnia), continual calling and crying, lying on the side with eyes closed, marked spasticity.

Very severe (danger of death): Docility in the normally excit-

able animal, dyspnea, pallor, strabismus, dehydration, weight loss, prostration, circulatory collapse, and occasionally, death.

These signs appear in somewhat the same sequence as in the human. It is obvious that every one of the above signs will not occur, or will not be observed, in every animal on withdrawal, as is true of the human addict. This depends largely upon the severity and duration of the addiction. When a severe addiction has progressed for a year or longer, a certain number will succumb during a seventy-two hour period of withdrawal in spite of a re-administration of morphine.

In man, the severity of the signs is to a certain extent subject to willful control on the part of the patient (10). Such is the case with the monkey. If the animal is removed to a strange environment, or frightened by some other animal, the signs will temporarily abate. We have had occasion to place the animals in a large oxygen chamber during a period in which the signs were very severe. For the first ten or fifteen minutes after the change, they will sit erect, look about inquisitively, and appear to be almost normal. Once accustomed to the change, however, the signs of withdrawal return with equal or greater severity. This fact might indicate that withdrawal symptoms have an origin in the lower brain centers or basal nuclei, since they are subject in some measure to cerebral control. If an observer is to see all of the signs of withdrawal during a forty-eight-hour period, it is obvious that casual observation during the working day will not suffice. Constant observation must be undertaken, which means that the animals must become so familiar with the presence of the observer that no fear will be shown at his approach.

ADDICTION METHODS

Two general procedures are open for a study of the problems associated with addiction in the monkey; a rapid increase in dosage to a point where the maximal quantity to be administered is reached in two to six weeks, or a gradual increase to the same total quantity of drug over a period of six to twelve months or longer. The latter method more nearly approaches the clinical condition and is less debilitating. Greater doses may be at-

tained and the characteristic signs, as indicated above, are more easily distinguishable during a long addiction. Kolb and DuMez make a point of trying to physically deplete the animals in order to produce addiction. The better policy, in our opinion, is to attempt to produce addiction and at the same time maintain the best possible physical condition, since we are not studying inanition but the specific effects of the drug. Unfortunately, the cost and time involved in a prolonged experiment is of some significance when a comparative study of the habit-forming properties of several opiates is undertaken. For that reason we have utilized the rapid in addition to the slow method, and find that it is possible to predict within a period of six to eight weeks whether a drug is potentially capable of producing addiction. Furthermore, this prediction will be based not alone upon the appearance of a hyperirritable state, but likewise upon specific signs similar to those which may be expected in man. Unlike the dog, the monkey will tolerate a rapid rise in dosage without the severe physical deterioration seen in the former animal. Many dogs will die during the first week or two if the rapid method is attempted. Such has not been the case, in our experience, with the monkey.

VALUE OF THE RAPID ADDICTION METHOD

In 1933, a morphine derivative was submitted to us for assay as to its addiction properties. The only information available concerning the nature of the substance was that it had been introduced in Germany under the name of R.G.F. as a non-habit-forming substitute, and that it contained 64.8 per cent of anhydrous morphine alkaloid as compared with the U.S.P. standard for morphine sulphate, which contains 75.2 per cent of the alkaloid.

Six animals were addicted, three each to R.G.F. and morphine sulphate, the dosage based in each case upon the actual alkaloidal content. The initial dose of 10 mgm. per kilogram of morphine and 11.6 mgm. per kilogram of R.G.F. given on March 10, 1933, was raised in twelve days to 90 and 104 mgm. per kilogram, respectively, by 10 mgm. per kilogram increments. By April 10, 1933 the doses had been raised further to 115 and 133 mgm. per kilogram, respectively. At this time, one month after beginning

of the experiments, the average weight loss for the morphine animals was 18 per cent; for those on R.G.F., 14 per cent. An abstinence period instituted at this time revealed very severe signs in both groups of animals—so severe, in fact, that we were able in this short period to tentatively predict that R.G.F. was not essentially different from morphine. This was subsequently proven to be the case at clinical trial. Morphine addicts, to which the drug was administered, obtained the same euphoria and relief of abstinence symptoms as with morphine.

The doses were raised to a level of 160 to 185 mgm. per kilogram in these animals by May 31, 1935, after ten weeks of addiction. At this time the signs were as severe as we have seen in any monkey. Prostration was extreme and it is felt that death would have followed complete withdrawal.

Doses of the latter magnitude do not aid materially in establishing the differential actions of the various drugs but only contribute to the general debility of the animal.

SUMMARY

Evidence is presented to indicate the superiority of the monkey to other laboratory animals as a test object for the comparative study of addiction to the opium derivatives.

Satisfactory methods of housing, care, and handling for a study of this type are described, and a description of the behavior during addiction and withdrawal is presented. The signs of abstinence are classified according to their order of appearance and relative severity and are compared with the signs and symptoms which occur in the human addict.

Behavior, which we interpret to be the establishment of a positive desire for the drug during abstinence, is described and the factors favoring the formation of such a response in this animal are discussed.

It is believed that the rapid method of addiction with the monkey as a test object, in which the largest doses to be given are attained in a period of two or three weeks, is satisfactory for the determination of the relative addiction potentialities of a series of different opium derivatives, although it does not give quite so

clear a differentiation as that following a more prolonged period of poisoning, such as occurs in the human addict.

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REFERENCES

(1) TATUM, SEEVERS AND COLLINS: J. Pharmacol. & Exper. Therap., **36**, 447, 1929.
(2) KOLB AND DUMEZ: U. S. Public Health Reports, **46**, 698, 1931.
(3) SEEVERS: J. Pharmacol. & Exper. Therap., **51**, 141, 1934. (Proc.)
(4) YOKOTA: Japan. J. Med. Sci., **8**, No. 1, 94, 1934. (Proc. Jap. Pharmacol. Soc.)
(5) AKAMATSU AND OKAMOTO: Cited by YOKOTA.
(6) HARLOW, UEHLING AND MASLOW: J. Comp. Psych., **13**, 313, 1932.
(7) HARLOW: J. Comp. Psych., **14**, 241, 1932.
(8) HARLOW: Personal communication.
(9) HARTMAN AND STRAUS: Anatomy of the Rhesus Monkey. Williams & Wilkins, Baltimore, 1933.
(10) LIGHT, TORRANCE, KARR, FRY AND WOLFF: Opium Addiction. A. M. A. Press, 1929–30.