Opioid Addiction: Rat Park Re-Visited

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Summary

Four decades ago, a team of researchers in Canada showed that rats living as a group in a comfortable box called "Rat Park" consumed far less morphine than rats housed in the tiny, solitary cages that were standard back then. Contrary to highly sensationalized views of opioid drugs, then and now, rats were not attracted to a powerful opioid, *unless they were housed in solitary confinement!*

Although these experiments received little attention then, they are now being widely publicized by excellent popular writers and artists and are helping to change the simplistic "devil drug" view of opioid drugs. This chapter describes some of the details and complications of the original Rat Park research that have been forgotten for more than three decades, and uses them to visualize the future. Much of this chapter is extracted from a 1985 publication by Bruce Alexander, Stanton Peele, Patricia Hadaway, Stanley Morse, Archie Brodsky, and Barry Beyerstein.

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"Opioids" or "opiates" are a large family of drugs that includes opium, morphine, heroin, oxycodone, methadone, the endorphins, buprenorphine, etonitazene, etorphine, fentanyl, carfentanil, and dozens of others. Because they all act on the brain's mu-opioid receptors, the various opioid drugs have very similar medical and psychological effects and side effects and similar peak effects, even though they differ greatly in the dose required to produce these effects and the time required to reach peak effect. Because opioids have an unsurpassed capacity to reduce severe physical and psychological pain, they have been indispensable in medical practice for since the 18th century, and remain indispensible today.

Several opioids have been involved in serious outbreaks of addiction, overdose death, drug-related crime at various times and places over the past two centuries. Currently, my country – Canada – and the United States are both suffering from a catastrophic and highly-publicized outbreak of opioid overdose deaths, most often attributed to the synthetic opioid, fentanyl.

Fentanyl is routinely used in medical practice in Canada and the US and is also sold illegally on the street. Illicit users expect it to produce an emotional state that is very similar to that produced by heroin or oxycodone. Fentanyl is quite likely to produce overdoses because the amount of the drug that is necessary to produce the desirable emotional state is so small that it is extremely difficult to measure accurately. A great deal of money and energy is being spent to bring this "overdose crisis" under control and to understand why many people are eager to use such a dangerous drug.

Fentanyl, like the other opioids, has been used extensively and safely in medical practice with little publicity for decades, even though, like some non-opioid drugs used in medical practice, overdose, addiction, and other side effects have occurred in a small minority of patients. Often, the same opioid drugs that have been used safely and effectively to control pain in one country have been, at the same time in history, banned and feared in other countries. For example heroin was safely used in medical practice in the UK for decades under the name "diamorphine" while it was feared and banned from medical practice in the US under the name "heroin" (Trebach, 1982).

Researchers have tried to determine the true effects of opioid drugs that are often overshadowed the exaggerated stories that are told during outbreaks of fear and panic so that reasonable drug policies can be instituted. Much of the research is done with rats and monkeys in animal laboratories.

Under some research conditions, laboratory research animals voluntarily self-inject or drink large doses of opioid drugs, as well as other drugs associated with human addiction. This fact was once taken as part of the proof that opioid drugs *cause* addiction in individuals of all animal species, from the lowly rat to *Homo sapiens* (see Ahmed, 2018). I call this sweeping generalization, the "old story" (Alexander, 2018).

The old story is often combined with gruesome images and exaggerated language in the midst of what sociologists call a "moral panic" (see Cohen, 1973/2011) over a surge in the harmful use of a particular drug in a particular place. The old story was already deeply rooted in ancient western culture many centuries before opioids became an issue, but it has been applied to opioid drugs since the 19th century, and it has been bolstered and justified by reference to the animal research since the 1940s (Ahmed, 2018).

The most ancient roots of the old story lie in tales of "possession" of human souls by demons. But even when supernatural demons are not included in the tale, the old story is usually is usually applied to drugs in extraordinarily dramatic terms. It asserts that all, or at least most people (or animals) who use opioids will lose control of their behaviour and be overwhelmed by irresistible addictive cravings for the drug. In Canada and the US today, the old story is usually explained in the language of neuroscience rather than demonology, but the loss of rational control is still claimed. The old story further holds that, if people who use opioid drugs can be saved from their addictions, it will only by professional treatment or membership in organized self-help groups. (Hoffman and Froemke, 2007; Volkow, Wang, Fowler, Tomasi, and Telang, 2011; Volkow, 2018; Editorial Board of the New York Times, 2018).

Although the old story has used to justify compassionate treatment of addicted people, rather punishment, it has also been enlisted to justify violence. If the old story were true, anyone selling an opioid drug would be knowingly subjecting each of their customers to eternal damnation as an incurable addict. Such psychopathic traffickers can reasonably be hunted down and destroyed. If the old story were true, anyone who had become addicted to opioids would have lost all self-control and judgement. Such a drug-zombie would be entitled to no human kindness or mercy, because they would be far less than human. The old story has been used in a number of countries to justify cruel governmental persecution of disfavoured racial or ethnic groups. These countries include Canada, where the war on drugs was used quite openly to oppress Chinese immigrant labourers in the first half of the twentieth century (Murphy, 1922/1973; Alexander, 1990, 29-32). At its worst, prior to 1970, the Canadian drug war was at least as brutal as the American drug war (Alexander, Schweighofer, and Dawes, 1996). The United States is infamous for using its drug war to suppress its black population (Hart, 2013; Hari, 2015; Baum, 2016). I have read arguments that Brazil is also using the drug war to suppress its underclass (Ribeiro, 2016; Rodrigues & Labate, 2016; Baird, 2017). These articles seem quite

persuasive to me, but I do not know enough about Brazil to be sure.

Although animal research is used to support the old story, extensive experimentation with animals and human beings since the late 1970s has actually produced far more complex results (Heilig, Epstein, Nader, & Shaham, 2016; Ahmed, 2018). These results include strong evidence that animals do not normally use opioids in a way that fits with the old story except under special circumstances. Until recently, the complex results have been largely remained hidden in the shadow of the old story's terrifying tales of loss of control, degradation, and, ultimately, salvation by professional treatment and management.

Although animal research on drug addiction has been carried out with many drugs and laboratory species, this chapter concentrates on opioid drugs and laboratory rats. We are giving special attention to the experiments that we know best. These experiments were conducted four decades ago, in a setting that came to be called "Rat Park". The first part of this article is extracted from a chapter summarizing the Rat Park experiments that was included in the book, *The Meaning of Addiction,* by Stanton Peele (see Alexander, Peele, Hadaway, Morse, Brodsky, & Beyerstein, 1985).

