Discovering Addiction

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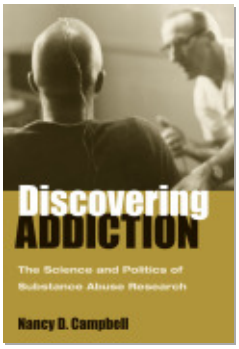

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CHAPTER 2

Creatures of Habit: Feeding the "Junkie Monkeys" of Michigan

Sociologist Howard S. Becker observed: "Science works when you make the world into the kind of place where that kind of science will work. That's the purpose of creating laboratories" (2005).[1] Scientific communities become committed to particular laboratory logics that form the practical basis of how they go about their work. Concepts alone do not guide scientific commitments, for the research materials, technologies, and methodologies available exceed the conceptual boundaries of theoretical approaches. A broad shift to experimental physiological research was under way during the 1920s and 1930s, when the addiction research enterprise came into being (Clarke 2005, 286). Monkey colonies were first organized as part of developing the infrastructural capacity to maintain reliable access to experimental subjects for a variety of scientific projects. The monkey colony can be seen as a project to create a research site where a particular kind of science could work—an experimental science designed to elucidate the neurophysiology of tolerance, dependence, and withdrawal.

Faced with psychological, or "subjective," desire for drugs, pharmacologists had either to incorporate desire into their experimental models or find some method to disqualify it. They turned to animal models both to bracket desire and to place their research on the more objective ground sought by the NRC Committee on Drug Addiction. Seeking to place drug policy on solid footing, the committee turned to the basic sciences, a move that effectively cut out social scientists and clinicians from the addiction research enterprise in its formative moments. Animals presented an expedient route to determine toxi-

city, of course, but some researchers set about using monkeys to learn more about desire. Questions immediately arose as to whether animals and humans responded similarly to drugs.

Animal models relied on a set of laboratory logics that enabled researchers to attribute meaning to their observation of the visual manifestations of animal behavior and to their measurements of physiological responses. Animals were interpreted as "addicted" once they reached a steady state of maintenance on morphine—for example, when administration of morphine produced no change in heart rate or respiration. They were then abruptly withdrawn from morphine, and another test compound, or "challenge" drug, was administered. Depending on the profile of effects observed during this substitution, the animals would either proceed through withdrawal or have withdrawal arrested by the test compound. Data produced on the basis of this logic of substitution revealed which drugs produced tolerance and withdrawal, and these drugs were considered "addictive."

Working collaboratively and conflictually with the pharmaceutical industry, the NRC committee systematically set out to review all compounds that promised to achieve analgesic effects without producing physiological symptoms of tolerance and withdrawal. When companies wanted to market drugs as painkillers, the committee would subject the drugs to human and animal testing to determine whether releasing them onto the market would pose a threat to public health. The idea that opiate addicts could be shielded from the consequences of their own physiological needs and psychic desires was central to the committee's efforts to contain the "opium problem" by identifying a nonaddicting painkiller and getting people to substitute it for morphine-based compounds. While industry supplied interesting compounds, the committee was never in thrall to the pharmaceutical industry, acting instead as an independent, nonregulatory source of oversight. Shuttling between basic medicinal chemistry, animal pharmacology, and clinical research, the committee was placed in the role of synthesizing competing findings between research sites. One of the research sites most integral to the committee's efforts was the monkey colony built by pharmacologist Maurice (Mo) H. Seevers at the University of Michigan to document primates' affinities for addictive substances.

Remarkably for his era, Seevers became a "harm reductionist" across a half century of laboratory life and long before the term was fashionable. He wrote, "The only realistic and achievable objective is to confine excessive drug use to a minimum and find better ways for society to live with it." He encouraged his colleagues that they should not become "puppets in international drug control" and simultaneously that they should combat the "plethora of pseudosci-

entists, false prophets, quasi-intellectuals, instant experts, self-seeking politicians, beaurocratic [*sic*] ignoramuses, soft-headed educators, and others of similar ilk" spreading a "hedonic plague" of drug abuse. Against this plague, he thought that scientists of his ilk should "educate individuals to have long range concern for health in the face of strong hedonistic desires" (Seevers 1972, 12). As a public spokesperson for pharmacology, Seevers was unusual in several respects. Most pharmacologists neglected the study of drug addiction, due to the stigma attached. Seevers's interest in all things drug-related spanned his career from the 1920s to the 1970s, during which the fates of pharmacology and addiction research fluctuated. The remainder of this chapter explores the changing situation of pharmacological research as enacted in the laboratory life of Seevers and in the monkey colony he brought to life.

Based on the laboratory logic of substitution, Seevers refined a technique whereby compounds were administered blind to a colony of morphine-dependent monkeys to determine whether human beings were likely to use or abuse them. The roots of the logic of substitution are located within the pharmacological enterprise and attempts to establish animal models for addiction (DuMez 1919; DuMez and Kolb 1925, 1931; Eddy 1973). Those studying the "junkie monkeys" of Michigan were obviously using animals in instrumental ways. Seevers is credited with the idea of establishing and maintaining a colony of morphine-dependent monkeys used as research tools.[2] In *Creating the American Junkie,* Caroline Acker argues that the "search for a nonaddicting analgesic emerged as a project typical of the 'classical pharmacology' of the 1930s, in which bioassay of compounds revealed therapeutic or toxic effects and their related dose ranges" (2002, 94). However, there was more to it. Whereas Acker argues that addiction research conducted in the laboratory reinforced the supply-side emphasis of drug policy of the classic era, Seevers himself was interested in the structure of desire, the demand side of the drug problem. Lacking a common language for thinking about desire for drugs, pharmacologists designed laboratory logics that enabled them to study desire without turning to the contested vocabulary of psychoanalysis. This chapter describes these logics as a prelude to reconstructing the use of human subjects in addiction research.

