nevi it has been possible to demonstrate melanin formation from labeled tyrosine, but inactive junctional nevi and dermal nevi seem to have a lower amount of tyrosinase (*3*). It seems quite possible that, with the sensitive fluorescence method we used, DOPA could be detected even in cells where the tyrosinase has not been demonstrated.

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Spontaneous Opiate Addiction in Rhesus Monkeys

Abstract. *Spontaneous drug-seeking behavior was established in 3 out of 4 rhesus monkeys that were given unrestricted access to morphine and placebo solutions. The monkeys were kept in their home cages throughout the experiment and were not subjected to conditions of stress; prior addiction was not established by the usual injection procedures. The animals became physically dependent on the drug and showed abstinence symptoms when injected intramuscularly with nalorphine (N-allyl normorphine hydrochloride). This method may be useful for studying individual differences in susceptibility to drug abuse.*

Studies of drug addiction in human populations are complicated by legal sanctions and social restrictions which tend to make addict societies closed and inaccessible to scientific scrutiny. Most investigators of drug addiction in animals have relied predominantly on methods of prior addiction induced by the regular injection of opiates percutaneously (*1*). In those experiments where oral administration has been used and the animals have been allowed free movement in their home cages, the addiction was induced first by providing drugged solutions alone; only after a period of "forced choice" were the animals given a choice between drugged and nondrugged solutions (*2*). Although the spontaneous choice of morphine has been observed in experiments where both water and morphine solutions were provided, the results of such experiments are not generally available in the literature (*3*). Other investigators have used a harness and intravenous canulation for drug administration, the animals first being addicted by injection and then allowed to maintain themselves on the drug by pressing a bar which delivers a dose of morphine intravenously (*4*). Such apparatus obviously abolishes spontaneous choice as an element of drug-seeking behavior.

We have studied the development of spontaneous drug addiction or drug-seeking behavior in four rhesus monkeys (*Macaca mulatta*). The animals were kept in their individual home cages without being subjected to conditions of stress and were given unrestricted access to a placebo (water) and a 0.1-percent solution of morphine sulfate. Food was provided according to a normal schedule. To test for taste preference, two additional monkeys were given access to the placebo and a 0.03-percent solution of quinine. The animals were adolescent males, approximately 18 months in age, weighing from 3.5 to 4.5 kg. The cages were equipped with Plexiglas doors with two nipples fastened into the door and protruding into the cage. The nipples were connected by plastic tubes to two 1000-ml calibrated burettes. Grason-Stadler electronic drinkometers and an Esterline Angus event-recorder were used to record the volume of each fluid taken by the monkeys as well as the number and temporal spacing of their drinking responses. Drug-seeking behavior was defined in terms of the relative number of times the monkeys drank from each nipple, as well as the volumes of each solution ingested.

Initially, a 1-percent solution of morphine was provided by one drinkometer and water by the other. Since very little morphine solution was consumed, we decreased the concentration to 0.1 percent and found that the solution was preferred in increasing amounts in relation to water by three of the animals over an extended period. Within the first week, one animal stopped drinking the morphine solution. The other three animals manifested a variety of abstinence symptoms when injected with nalorphine. Their different patterns of drug-seeking behavior are shown in Fig. 1. The amount of drug taken by animal 1 increased for 120 days; the intake reached a maximum of 520 mg of drug every 24 hours, 10 days after nalorphine precipitated abstinence. Animal 2 increased its intake of morphine and water over an 80-day period; after nalorphine was administered, the intake of both water and morphine declined. At the same time that animal 3 showed a preference for the drug, it reduced its total fluid intake and showed a loss of weight and physical deterioration. When these changes in physical status occurred we discontinued the tests. Nalorphine was given at the end of 80 days to establish that physical dependence had taken place.

The data for the volumes of morphine consumed were evaluated statistically. Analysis of variance for differences among trends for each subject was performed on the data for morphine intake over 80 days (*5*). A mean value for eight intervals of 10 days each was computed, data for the total daily intake of morphine prior to the injection of nalorphine being used. Each 10-day interval was divided into two parts to estimate the variability within each interval. The interaction of subjects and intervals of 10 days was highly significant ($p < 0.0001$; $f = 13.7$; $df = 14/24$). Variation due to differences in linear and cubic trends among subjects accounted for 25.2 percent and 27.4 percent of the total interaction, respectively. Subject differences in quadratic trends explained the largest portion of interaction variance, 46.3 percent. Deviations from these trend differences amounted to only 1 percent of simple effects variation.

The relation between physical and psychological factors in addiction are complex, and differences of opinion exist regarding the relative importance of each factor. It is contended on one hand that addiction or physical dependence begins with the first dose (*6*). Other investigators insist that habituation is distinguished from addiction by the presence of abstinence symptoms, primarily autonomic in origin, which are the hallmark of the addicted state (*7*).