After 1985, the Rat Park results were largely overlooked, because the dramatic imagery of the old story and of successive "moral panics" overshadowed them. The laboratory that housed Rat Park was closed after its grant funds were cut off in the early 1980s. The Rat Park experimenters moved on to different topics of research. Over the decades, two of the original researchers, Patricia Hadaway and Barry Beyerstein, have died.

Over this same long period, however, Rat Park gradually became widely known in the international literature on addiction. The basic findings have appeared in widely read popular books and articles (*e.g.*, Slater, 2005; Maté, 2008; Macmillan, 2013; Hari, 2014.) Meanwhile, a new generation of animal researchers were repeating the original Rat Park results with other drugs, and extending the idea in new directions.

This chapter is our first detailed review of the original experiments since our joint publication in 1985, a third of a century ago. It describes some of the complications that have been left out in simplified retellings of the Rat Park story in the popular literature. It also summarizes some of the new research and thinking from other laboratories in the decades since Rat Park was abruptly closed.

Animal Research on Opioid Addiction

Systematic laboratory studies of animal opioid self-administration began eight decades ago (Seevers, 1936; Spragg, 1940; Ahmed, 2018). Spragg showed convincingly that socially isolated chimpanzees that had been given a series of morphine injections willingly submitted to continued injections. When these chimps were experiencing withdrawal symptoms, they consistently chose morphine injections over food in a choice test. Subsequently, *Nichols* et al. (1956) demonstrated that rats would drink morphine solutions in preference to water under particular conditions designed to enhance learning that drinking the drug reduces withdrawal symptoms.

Then, in the 1960s, investigators at the University of Michigan developed a simple and photogenic technique that enabled rats in a Skinner box to inject themselves with drug infusions through a permanently implanted catheter (see Weeks and Collins 1968, 1979; Woods and Schuster 1971). This led to a series of studies of the self-administration of heroin, morphine, methadone, cocaine, amphetamine, alcohol, tobacco, and hallucinogenic drugs, much of it using the Skinner box technique. Self-administration was highest for the stimulants but was also high for the opioid drugs. Tobacco, alcohol, and hallucinogens were self-administered less consistently, although this may have resulted from unsuitability of the self-administration apparatus to these drugs (Kumar and Stolerman 1977).

Researchers used the Skinner box self-administration apparatus to investigate the effects of various physiological states and different schedules of reinforcement on self-administration rates. The greatest impact of this early work, however, was that it seemed to provide scientific evidence for the old story, and to extend it from human beings to all other mammals like a great cosmic principle (see Wikler and Pescor 1967; Bejerot 1980; Dole 1972; Goldstein 1972, 1976; Jaffe 1980; McAuliffe and Gordon 1980; Ahmed, 2018).

It is now more obvious than it was half a century ago that merely self-administering a drug is not the same thing as being addicted to it and that the laboratory animals that inject the drugs into themselves are deprived of normal social life, natural habitat, and mobility. Most of the experimental animals were caged and harnessed to an implanted catheter, a condition that may be painful and that certainly prohibits the normal activities of a free-living animal. Long ago, a few animal researchers like Yanagita (1970) declared strong reservations about generalizing from animal behaviour to human addiction under these conditions.

The Rat Park Experiments

Our group of researchers at Simon Fraser University in Canada, initially including Patricia Hadaway, Robert Coambs, Barry Beyerstein and Bruce Alexander, set out to experimentally

investigate how physical and social environments affect opioid use by rats. We used Wistar “Old Colony” laboratory albino rats, which are extremely gregarious, curious, and active creatures. Their wild ancestors, Norway rats, are intensely social animals (Lore and Flannelly 1977) whose social responses remain largely intact even after hundreds of generations of laboratory breeding (Grant 1963). The opioid drug used in the Rat Park experiments was morphine hydrochloride, a salt of morphine that was used in morphine tonics that were medically prescribed for oral consumption in those days. Morphine is readily interchangeable with today’s more notorious opioids for human beings both in medical treatment and in illicit settings. Today’s opioid overdose crisis in the United States and Canada provides a powerful reminder that injection is not a necessary part of opioid addiction. Terrifyingly large numbers of people have become dangerously addicted to opioids taken orally (e.g., Quinones, 2015).

We designed the Rat Park studies to determine whether rats in the isolated, barren housing that was similar to that used in the Skinner box studies would ingest more morphine than animals in more natural surroundings. We constructed a housing environment mimicked the rats' natural environment and named it “Rat Park.” It was spacious, with about 200 times the floor area of a standard individual housing cage or a Skinner box. It was also stimulating: Painted walls and objects, such as tin cans and wood shavings, for the rats to explore and manipulate. Perhaps most important, it housed an entire rat colony 24 hours each day: sixteen to twenty rats of both sexes, and, as time passed, lots of baby rats toddling about.

We measured the morphine consumption of rats that were individually housed 24 hours each day simply by fastening a drinking bottle containing the morphine solution next to the rat's

regular water drinking bottle on the side of the cage. Weighing both bottles regularly provided a measure of how much drug solution and drug-free water was consumed each day.

A more elaborate device to measure fluid consumption of animals living in a colony was invented and built by Robert Coambs to measure individual consumption in Pat Park. The device provided a short tunnel opening into Rat Park that allowed one rat at a time to enter. The rat could chose between two drop dispensers. One dispenser contained the drug solution and the other contained the inert control solution. The device automatically recorded how many times a rat in the tunnel activated each drop dispenser, while a photoelectrically activated camera recorded an identifying dye mark on the back of the animal (see Coambs et al. 1980 for full description). Raw consumption data were converted into three measures of each rat's daily morphine consumption: milligrams of morphine solution, mg morphine/kg body weight, and proportion of morphine solution to total fluid consumption.

Morphine solutions taste unpleasantly bitter to human beings and also, apparently, to rats. Rats reject morphine solutions with the same signs of distaste that they show towards any extremely other bitter solution such as quinine sulphate and water. Offered a simple choice between water and morphine solution, rats take only a drop or two of the drug solution and ignore it thereafter. However, Khavari et al. (1975) researched mixtures of morphine and sucrose that were sweet enough that rats would drink them in preference to water in quantities sufficient to produce signs of withdrawal when the solution was removed.