EMBODYING PHARMACOLOGY: THE TURN TO ANIMAL MODELS IN ADDICTION RESEARCH

Interdisciplinary since its inception, pharmacology has been "a multifaceted discipline that has gained strength and vitality from its dependence on and

relationship to other disciplines as they have grown and developed" (Bass 1969, 157). Well into the mid-twentieth century, pharmacologists found it difficult to "circumscribe a specific body of scientific knowledge and say, this is the substance of, and therefore belongs exclusively to, the science of pharmacology" (Seevers 1969b, 208). Rooted in botany, experimental biology, chemistry, and medicinal chemistry, pharmacology bore some relation to clinical medicine yet enjoyed far less prestige. As late as the 1960s, according to Seevers, "a majority of the leaders in the biomedical sciences viewed pharmacology as an applied branch of physiology or biochemistry, not worthy of recognition as an independent discipline" (1969b, 208). Several factors converged to expand opportunities for U.S. pharmacologists prior to World War II, including movements toward drug standardization and the wholesale reform of medical education in the United States. Today, pharmacology plays the role of a respectable basic science; others determine its therapeutic applications, clinical relevance, and policy implications.

On January 28, 1939, the Rockefeller Foundation, which had assumed funding of the addiction research project from the New York Bureau of Social Hygiene in 1932, transferred responsibility for the "opium problem" to the federal government (May and Jacobson 1989, 186). The newly constituted NRC committee operated under the name Committee on Drug Addiction and began to expand and consolidate the pharmacological research infrastructure in the United States.[3] The committee chose the University of Michigan Department of Materia Medica, under the direction of Charles W. Edmunds, as one of the premier laboratories for its purposes. According to Reid Hunt, a Harvard pharmacologist instrumental in getting the NRC involved, Edmunds now had "the most active department in this country, and, I presume, in the world."[4] In 1930, Edmunds hired Nathan B. Eddy to oversee the pharmacological testing of compounds provided by Lyndon F. Small's chemical laboratory at the University of Virginia. Eddy took on the role of liaison between members of the coordinating body, a part he played for the remainder of his distinguished career as one of the world's leading pharmacologists of the opioid drugs. In 1939, Eddy moved from Michigan to the National Institutes of Health (NIH), from which he steered the research agenda of the NRC committee for the ensuing decades.

The laboratory life of Maurice H. Seevers began with some of the earliest systematic animal studies on the effects of morphine and cocaine. While awaiting admission to Rush Medical School in 1925, he studied with Arthur Lawrie Tatum, MD, of the Department of Pharmacology and Physiological Chemistry at the University of Chicago, for whom he injected morphine into rhesus mon-

keys (Deneau 1970). Tatum was a "virtual consulting machine" whose research was tightly tied to commercial interests (Swann 1988, 103, 116). He started working on antimalarials for Parke-Davis in 1937, five years before the start of government-coordinated collaboration on antimalarials (Swann 1988, 112–13). However, his interest in morphine, cocaine, and the use of barbiturates as an antidote to cocaine overdose predated any commercial sponsorship. In 1929, Tatum became chair of the pharmacology and toxicology department at the University of Wisconsin at Madison. Seevers followed him, and they continued studying chronic morphinism (addiction) and the actions of barbiturates and central nervous system depressants in monkeys. Predating Seevers's 1930 dissertation, their early publications concerned experimental cultivation of chronic morphinism in rhesus monkeys and cocaine addiction in dogs, monkeys, and rabbits (Tatum, Collins, and Seevers 1927, 1929; Tatum and Seevers 1929). They observed morphine's paradoxical "dual effect," consisting of "a strange mixture of simultaneous stimulation and depression on different parts of the central nervous system" (Tatum, Collins, and Seevers 1929, 459). They found two lethal doses of morphine in rhesus monkeys: a lesser dose that killed by respiratory depression and a greater dose that killed by convulsions. Although these early experiments resulted in the death of animal subjects, Seevers and Tatum later tried to keep research subjects alive in order to study the long-term effects of repeated cocaine use, seeking to determine whether cocaine built tolerance as did morphine.

Questioning whether taking larger and larger doses of cocaine was evidence of tolerance or simply individual variation in the amount necessary to cause intoxication, Tatum and Seevers embarked on longitudinal experiments but reported that they were unable to bring about the "psychologic effects which are so characteristic of chronic cocainism in man" or the "sexual irregularities" observed in humans (1929, 403, 405). Concerned with extending their animals' lives, they administered intravenous cocaine to four dogs (one female and three males) for more than two years. Mere sight of the syringe excited the dogs, in whom they observed priapism and "nymphomania," but there was no evidence of abstinence symptoms when the researchers withdrew the drug (1929, 405). They reported that monkeys, in comparison, evinced neither desire for the drug nor abstinence symptoms but instead "presented a picture of extreme terror entirely resembling that immediately following the injection of the drug and during the course of its action" (1929, 407). Tatum and Seevers concluded that only dogs exhibited a "true cocaine psychosis with marked desire for the drug," while other species, including humans, were "sensitized

rather than tolerant to cocaine when habitually administered" (1929, 409). They reported experiments similar to those of Claude Bernard,[5] who administered combinations of morphine and cocaine, codeine, thebaine, caffeine, strychnine, or barbital to dogs and other animals.