The test of addiction in common use with human subjects is the ab-

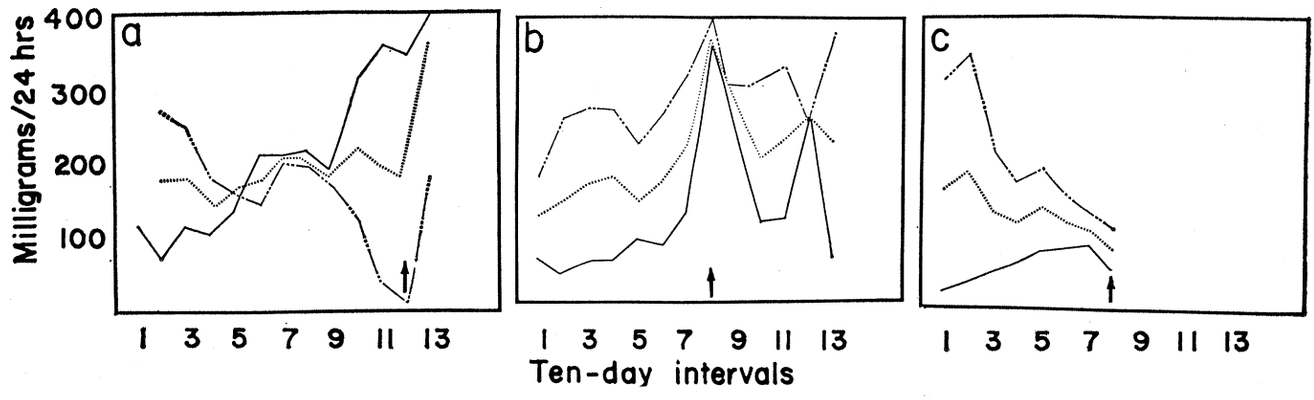

Fig. 1. Development of preferences for morphine solution as opposed to water (the ordinate shows the amount of morphine consumed; 1 mg is equivalent to 1 ml). Solid line, volume of morphine solution consumed; dotted line, mean volume of fluid consumed; broken line, mean volume of water consumed. Arrows indicate when morphine was administered. (*a*) Animal 1; (*b*) animal 2; (*c*) animal 3.

stinence-withdrawal method. In rhesus monkeys, this test results in increasing the symptoms of withdrawal over a 36- to 48-hour period. A more rapid onset of abstinence can be made by injecting nalorphine, which antagonizes the action of morphine, precipitating abstinence symptoms. Withdrawal illness may range from mild, nearly imperceptible changes such as yawning, rhinorrhea, lachrymation, hiccup, shivering, perspiration on face, chattering, and quarreling, to more severe symptoms such as dyspnea, pallor, dehydration weight loss, circulatory collapse, and at times, death. These variations in symptoms are related to the total daily intake of the narcotic drug taken prior to withdrawal. All three "addicted" animals were injected intramuscularly with 10 mg of nalorphine, and all displayed typical abstinence symptoms, though there were marked differences in severity of symptoms. Minutes after injection of nalorphine, emesis, scratching, posturing, vocalization, rhinorrhea, yawning, and lying on the side with eyes closed were noted in animal 1. In animal 2, which consumed less morphine, the symptoms consisted of bizaare posturing for long periods of time, copious rhinorrhea, vocalization, lying on the side, and greatly decreased motor activity. For animal 3, the symptoms included posturing in the corner of the cage, unresponsiveness except when actively stimulated, and lying on the cage floor with eyes closed.

As a control for drug preference based on taste, two additional animals were given a choice of quinine solution and water. Quinine is relatively insoluble in water, but a concentration of 0.03 percent will go into solution and become comparable in taste, to the experimenter, to 0.1 percent morphine sulfate and water. Quinine is used in the adulteration of opiates sold on the market illegally for human use. Its bitter taste is similar to that of heroin and morphine and its addition aids in disguising the dilution. Maximum average quinine intake for a 5-day period was 20 ml. Intake of quinine fell over a period of 2 weeks. At this time the animals showed a preference for water and failed to respond to the quinine test solutions, drinking only from the nipples which provided water. However, the fact that the monkeys did not respond preferentially to the quinine solutions is by itself not conclusive evidence that taste did not play a role in the preference for the morphine solutions.

After determining the amount of motor activity for each monkey in its home cage, 10-mg doses of nalorphine were given intramuscularly as a control for the pharmacologic action of nalorphine. In contrast to the previously observed behavior of all three drugged animals, no changes in motor activity were observed in these control tests. Activity remained at normal levels without motor or autonomic changes such as characterized drug-induced abstinence symptoms seen earlier. Symptoms seen in the drugged animals were clearly not effects of nalorphine.

Narcotic addiction is a complex medical, social, legal, and psychological problem of worldwide extent. At various times, opiates have been taken in every conceivable form. Opiates have been smoked, swallowed, and, more recently, self-injected. Among human populations exposed to opiates, not all individuals yield to social pressure and presumed conflicts to become addicted to drugs. Of those individuals becoming "addicts," wide individual differences in drug-seeking behavior can be found; they range from subjects who claim addiction but are intolerant to drugs, to subjects who develop an escalating need which, when unsatisfied, leads to severe abstinence symptoms (*8*). In most previous reports of studies with animals, prior addiction of the test animals effectively prevented investigation of the question as to what factors may lead to drug addiction in human subjects. Our demonstration of spontaneous drug addiction in monkeys can provide an experimental approach to study the role of individual differences in susceptibility to drug abuse.

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10. Films of addicted and nonaddicted animals before and during withdrawal are available at our laboratory.
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