Morphine Consumption in Rats Without Prior Opioid Drug Experience

The experimental design that became our standard Rat Park experiment measured differences in the consumption of sweetened morphine solution between eighteen rats (nine of each sex) individually housed in small cages, and the same number of rats living in a Rat Park colony (Hadaway et al. 1979). None of the rats had any experience with opioid drugs prior to the experiment.

In order to determine whether the two housing environments produced any differences in attraction to the taste of sugar, the initial phase in the experiment offered the rats a choice between unflavoured water and sugar solution without morphine. The second phase offered rats a choice between water and morphine solution. In five subsequent phases of the experiment, the solution containing morphine was made increasingly palatable to the rats in each successive phase by either raising the concentration of sugar or lowering the concentration of morphine. In a final phase, the rats again had a choice between plain water and sugar solution.

The individually housed rats ingested significantly more morphine than the animals housed in Rat Park (see Figure 1). There was no housing effect on preference for the plain sugar

water in the initial phase, and the Rat Park animals actually drank significantly more of the sugar solution in the final phase (whereas they drank less of the sweetened morphine solution). In the first couple of phases in which morphine-sugar solution was used, some rats in both environments drank no morphine solution at all. As the flavour improved, caged rats increased their consumption of morphine dramatically while those in Rat Park increased theirs by only a small amount. The differences in morphine consumption were large and statistically significant in the last three morphine-sugar solution phases.

This experiment suggests a gender effect, with female rats consuming more morphine than males. We have not discussed this gender difference in this chapter, because the gender differences appeared in some of our experiments but not others. For our present purposes, the housing effect, which we found in rats of both genders, is more important.

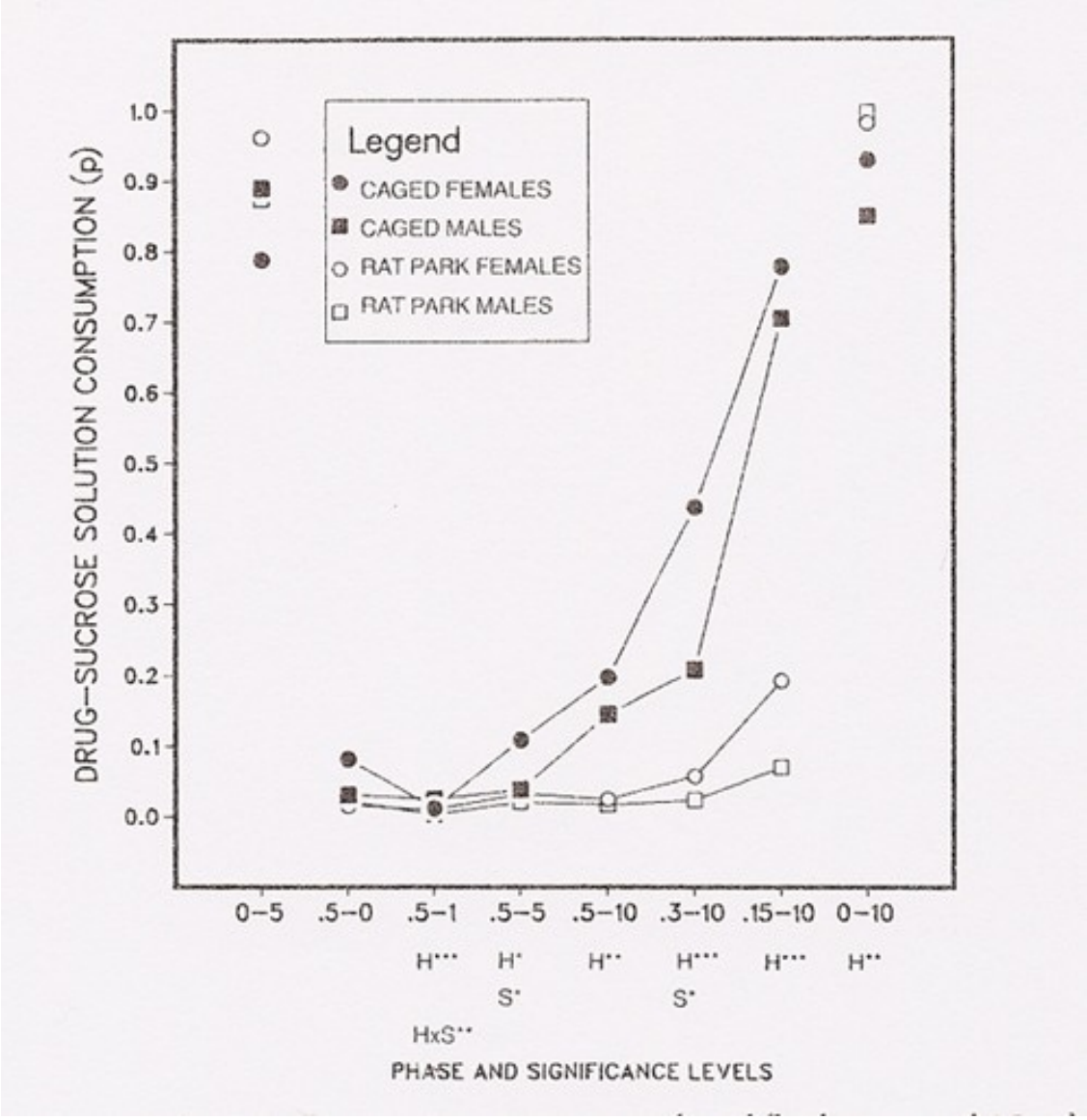


Figure 1. The Standard Rat Park Experiment (Hadaway et al., 1979). This figure depicts morphine-sucrose solution consumption as proportion of total fluid consumed. Thus, phase .5-1 offered the rats a choice between unsweetened water and solution of O.5 mg morphine hydrochloride in a 1% sugar solution. Numbers identifying successive phases give the composition of the drug solution: mg morphine hydrochloride per ml water followed by percentage of sucrose in solution by weight. Significance levels from analyses of variance for each phase use following symbols: H = housing effect, S = sex effect, H x S = housing by sex interaction; * = $p < .05$, ** = $p < .01$, *** = $p < .0001$.

We later replicated the housing effect that had been demonstrated in this experiment, as

part of a larger experiment (Alexander et al., 1981). This experiment is discussed in detail later in this chapter.