The goal of these animal studies was to create an experimental system useful for elucidating how morphine and cocaine affected humans—studies complicated by the human subject's state of mind. Preoccupied with separating psychological drug effects from physiological effects, the researchers raised no ethical questions. By controlling laboratory conditions, Tatum and Seevers believed they could carry out experiments with "no preconceived opinions but with the idea of gathering facts from close observations that might ultimately lead to a rational and consistent view of chronic morphinism" (1929, 447). Finding it puzzling that monkeys appeared to lack desire for the drug, they tried to turn to human subjects. To demonstrate cross-tolerance (i.e., when the "activity of one drug renders another drug, chemically unrelated but pharmacologically somewhat similar, less than normally effective"), they described a "chronic morphinist" who betrayed no change in blood pressure, respiration, or subjective symptoms when barbital sodium was administered (1929, 462–63). They interpreted this lack of change to mean that morphine made the subject "cross-tolerant" to the barbiturate. However, Tatum and Seevers rarely worked with human subjects. Their animal experiments were designed to control for confounding variables present in humans due to state of mind or desire.

The animal experiments conducted by Tatum and Seevers were meant to model human addiction, which they defined as a "condition of mind or body induced by drugging which requires a continuation of that drug, and without which a serious physical or mental derangement results." For them, "habituation" meant becoming accustomed to a drug but not being seriously dependent on it; "tolerance" meant that more and more of a drug was required to produce equivalent effects. They defined "true addiction" as a condition in which "the organism needs a repetition of the drug . . . in order to approximate normality more nearly and, in the case of man, also to satisfy conscious desires or to escape painful sensations or painful thoughts" (1929, 466). Seeking to reconcile the vast and disconnected facts produced by observers into a "harmonious schema," Tatum and Seevers presented a diagram depicting a well-integrated nervous system that balanced depression and stimulation (1929, 467, 472). Addiction, they postulated, was a vicious cycle in which increased dosages augmented nervous excitability to the point that sedation was required; it was

the result of subjects' attempts to address states of physiological imbalance. Citing all previous European and American attempts to experimentally addict dogs, mice, and monkeys (DuMez 1919; DuMez and Kolb 1925), Tatum and Seevers advanced the "dual-action hypothesis" to make sense of the paradoxical coexistence of central nervous system depression and stimulation.[6] This hypothesis attempted to render the imbalance induced by morphine as physiological, not psychological.

Seevers's 1930 dissertation, "Acute and Chronic Narcotic Drug Poisoning," disproved an accepted belief that tolerance was the result of the organism building up a "general cellular immunity to the drug." Instead, Seevers postulated that some people needed increasing doses of morphine just to maintain normal equilibrium. He explained in his dissertation abstract, "Thus, by ever increasing doses a vicious cycle is established, and a state of exaggerated excitability of the central nervous system is reached with a raised threshold for depression whether it be by morphine or other depressants, allowing an individual to withstand doses of morphine that would cause fatal depression in the unaccustomed." Seevers's dissertation argued that abstinence symptoms were the body's signals that a depressant was needed in order for the subject to maintain physiological equilibrium between stimulation and depression; thus the severity of abstinence symptoms would be in direct proportion to the overall increase in the organism's nervous irritability. This work described the physiological need states apparent in morphine abstinence phenomena, but not the nonphysiological needs displayed by those deprived of cocaine. Lacking a scientific vocabulary for need states that were not physiological, Seevers's dissertation attributed them to "deranged mental conditions" and intense states of "subjective desire" experienced by regular users of cocaine.

Concluding that morphine addicts were simply seeking to maintain equilibrium led Seevers to think there might be something functional about the use of central nervous system depressants. Users of such other drugs as cocaine and cannabis, however, desired a dysfunctional disequilibrium. Venturing into the ongoing controversy about the nature of addiction as a scientific problem, Seevers and his contemporaries placed the study of addiction on a scientific footing to counter negative images of it in the medical profession and popular media. He explained, "To the average medical layman lacking firsthand experience with addiction, the term 'drug addict' may conjure a mental image of a sallow-skinned, hollow-eyed Oriental, who in his utter depravity is clutching with bony, long-nailed fingers at the throat of a young girl or suckling babe. Such a picture of addiction is commonly portrayed in the Sunday supplements

or in the literature of the professional reformers" (Seevers 1939, 91).[7] Scientists identified with addiction research countered these representations by invoking hardheaded physiology and disavowing any connection with psychoanalysis or psychology.

Differentiating between states of physiological need induced by morphine and states of desire for cannabis or cocaine, Seevers spoke with the confidence of science.

> Addicts to cannabis and cocaine are of a different stripe. Addiction, in [the case of stimulants], is usually a manifestation of a psychopathic desire to escape from reality—a sequel to vicious associations—or the need for an inflation of the personality. . . . Peculiarly enough, no definite and characteristic physical signs or symptoms follow withdrawal from these compounds, as is the case with the opiates. The cocaine addict is subjectively depressed and desires his drug intensely; he may even commit murder to obtain it; yet the physical manifestations of withdrawal are not characteristic. The same may be said of the addiction to the resin of the hemp plant, Cannabis. (1939, 95)

Seevers divided drugs into three categories: those that produced habituation (caffeine); depressants that produced a "definite train of physical, as well as psychic, disturbances" if withheld (morphine); and those, such as cocaine, that produced excitatory or stimulant effects but only "psychic addiction," which, Seevers noted, was no less severe or difficult to cure than physical addiction (1939, 95). Psychic addiction was, however, more difficult to model in the laboratory.