Morphine Consumption in "Pre-Addicted" Rats

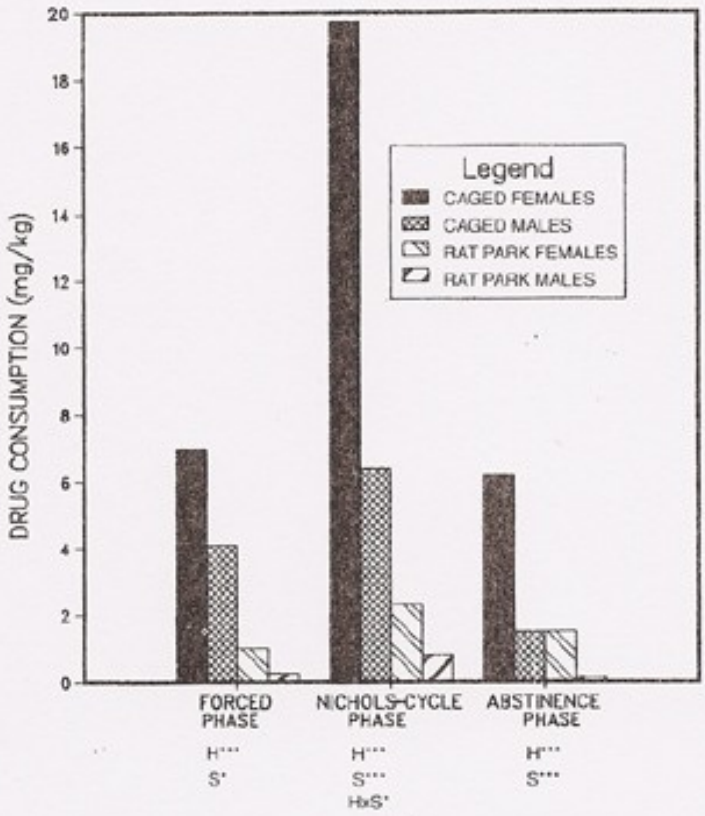
But would Rat Park animals ingest less morphine than caged animals when both were suffering from opioid withdrawal symptoms because they had been presumably pre-addicted?

To answer this question, Alexander et al. (1978) used unsweetened morphine solution (0.5 mg morphine hydrochloride/ml water) the only source of fluid for both individually caged rats and Rat Park rats for fifty-three days. Similar experiments in other laboratories indicated that the amount of opioids these animals ingested was more than enough to cause withdrawal symptoms (e.g., Fuentes et al. 1978).

Interspersed in this forced consumption phase were four choice days during which the rats in both environments were given access both to water and to morphine solution. At the end of this fifty-seven-day period, the rats were put on a training regimen designed by Nichols et al. (1956) to teach rats that drinking morphine solution would relieve their withdrawal symptoms. The Nichols phase of the experiment consisted of repeated three-day cycles comprising one day of no fluids, one of only morphine solution, and one of only water. This cycle was repeated eight times interspersed with four morphine-water choice days that occurred after each pair of cycles.

In the final, abstinence phase of this experiment, all morphine was withdrawn except for two morphine-water choice days, one each at two weeks and five weeks after the Nichols cycle phase.

Again results were large and statistically significant. In all three phases of the experiment, individually caged rats consumed the most morphine; during the Nichols phase, caged rats average about eight times as much morphine during the four choice days as did the Rat Park rats and generally ingested more as the phase progressed. (See Figs. 2 and 3).



Morphine consumption on choice days in three phases as mg MHCl/kg body weight. Significance levels indicated as in figure 4–1.

Figure 4–2. Second Rat Park (Forced Consumption) Experiment

Figure 2. Forced Consumption Experiment (Alexander et al., 1978). Morphine consumption is given as mg/kg body weight. Statistical significance is indicated as described in Figure 1.

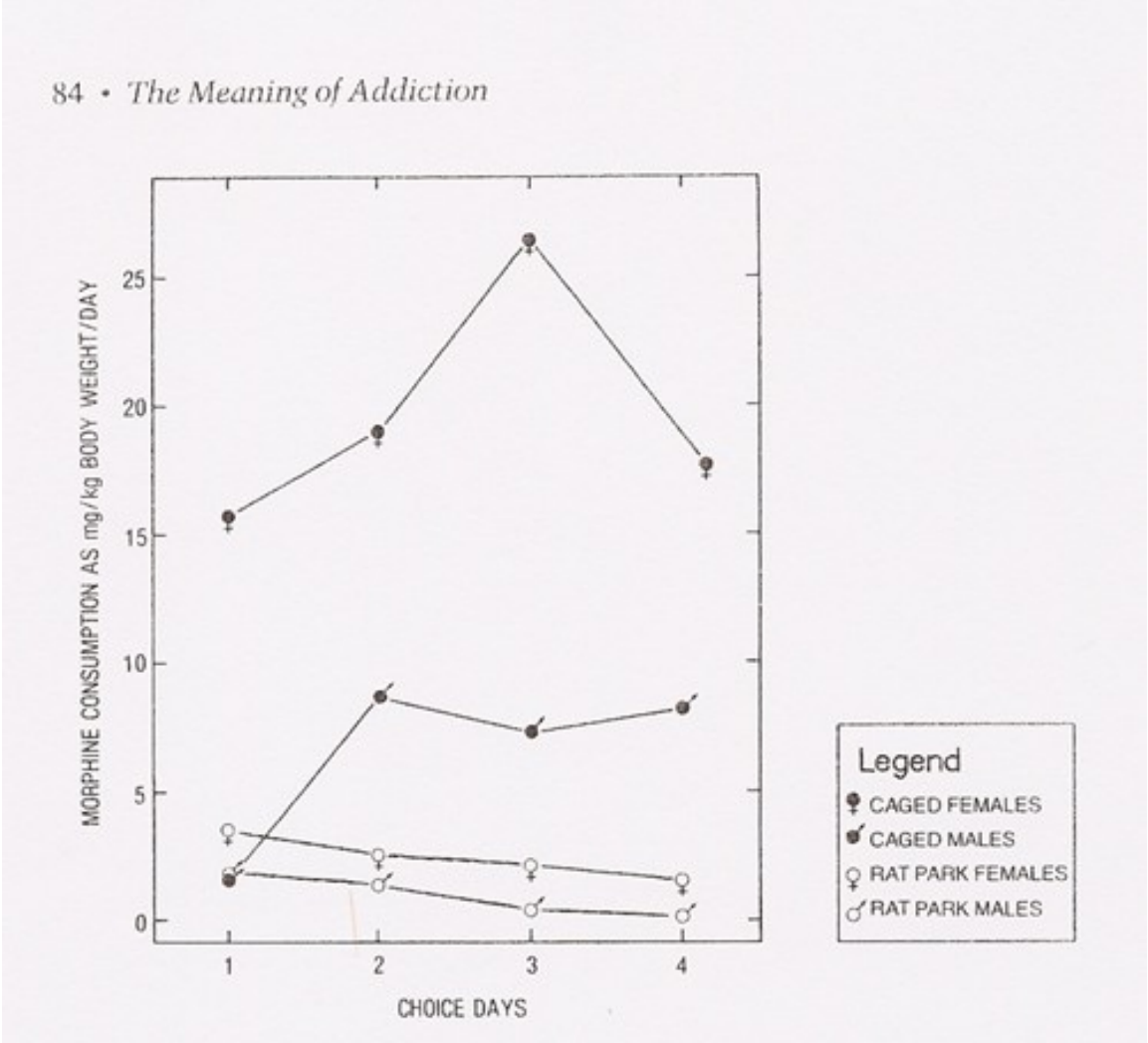


Figure 3. Nichols Cycles. (Alexander et. al., 1978). Morphine consumption during the successive cycles of the Nichols phase is given as morphine hydrochloride consumed per kilogram of body weight. Over successive cycles, the individually caged rats – but not the Rat Park rats – substantially increased their morphine intake.

The results of this Rat Park experiment with "pre-addicted" rats called into question the theory of addiction that was conventional in those days: That withdrawal symptoms were so powerful that they provided an irresistible impetus to opiate addiction. Just as with human beings, a rat's response to being withdrawn from a narcotic is influenced by situational factors. When housed in Rat Park, animals in this experiment did not act as though the need to avoid withdrawal discomfort was an irresistible imperative.

What Caused the Rat Park Housing Effect?

The Rat Park experiments that have been reviewed so far disprove the old story about the irresistibility of opioid drugs that had been drawn from previous research on rats and other animals isolated in laboratory cages and Skinner Boxes. The Rat Park data indicate that the supposed irresistibility of opioids to rats does not hold when the rats are living in an environment that resembles their natural habitat, even after the rats have been "preaddicted" by a lengthy period of forced consumption of opioid drugs.

But *why* do Rat Park rats ingest less morphine than caged rats? The many distinctions between Rat Park and a standard individual cage make it impossible to pinpoint the specific factors that affect the animals' morphine intake. Rat Park differs from an individual cage in that it affords rats not only a social environment, and the opportunity for sexual activity, but also more space per animal and greater diversity and complexity of physical surroundings. There are also many other seemingly minor differences between the two environments that may or may not affect morphine consumption. All of these differences between the two laboratory environments affected that rats both early in their lives, in the weeks immediately after weaning when they were habituated in their respective housing environments, and at the time when they were actually choosing between opioid and non-opioid solutions as sexually mature animals. Either of these time periods could be critical to the effect of the two environments on morphine consumption.

This section reports many variations on the standard Rat Park experiment that our group undertook, some of which were never published as full journal articles although they were discussed in our 1985 review article. These experiments were an attempt to identify the most important reasons for the consistently greater consumption of morphine in individually caged rats, compared to rats living in Rat Park.

Timing of the Housing Effect. The experiment that produced the clearest results (Alexander et al., 1981) was designed to separate the housing effects of the rats' early post-weaning environment from the environment at the time that the rats were actually choosing between opioid and inert solutions.

We housed thirty-two male and female rats in either individual cages or Rat Park at weaning (age 21 days) placing half of the rats in each housing environment. At age 65 days, when the rats had reached sexual maturity, we moved half the rats in each housing condition to the other, creating four housing conditions: C-C, or individual caging both early and late; C-RP or caging early and Rat Park late; RP-C, Rat Park early and caging late; and RP-RP, Rat Park both early and late. At age 80 days the rats began the standard experiment, starting with both a sucrose and a quinine-sucrose pre-test, proceeding through the usual sequence of morphine-sucrose

solutions, and ending with a sucrose post-test.

Figure 4 depicts results of this experiment for one of the measures of opioid consumption for male rats (data for the other measures and for female rats indicate the same effects, although not with the same degree of statistical significance; see Alexander et a1. 1981 for the full data set).