The scientific interests of Seevers's laboratory clearly lay with depressants that produced addiction and characteristic symptoms of abstinence in monkeys. In 1936, he published two classic papers titled "Opiate Addiction in the Monkey" in the *Journal of Pharmacology and Experimental Therapeutics.* Far from declaring cocaine, cannabis, or caffeine nonaddictive, he simply designated them as beyond his scientific purview. He told a 1938 lecture audience:

> Few of us would like to admit that we are caffeine addicts; yet, I will venture to say that there are many in this room who will develop a headache before noon if they are deprived of their habitual cup of breakfast coffee, or its equivalent in caffeine from tea or coca cola. Do we have, then, in caffeine, a drug which possesses in a small measure the requisites of a drug of addiction? Do the blood vessels of the brain become dependent on caffeine so that its presence is necessary to relax them and permit an adequate blood flow to this organ? These are questions which I will not assay to answer. (95)

Such remarks indicate the everyday routine of drug addiction, as well as Seevers's belief that misrepresentations could be countered by public presentation of factual knowledge.

Ironically, Seevers had begun to notice that his chosen profession was dwindling, and he nearly defected to do clinical research on anesthesiology. He later derogated pharmacology as the "weakling of the medical sciences" (1969b, 130). Describing American pharmacology as having been "in the doldrums" during the 1930s, he explained: "The older generation was discouraged; the field was unattractive to young men and few were trained; those who were contemplated moving to more promising fields; industrial pharmacologists were excluded from Society membership; important chairs were being filled by people from other disciplines" (1969b, 129). Seevers joked that in the 1930s, the main research question in pharmacology was, "What is the matter with pharmacology?" (1969b, 209). He was attuned to the low social status that dogged the field of pharmacology through much of the twentieth century (discussed in the next section of the present chapter).

Gaining experience with monkeys in Madison,[8] Seevers began to make what he called "monkey movies."[9] He shared their scripts with psychologist Harry Harlow, whose experiments on deprivation of maternal love are among the most notorious examples of primate research.[10] Based on the laboratory logic that "such slight differences exist between the signs of abstinence in this animal and those of the human addict that the monkey surpasses any other animal as a test object for the study of experimental addiction," these movies explored the puzzling problem—as Seevers wrote in the margins of one of the scripts—that "monkeys fail (usually?) to show signs of desiring injections of narcotic drugs."[11] Despite showing physiological symptoms of abstinence and possessing "sufficient cortical development to associate the administration of the drug during abstinence with relief of its distressing symptoms," these monkeys, "addicted" to codeine, morphine, heroin, and Dilaudid for periods ranging from nine to twenty-one months, did not appear to "desire" injection. The animals displayed grossly visible signs—sunken eyes, prostration, or muscle twitching—but they also showed social responses that researchers had to interpret, such as opposition to capture, desire for handling, discomfort, irritability, and quarrelsomeness.

The monkey movies joined other attempts to document visible markers of desire or develop methods to measure "desire or striving" (Spragg 1940). What Seevers called "positive desire-responses" were based on a conditioned, posi-

tive association between the needle and relief of symptoms. Because monkeys generally associated the needle with negative events, such as "disturbance at being caught" or the pain of injection, the total experimental situation worked against monkeys making overt, positive expressions of desire for the drug.[12] To get around the problem of negative associations, another primate researcher, S. D. S. Spragg, working under Robert M. Yerkes at the Yale Laboratories of Primate Biology in Orange Park, Florida, developed a "choice procedure." He trained chimps to cooperate with morphine injections by first adapting them to saline injections and rewarding them with fruit, praise, and patting (Spragg 1940). The chimps were then trained to "readily cooperate" for injection, with "only verbal approbation as reward," before they began receiving injections of morphine (which were not followed by reward). This "preliminary adaptation" was, in Spragg's view, responsible for his successful demonstration that chimpanzees would "work" for a dose of morphine (Laties 1986). Sheer force would not have worked, because the chimpanzees were heavy and active, but "preliminary adaptation" enabled twice-daily injections to become routine in Spragg's pathbreaking studies.

Once Spragg's experimental subjects were habituated to morphine injections, situations could be set up in which they could follow the dictates of desire, by choosing a color-coded key to unlock either a white box containing a syringe filled with morphine or a black box containing a banana. Their choices depended on whether they had most recently been deprived of food or morphine. When morphine-deprived, not only would the chimp unlock the box containing the syringe, but the animal would hand it to Spragg in urgent anticipation of injection. Another demonstration of the strength of animal desire was a movie made by Spragg showing a chimp forcefully pulling on a rope to drag the white-coated scientist into the injection room.[13] Similarly, Seevers's monkey movies tried to capture identifiable expressions of desire, which were seen as central for drawing connections between human and nonhuman primates. This strategy was part of Seevers's overall effort to keep pharmacological work in the animal laboratory relevant to the all-too-human problem of desire for drugs. Seevers wanted to augment pharmacology's public relevance by expanding beyond animal studies. His selection of research questions reflected these desires, but his laboratory logics were trained on animal models.

While still at the University of Wisconsin, Seevers continued to build toward establishing the biochemical basis for the action of morphine and its derivatives by seeking support from the NRC Committee on Drug Addiction.[14] Rather than

request financial subsidies, he sought the "large quantities of confiscated opiates that are destroyed by the Narcotic Division," for use in studies of "chronic morphine poisoning" in monkeys.[15] Researchers on the committee program enjoyed courtesy appointments with the U.S. Public Health Service that enabled them to obtain "quantities of condemned material from the Bureau of Prohibition of the Treasury Department" and "to receive alkaloids in interstate commerce" from chemist Lyndon F. Small (Acker 2002, 75–76). Seevers's request was relayed to Lawrence Kolb, who had done some of the earliest experiments on monkeys and who was then chief of the Division of Mental Hygiene of the Public Health Service. Kolb granted Seevers a portion of the purified morphine and appointed him a consultant to the Public Health Service. In return for the morphine, William Charles White, then chair of the NRC committee, requested that Seevers share his results with the committee. He placed no other conditions on Seevers "except a footnote in the publication recognizing this correlation [with the committee] without mention of the specific grant of the morphine."[16] White praised Seevers and closed his letter with the hope that great care would be exercised as to the security of the material.