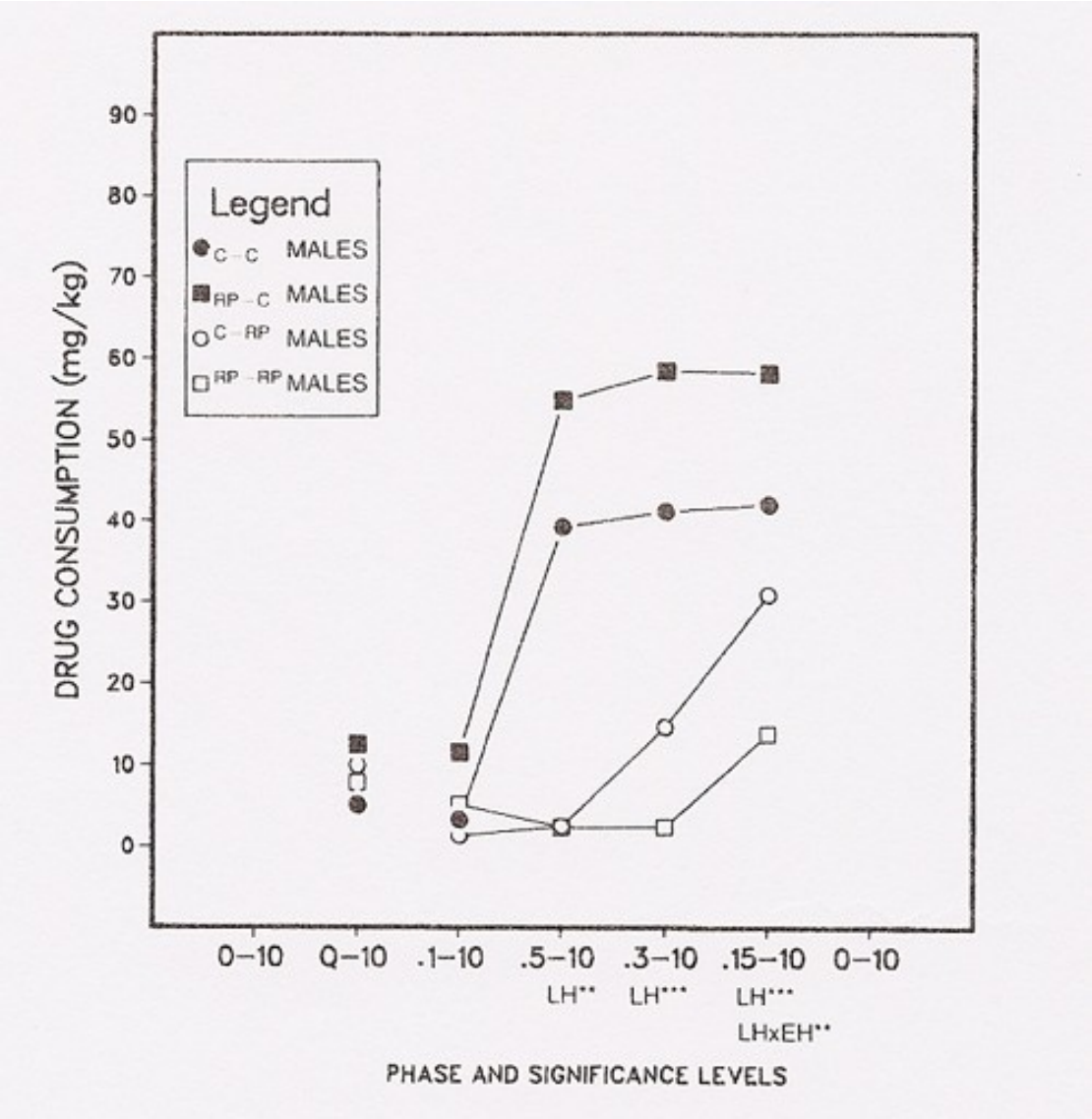


Figure 4. Morphine consumption per kg body weight for male rats housed early or late in cages and Rat Park. (Alexander, et al., 1981). Abbreviations for housing conditions are C for caged and

RP for Rat Park. Thus, the C-C Males were housed in Rat Park both early and late and the RP-C males were housed in Rat Park early and individual Cages late in the experiment. Analysis of variance significance levels are EH for early housing and LH for late housing. Statistical significance is indicated with asterisks as described in Figure 1.

These results are quite complex and require some study – even for their original authors three decades later! The results are best studied with the full data of the original journal article at hand (see Alexander et al., 1981).

As Fig 4 shows, statistically significant differences in opioid consumption were found for late housing, but not for early housing. The rats housed in cages at the time when they were choosing between morphine and inert solutions consumed more morphine than did rats housed in Rat Park. This indicates that, the housing effect in Rat Park was primarily produced by the housing environment *at the time of choosing* between the morphine and inert solutions rather than the housing environment early in life.

Please note that a full replication of the standard experiment is embedded in this more complex experiment, since the rats that were housed in Rat Park both early and late (RP-RP) and those that were housed in cages both early and late (C-C) were subjected to the same housing conditions as the Caged and the Rat Park rats described in Hadaway et al., 1978 (See Fig. 1). The effects of housing on morphine consumption of the rats of both sexes in the two experiments are very similar.

However, further examination of these more complex data suggested a conclusion that we had not anticipated. Although the housing at the time of choosing had a consistent, statistically significant effect on drug consumption, early housing in Rat Park *decreased* morphine consumption in the rats that were given the choice test in Rat Park, but it *increased* morphine consumption in rats that were given the choice test in individual cages. Another way of saying this is that the rats that had been shifted from one environment to the other consumed more morphine solution than those who ended up in the same housing environment at the time of choosing. We could say that *environmental change* or *dislocation* enhanced choosing to consume morphine even though that effect only reached statistical significance (the EH x LH interaction) at the final experimental stage.

Which Aspects of the Environmental Differences Produced the Housing Effect? Ambiguous Results. The first specific environmental feature tested for its effect on morphine consumption was isolation. Perhaps social isolation is the single factor that leads to high morphine consumption, whereas any kind or degree whatsoever of social interaction in any kind

of space whatsoever deters morphine consumption. To test this simple hypothesis, one, two, or four rats were housed in single cages of the same size (about two-and-a-half times the size of a standard cage.) Some of the duos and quads were all female, some all male, and some mixed. The animals were then the phases of the standard Rat Park experiment and their consumption of morphine measured by weighing the bottles in their cages. The perfectly simple hypothesis turned out to be perfectly false. Groups of four rats (whatever the sexual composition) ingested about four times as much morphine as one rat and twice as much as two. In other words, social housing had no effect on morphine consumption when the size of the housing environment was held constant.

Our next experiment hypothesized that living space alone had caused the differences in morphine consumption in the previous Rat Park experiments. We constructed twelve pens, each five-feet square (making them one-third the size of Rat Park but still more than sixty-five times as large as standard cages). We then preformed an abbreviated form of our standard experiment in which four of the pens contained single males, four single females, and four male-female pairs. A comparison group of twelve rats (six male and six female) were housed in individual cages. The hypothesis was that all the rats that had a relatively large space to live in, regardless of social isolation, would resist drinking morphine.

In the abbreviated form of the standard experiment, we gave the rats a quinine-sucrose solution vs. water pre-test and post-test along with the choice between three increasingly sweet morphine solutions vs. water. Space alone had no apparent effect on morphine consumption of isolated rats: No significant differences were found between the caged and the penned singles in the pre-test or post-test or in any of the morphine-intake phases. However, as figure 5 shows, the penned pairs drank less morphine than both the penned and the caged singles. The housing effect for the .3-10 phase was significant for the proportion data. (See Fig. 4).