The quest to organize a reliable supply of research material yielded Seevers far more than a source of purified morphine. The monkey colony would place him squarely within the social network of addiction researchers. From his vantage point within the scientific and policy-coordinating bodies, Clifton Himmelsbach saw Seevers as helping "break down barriers between individuals and individual institutions so that a correlated attack may be made on the problem as a whole."[17] As Seevers replied in a 1941 letter to Himmelsbach, "I have spaded up a lot of oysters in the past three years and it begins to appear as if a 'pearl' or two might be forthcoming when they are opened. If so, it must be applied to the human, [and] the only logical way to do it, I believe, is at your institution [Lexington] through some sort of cooperative venture." He saw this cooperative approach as "clear[ing] the way for pharmacology."

Advent of war officially suspended the NRC committee's work on June 19, 1941. That year, Charles W. Edmunds died suddenly, and Seevers was recruited from Wisconsin to assume the reins of the University of Michigan department. Several principal members of the addiction research network were asked to participate in the government-coordinated development of antimalarial drugs. Drug toxicity and efficacy was assessed in rhesus monkeys by various government contractors, including Seevers from 1944 to 1945. The antimalarial program absorbed the efforts of those few scientists who had pursued the subject of drug addiction prior to the war. Although personnel were temporarily

diverted from the nascent addiction research enterprise, the war ultimately enhanced the feasibility of federally coordinated scientific assaults on such problems as venereal disease (Brandt 1985), the anemias (Wailoo 1997), and addiction, all once considered outcomes of sin and vice.[18] Ultimately, the renamed NRC Committee on Drug Addiction and Narcotics (CDAN) resumed meeting in 1947. By then, Seevers and Samuel Irwin had set up shop to use monkeys as preclinical bioassays to test the abuse liability of compounds, based on the logic of substitution established by Himmelsbach and Eddy prior to the war. However, they also continued to pursue the basic mechanisms, including "desire," that brought about addiction.

In its attack on the "opium problem," the postwar CDAN aimed, first, to reduce the socially legitimate use of habit-forming drugs, by convincing physicians not to prescribe them and by convincing the public to steer clear of proprietary remedies containing such drugs. Second, the committee wanted to replace "each use of habit-forming drugs with a substance not habit-forming but capable of producing the medicinal action required of the habit-forming product." The committee maintained that through substitution, industrial production of alkaloids could be "reduced to a minimum," thus lessening the "police authority necessary to control the situation."[19] The logic of substitution transcended the laboratory. As illustrated by the committee's sense of its goals, substitution was a public health measure designed to reduce reliance on law enforcement. The problem, as the committee saw it, was the lack of viable substitute drugs that it could recommend to physicians or the public. Failing to grasp the social meaning of "habit-forming drugs" and cultural aspects of their use, the committee set to work in the fields of pharmacology.

AT WORK IN THE NEW FIELDS OF PHARMACOLOGY: DISEASE AND DISEQUILIBRIUM

Prior to World War II, U.S. pharmacologists weathered a formative "identity crisis" during which they feared "engulfment" and the "unethical" taint of commercial enterprise (Seevers 1969b, 210). The founding fathers of U.S. pharmacology recognized the lack of research infrastructure and set out to build one. In 1924, John J. Abel wrote to Abraham Flexner that pharmacology should not be subordinated to physiology. He defined "drugs" as the proper object for the field, writing: "I am fully aware that they also constitute the field of study for the physiologist, the pathologist, and other medical scientists. The scope of this domain is so large that there is ample opportunity for all the above-named

individuals to work without ousting the pharmacologist or subordinating him to some other field." Abel described pharmacology as a vibrant enterprise that was "almost daily making new additions to our armamentarium of drugs, which cannot be subordinated to physiology which has its own problems which may or may not interlock with pharmacology" (Seevers 1969b, 209).

Famously, Abel advocated pluralism. He called for the scientific community to "let one pharmacologist be more of a chemist, another more of a physiologist, another more of a clinician," in a unified, cumulative, and—most important—independent enterprise within the broad field of experimental medicine and biology. His vision went unrealized for several decades. The differentiation of pharmacology from physiology occurred earlier in Europe. By the 1930s, European pharmacologists had a coherent sense of identity and a degree of organizational autonomy. Cognizant of their relatively underdeveloped state, their American counterparts set out to raise the field's reputation through ambitious research programs. This effort propelled pharmacology and medicinal chemistry into becoming the "most frequent foci" of research collaborations by the onset of World War II (Swann 1988, 3). Pharmacology expanded its emphasis on experimental therapeutics, although the leadership resisted moving toward practical, therapeutic application. "For us to go clinical is, to my mind, as disastrous as to remain what we are," wrote the editor of the *Journal of Pharmacology and Experimental Therapeutics* (quoted in Chen 1969, 131). The main engine for growth proved to be the general expansion of biomedical research during and after the war.

Postwar pharmacology was characterized as immature but growing rapidly. One thing that was emphatically not a part of its growth was overlap with addiction studies—when perusing the membership of the American Society for Pharmacology and Experimental Therapeutics (ASPET) in its first sixty years (1908–69), it was rare to find anyone but Seevers who worked primarily on opiate addiction. The differentiation between toxicology and pharmacology came about in the early 1960s, when the first society devoted to toxicology was established. Finally, the evolution of tools in biophysics and molecular biology allowed pharmacologists to explore drug action at the subcellular and molecular levels. The 1950s and 1960s witnessed a proliferation of new forms of neuropharmacology, psychopharmacology, and neuropsychopharmacology that incorporated experimental psychology and biological psychiatry. There was, however, a postwar workforce crisis in the field.

Expansion of pharmacology departments and a higher profile of pharmacology in the medical school curriculum had been among Abel's goals during

the formative stages of ASPET. As the main professional society in the field, ASPET lobbied for federal investment to strengthen graduate education and increase the number of pharmacologists produced through NIH training grants (Bass 1969, 167). Public visibility grew due to the popular press's portrayal of Frances O. Kelsey, the FDA pharmacologist who prevented thalidomide from becoming a public health disaster in the United States.[20] Organized pharmacology had a contradictory relationship with the FDA. Although increased drug regulation meant more work for pharmacologists, many believed that the FDA hampered innovation, so ASPET's Public Affairs Committee sought to influence health legislation and broaden the FDA's interpretations of regulation. ASPET strengthened professional networks not only among academic pharmacologists but among their industry counterparts. The private sector absorbed most of the pharmacologists produced by federal workforce investment. Although ASPET initially barred industrial pharmacologists from membership, they were admitted starting in 1941, and by 1969, the organization boasted there was "no difference between academic and industrial pharmacologists" (Chen 1969, 151). Academic pharmacologists increasingly worked as industry consultants. No longer Seevers's "weakling of the medical sciences," pharmacology is synergistic with the pharmaceutical industry and with other fields concerned with drugs and drug-cell interactions. The level of analysis in which pharmacology should be engaged has long been contentious, with scientists questioning how knowledge of the molecular-level activities of a drug could be best situated within the "whole organism," much less how whole organisms could be best situated within the complex social contexts in which humans ingested drugs or became addicted to them.

Pharmacologists sought to insert their expertise into the periodic social controversies in which drugs were increasingly embroiled. In the wake of the war, Seevers helped the Japanese government control a popular epidemic of amphetamine use. He participated in the Second U.S. Medical Mission to Japan, in May 1951, and initiated an ongoing capacity-building educational exchange with Japanese pharmacologists that persists to this day (Domino 2004, 149). Seevers played a similar role in the postwar heroin crisis in the United States and later claimed to have been privileged to examine the problems endemic to the "drug scene in most of the principal countries of the world" (1972, 5). He was often the only pharmacologist at gatherings convened to respond to drug addiction as a social problem or cultural crisis. "Drug use is a symptom or sign, not the primary disease," Seevers intoned at the New York Academy of Medicine conferences titled "Drug Addiction among Adolescents"

held in the fall of 1951 and the spring of 1952. "The adjustment of these individuals to society," he added, "is in inverse relation to the stress to which they are subjected." Rather than define adolescent addiction as "crime" or "disease," Seevers interpreted it as an abnormal psychological response to modern stresses—such as "fear of the future, fear of impending war, fear of atomic bombs, and fear of military service"—that exceeded the individual coping skills of adolescents. Finding rising heroin use unsurprising, Seevers confidently stated that adolescents were unusually susceptible to outside influences and "dominated by herd instincts" (Committee on Public Health Relations 1952, 109). He concluded that stress took its greatest toll among the most maladjusted—and hence least immune—individuals.

During this period, disease was coming to be redefined in pharmacological terms as disequilibrium within a homeostatic system, borrowing language from cybernetics. Drug use was an attempt to restore homeostasis or an equilibrium of the kind that Seevers posited in his dissertation. His earlier definition of addiction as a "condition of desire" had shifted to an explanatory model in which stress and anxiety played a leading role. By the mid-twentieth century, there were other sources of the idea of homeostasis, such as neuroendocrine research and systems theory. Addiction researchers drew on these despite drug addiction being thought of as a social problem that manifested in clinical abnormality. Some characterized pharmacology as a clinical science from its inception, and pharmacology departments were generally housed in medical schools. For Seevers, clinical medicine played an interpretive role for pharmacology: "it is important to pharmacology as a discipline that it be interpreted to the clinician by one who knows from experience how the problems of the clinic differ from those of the laboratory" (1969b, 215). The problem was sorting out the division of labor between the clinic and the laboratory.

Seevers maintained that pharmacologists played an interpretive role for the effects of drugs and chemicals. "True" pharmacologists "spoke for" drugs and might come from several disciplines.

> The biochemical pharmacologist fragments the organism in order to study its component parts; the organ-oriented subdivisions of pharmacology are engrossed with specific technics and interests; the clinical pharmacologist, while dealing with drug effects on man, is also a specialist; toxicology is too often identified only with small animal pharmacology. In order to bring perspective to medical and health problems concerning drugs, information from all sources, subcellular to the whole organism, must be evaluated with a minimum of bias. Often the pertinent information is found only in indigenous

> medicine. Often the picture must be constructed primarily from witnesses from the past. Competence for such reconstruction requires a broad background in the laboratory with more than a passing knowledge of the clinic, a "composite" pharmacologist, if you please. *This* is pharmacology. (Seevers 1969b, 216)

Differentiating between "true pharmacology" and "pseudopharmacology," Seevers disdained extrapolations based on "inconsequential" or "inadequate" data obtained through "unrealistic doses in small animals" (1969b, 212). He did not respect hasty moves from drug-cell interactions to human therapeutics by persons with "little, if any, knowledge of the principles that govern such interactions or the complexity of the biological systems with which [they are] dealing" (1969b, 211). The knowledge production problems to which Seevers pointed sharpened with the separation of preclinical from clinical research. The conflict between researchers who used intact organisms and those who worked at cellular or subcellular levels went beyond training or laboratory technique—the conflict was about the public value of pharmacological knowledge claims and the social status of those who made them.