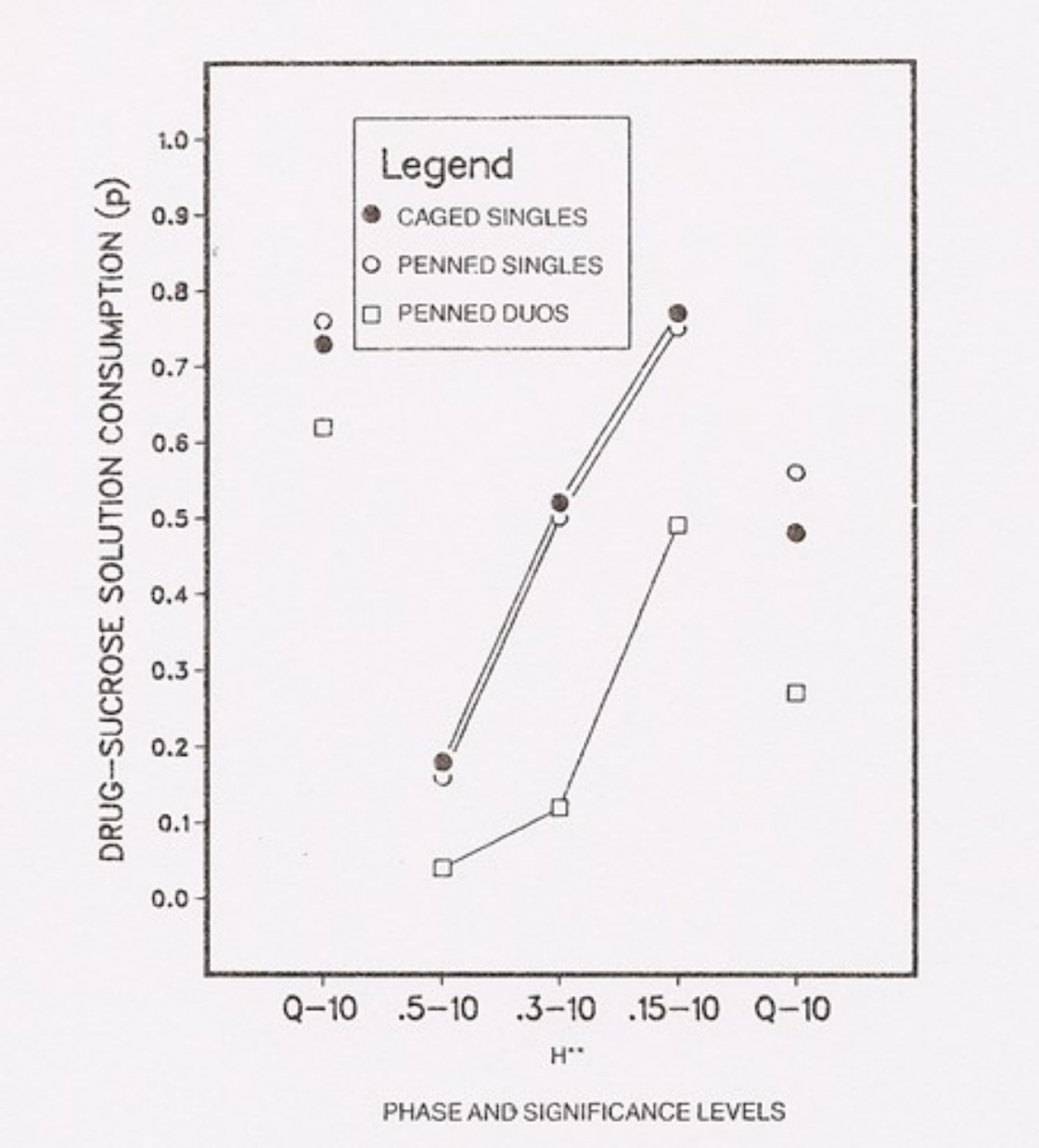


Figure 5. Morphine consumption as proportion of total fluid consumption by individual rats in cages and individual and paired rats in pens. (Unpublished study.) Morphine consumption as proportion of total fluid consumed. All abbreviations same as for figure 1, with the addition of Q-1O to represent 0.06 mg quinine sulfate/ml water + 10 percent sucrose.

These results suggested that neither isolation nor space alone is the key cause of the difference in the original Rat Park experiments: rats that had both more space and a companion

ingested significantly less morphine in the .3-10 phase than those lacking either or both of these assets (see figure 4).

Unfortunately these results were only significant at a single phase of the experiment. The results are also weakened by the large (but statistically nonsignificant) differences between the groups in the pre-test, which suggest that taste, as well as drug effects, may have accounted for the difference in morphine consumption between the penned duos and the other two groups in the experiment.

We designed another version of the standard experiment to clarify this disappointing result. In this experiment, there were four housing conditions: caged singles, caged pairs, penned singles, and penned pairs. Unfortunately the results of this experiment were not usable, because there were significant differences in the results of the pre-test (in which the rats chose between a quinine sugar-solution and water) in the same direction as the differences between in the experimental stages when the rats chose between sweetened morphine solutions and water. It is therefore probable that differences in morphine consumption among the groups resulted, at least partially, from an aversion to bittersweet solutions somehow produced by the different housing conditions. This was a beginning of a series of more serious complications.

Failed Replications in Rat Park with "New Colony Wistars"

In order to resolve the possibility, suggested by the experiment just described, that taste preference differences played a large role in our previous results, we re-ran a standard Rat Park experiment employing a virtually tasteless opioid, etonitazene. (Etonitazene is tasteless because, like fentanyl and carfentanil, it is much more potent than heroin and morphine, and must therefore be used at much lower doses. At effective doses etonitazene is tasteless to human beings, making it both more useful and more dangerous than less potent opioids.) The new experiment utilized a new and improved device for measuring fluid consumption in Rat Park. The Rat Park housing effect was not confirmed under these conditions.

Nor was the Rat Park housing effect confirmed in two subsequent experiments that utilized morphine in the standard Rat Park experimental designs. (Petrie, 1985; 1996). The failed replications did not occur because the Rat Park animals consumed more morphine than in the earlier studies but because the isolated animals drank less, approximately equalizing the amount of morphine consumed in the two housing conditions.

Non-replication is not a fatal problem in laboratory research, but it requires follow-up studies to determine why has occurred. Many factors can determine the outcomes of

experiments and not all of them can be controlled. Did the non-replication occur because we were using a new substrain of rats, or because the modified, presumably improved, apparatus that measured drug and water consumption in Rat Park did not work as well as the original machinery, or simply because the Rat Park effect was not as robust as we originally thought?

We still cannot say with certainty why these non-replications occurred. A close analysis by Bruce Petrie, the researcher who actually conducted the non-replication experiments in our laboratory, uncovered the most likely reason (Petrie, 1985, pp. 65-83). The most likely reason is the fact that the strain of rats that we used, supplied by Charles River Canada changed in November 1979 after the completion of data collection for Alexander et al., 1981).