Seevers argued that individual pharmacologists could only be expected to make significant contributions in very limited areas, in which they should persist until they became "masters" (1969b, 213). Thus the broader pharmacological research enterprise was one in which the components of "clinical-pharmacological knowledge" were coordinated (as illustrated in the quote that follows). Having survived the doldrums of earlier generations, Seevers saw pharmacology as an autonomous discipline that should define itself so as to remain publicly visible without being subsumed by clinical medicine.

> If pharmacology is submerged it will be in institutions where the pharmacologist, even though medically trained, identifies pharmacology only in laboratory terms. It is not likely to happen where pharmacology occupies an important position in the basic and clinical teaching of medical students throughout their educational program; where clinical pharmacology conducts training programs at the postdoctoral level and is recognized as a bridge between general pharmacology and clinical medicine; where the clinical pharmacologist is trained in both; where he/she is formally and physically associated with both; where he/she interprets laboratory findings in clinical terms and serves as a coordinator in all things of a clinical-pharmacological nature. In the long run, it may be that this type of cooperative activity will be a principal reason why general pharmacology as an independent discipline will survive in medical schools. (1969b, 21–22)

By the end of his career, however, Seevers felt pharmacology "received little but scorn in the scientific and medical communities" (1972, 3). Because he positioned himself as the embodiment of his science, an affront to pharmacology was a personal affront to him. Pharmacology remained a subordinate research enterprise. Within pharmacology, addiction research was even more easily tarred with the brush of an illegitimate science (Clarke 1998).

ANIMATING A RESEARCH ENTERPRISE: THE LABORATORY LOGICS OF ANIMAL DESIRE

Sorting out animal models to clarify relationships between physiological need and psychological desire occupied Seevers and his colleagues for decades. Along with Lauren Woods and James Wyngaarden, Seevers used six monkeys in a 1947 comparative study of methadone and morphine. The process made him eager to continue work on abuse liability of the opiates with monkeys, which required overcoming the technical difficulties of organizing and maintaining monkey colonies (Swain 1991, 21). Such colonies were part of the developing international primate research infrastructure integral to experimental physiology (Clarke 2006, 286). The morphine-dependent monkeys of Michigan literally embodied this emerging institutional form but took specific shape for the purposes of addiction research. Ensuring the monkeys were tuberculosis-free plagued Seevers, as monkeys are so susceptible to the disease that entire colonies can be quickly wiped out. Then as now, moreover, primate research facilities were expensive to operate because they involved ongoing costs that were hard to justify to external sponsors and university administrators. The university initially invested three thousand dollars in the laboratory, and Seevers turned to CDAN (at the committee's sixth meeting after war's end) for another twelve hundred dollars. On March 10, 1950, CDAN agreed to fund both Henry K. Beecher's research at Massachusetts General Hospital, discussed in chapter 4 of the present book, and Seevers's project, titled "Studies in the Monkey Designed to Determine the Value of this Animal for Predicting Addiction Liability to the Newer Synthetic Analgesics" (Committee on Drug Addiction and Narcotics 1950, 112).

Perennially underfunded due to industry reluctance to pay for testing, CDAN was looking not to fund research infrastructure but to obtain short-term results. But Seevers wanted continuous funding, because he planned to "carry out in the monkey all of the procedures at present employed at Lexing-

ton for the study of addiction liability" (Committee on Drug Addiction and Narcotics 1950, 112). He intended to build up a colony of between sixty and seventy animals.[21] The real reason that CDAN could not guarantee Seevers continued funding was that some of its members were unconvinced that animal results corresponded to human addiction in any meaningful way. Taking every opportunity to reassure the committee that the similarities between animal models and humans were significant enough to warrant further work on animals, Eddy and Seevers patiently explained what results in the monkey meant for humans. For instance, when Isaac Starr, chair of the committee, asked what morphine-addicted monkeys looked like during withdrawal, Seevers replied: "They are very like man in withdrawal. It shows nausea, vomiting, rise of temp, etc. It is the only time an otherwise wild monkey seems to become tame, amenable to handling. The animal wants relief of his discomfort and seems to associate that in some way with the handling" (Committee on Drug Addiction and Narcotics 1950, 114). Still, the committee had to be repeatedly convinced that Seevers's results were relevant to problems within CDAN's purview.

Interpretive work was necessary to render animal behavior meaningful, and thus Seevers had to translate what he was observing into a comparative catalog of drug effects that drew parallels between animals and humans. Desire for the drug was evidenced by an animal that would "come and hang on to the attendant's clothing as if seeking something" (Committee on Drug Addiction and Narcotics 1950, 114). Perhaps in response to the question of animal desire, Seevers began to make data films in the early 1950s like those he made previously in Wisconsin. The films depict monkeys in various stages of withdrawal and show vomiting, convulsions, seizures, hallucinations, tongue biting, and abdominal cramping (monkeys holding their abdomens tightly). Even hard-to-observe peripheral neuropathy, which occurs in extreme cases of alcohol dependency, could be glimpsed. One film made in the early 1950s showed "sick" (withdrawing) monkeys housed individually and in groups. When housed together, monkeys that feel healthy "pick on" those who are "sick" (going through withdrawal). According to James Woods, who later inherited the colony, group-housed monkeys can be aggressive toward each other. Noting inequality in nutritional intake and other problems relating to social behavior, he said, "We don't group house at all now; if we ever do again it will be in a very limited way" (2005).