New Colony Wistars replaced the so-called "Old Colony Wistars," which had been used in all our experiments demonstrating the Rat Park effect. The New Colony rats were not direct genetic descendants of the Old Colony rats (Petrie, 1985, p. 71), but they were closely related. They were considered "new" because they had been purged of being "antibody positive" for several viruses that had plagued the old colony. The housing conditions during breeding also differed between the old and new colony animals, as did the litter size. The new colony females produced an average of two more pups per litter.

According to Bruce Petrie's conversations with other Canadian researchers, New Colony Wistars differ behaviourally and temperamentally from Old Colony Wistars on number of dimensions, including being less willing to drink solutions containing alcohol (Petrie, 1985, p. 68-69; 1996). A published experimental comparison of Old Colony and New Colony Wistars demonstrated a difference in the responses of the two sub-strains to chronic administration of naltrexone (Ng Cheong Ton, Blair, Holme, and Amit, 1983). Naltrexone is an opioid antagonist. These researchers suggested that these results may be caused by differences between the two substrains in "modulation of dopamine function by opioid peptides via opiate receptors" (Petrie, 1985, p. 68).

Thus, the most likely cause of the non-replications of the original Rat Park experiments were that a new sub-strain of experimental rats had much less appetite for consuming opioid drugs overall than our original "old colony" Wistar rats. However, confirming this interpretation would require extensive experimentation, which never occurred because our laboratory was closed.

Rat Park Retires

We unable to conclusively solve the mystery of our non-replications, because Rat Park

was closed down for good by our university due to an expensive problem with the air conditioning system in the laboratory that we could not repair since we had no grant funds. We had no grant funds because the granting agencies of 4 decades ago, in the midst of a ferocious War on Drugs, were not interested in research which radically contradicted the conventional and official wisdom that opioid drug caused opioid addiction.

In spite of the abrupt and inconclusive ending to the Rat Park story, we remain confident in the housing effect on opioid consumption that appeared in our original experiments, because we repeated the experiment several times in different ways with Old Colony Wistar rats. Rat Park provides solid evidence against the old story.

We also remain confident because other researchers have supported – and extended our findings that social isolation increases drug consumption, using heroin (Bozarth, Murray, & Wise, 1987), alcohol, (Wolffgramm & Heyne, 1991), and cocaine (Schenk, Lacelle, and Amit, 1987). Rats housed in "impoverished" environments have also been shown to self-administer more cocaine than rats housed in "enriched" (although not social) environments (Solinas, Thiriet, Chauvet, and Jaber, 2010). Mice that are subject to "immobilization stress" have been shown to self-administer more morphine and fentanyl than unstressed mice (Shaham, Alvares, Nespor, & Grunberg, 1992)

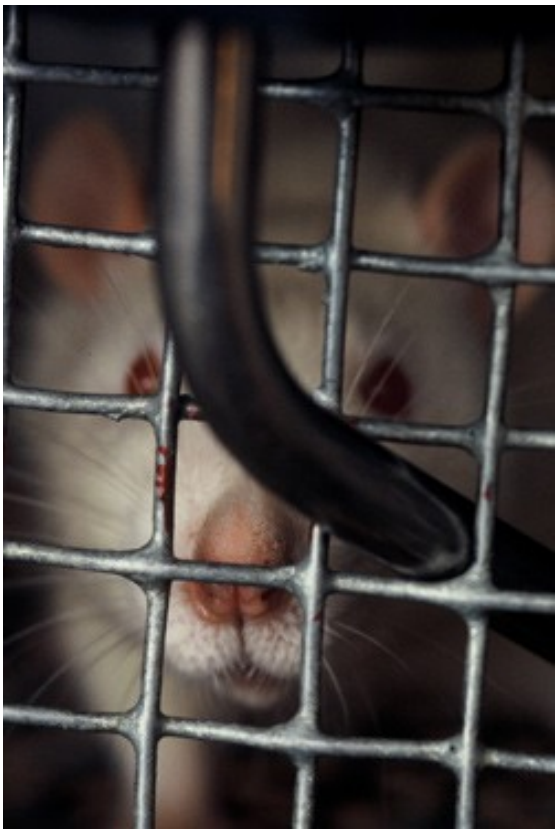
The Rat Park research is no longer the strongest animal evidence that discredits the old story. There is now more sophisticated animal research on social stressors including isolation, social exclusion, and low rank in the pecking order. These social stressors not only increase drug consumption in laboratory animals and human beings, but they also lower sensitivity to drugs and produce neurochemical changes in areas of the brain that have been linked to the establishment of addictions (e.g., Schenk, Hunt, Malovechko, Robertson, Klukowski, & Amit, 1986; Whitaker, Degoulet, & Morikawa, 2013; Zeilokowsky et al., 2018; review by Heilig, Epstein, Nader, and Shaham, 2016).

Other research has built on the observation that the absolutely simple environment of a Skinner box is not comparable to the complex choice-filled environment of human beings who become addicted to drugs. When rats are given a more normal set of choices and contingencies, the opioids are far from irresistible (see review by Heilig, Epstein, Nader, and Shaham, 2016). Therefore, *research on isolated or socially stressed animals can tell us nothing about the causes of addiction in normal animals and normal human beings*!

In view of all the research on animals, and an even larger body of research on human beings (see literature reviews by Alexander, 2008/2010, chap. 8; Alexander, 2014) that has accumulated over the last four decades, the sweeping overgeneralization that provoked the Rat Park studies in the first place –that individuals of all species who use addictive drugs become addicted, regardless of their other circumstances – has long since lost any claim to validity. The

Rat Park experiments can now be retired from the fray of academic disputation. Perhaps, however, our early experiments will retain the retirement role of serving as a simple illustration of the bald fact that the old story of addiction is wrong for people who do not have the time to review the more extensive literature.

But provocative questions linger. *If mere exposure to drugs does not cause addiction, what does? Is there a sense in which those people who become addicted actually feel "caged"?* We believe that the metaphor of "cages" is a deep and fruitful one, and this belief has been built into for our continuing research since Rat Park was taken down and stored away, a third of a century ago. Our understanding of the nature of invisible human "cages" has developed slowly over this period but has now reached some firm conclusions. We hope you will be tempted to explore the conclusions that grew from the rat experiments conducted so long ago (see Alexander 2008/2010; 2017; 2018; Peele,1998) and that you will join us is welcoming the new paradigm that will inevitably replace the tired old story.



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