Films from the early 1950s depict the first high-throughput system for testing addictive potential of new compounds. The films show a lab technician who administered shots four times a day to each monkey. Housed in groups of

six, the monkeys were released in a fixed order. The animals entered a corridor, jumped through a trap door, and received their dose. Speedy administration meant that the technician handled each monkey only long enough to inject it before moving to the next animal. The University of Michigan laboratory maintained about twenty morphine-dependent monkeys in the 1950s, giving them the capacity to determine dependence liability for between fifty and sixty drugs each year. They used a scoring system to measure severity of withdrawal based on the morphine abstinence syndrome described in chapter 3 of this book. The work in the monkey colony was modeled on studies of human beings coordinated by CDAN and conducted by the Public Health Service.

Students and colleagues of Seevers continued his tradition of making monkey movies. One such film, *Studies on Drug Dependence in the Monkey,* was filmed in 1979 at the Central Institute for Experimental Animals of the Medical Research Laboratory in Nogawa, Kawasaki, Japan. Foregrounded inside a box-like apparatus, the monkeys in the film undergo effects of stimulants, hallucinogens, and depressants. The narrator intones that a monkey, seemingly engrossed in stereotypical and repeated activity, "never forgets to press the lever when the red light is on." The films depict monkeys self-administering cocaine to the point of convulsions, something no longer allowed. A narrator explains that one experimental subject died two hours after filming, from exposure to high doses of meperidine (Demerol). It is difficult to watch these films, with their lone subjects engaged in their own "experiment perilous" (Fox 1959/1998). As the voice-over occasionally points out, their expressions are pained, and some of their gestures are suggestive of human beings.

Respectful of their animal subjects and protective of their scientific practice, behavioral pharmacologists have something of a siege mentality, given some of the tactics that animal rights activists have adopted toward them. When I watched the monkey movies with researchers who work with monkeys today, the researchers engaged in interpretive work: they pointed out with irony when animals on-screen were said to "appear to be visually hallucinating," and they instructed viewers on the observable phenomena they use as the basis for interpretations. The researchers were and are careful not to attribute human-like traits to the monkeys. At one point, a film narrator carefully said: "The monkey is here presumed to be experiencing visual hallucinations. Observe here the eyeball movements." Subjects in the film were profoundly alcohol- and opiate-dependent monkeys who were used to demonstrate the comparative lack of objective signs of abstinence when withdrawing from drugs that do not produce physiological dependency (such as LSD). In the

making of these movies, observables had to be interpreted for audiences to make sense of what they are viewing. For example, the Japanese film narrated what was thought to be going on in the brain when central nervous system depressants were administered. The film's narrator explains: "[The brain] requires the presence of the drug to retain normal cellular activity. . . . Thus the nerve cells are never drug free and the brain becomes resistant to drug action to the point that the drug becomes necessary for normal functioning." A tension between observation and interpretation, practice and theory, runs through these visual texts.

Few viewers of these movies would dispute the profoundly visual effects of withdrawal from high doses of intravenous ethanol on the monkeys. These were particularly obvious in a film titled *Behavioral Effects of Alcohol in the Rhesus Monkey,* made in the 1960s at the Southern Research Institute in Birmingham, Alabama, by Barbara McEwen and Gerry Deneau, who had recently departed Ann Arbor. During filming, the "drugged monkeys," normally curious when not drugged, were administered curiosity and dexterity tests that documented poor coordination and lack of interest in their surroundings. The film showed not only delirium tremens during withdrawal but also the peripheral neuropathies that accompany severe dependence on alcohol. As the monkey reached the twenty-ninth hour of alcohol withdrawal, severe tremors began. At forty-eight hours, the animal appeared to be picking cobwebs out of space and seemed to be undergoing visual hallucinations. Woods noted that monkeys "do this under the circumstances that you would think, the same circumstances that you would expect in people. Hallucinations in alcohol withdrawal are only observed in humans who are quite strongly dependent" (2005). The film ended with a happily anthropomorphic event, the animal's recovery and restoration to normalcy.

This sequence of films in the tradition of Seevers, to my knowledge the only monkey films that remain extant, depicted evolution in the technical apparatus used to study animal models of addiction. The technical problems initially posed in drug self-administration studies were considerable because the original metal harnesses were heavy and could chafe the monkeys, who were quite capable of reacting in ways that damaged harness or tether. Rubbing wounds made by the original metal harnesses were painted with medications. Today's polyester jackets, harnesses, and lightweight aluminum springs allow more freedom of motion than the formerly used tubular tethers, and the animals chew the jackets to "customize" their fit. Another condition that had to be in place for drug self-administration studies was an apparatus allowing animals to

self-inject. In 1961, James Weeks, a cardiovascular pharmacologist working at Upjohn Pharmaceuticals in Kalamazoo, Michigan, invented an indwelling intravenous catheter system for rats (Weeks 1961, 1962). The apparatus was adapted to monkeys by Tomoji Yanagita in Seevers's lab. A late 1960s film made by Seevers and Yanagita on self-administration of pentobarbital showcased cages, harnesses, and tethers. The monkeys in the film clearly manifest symptoms of drug intoxication; pensive, yawning monkeys repeatedly press a lever until they nod off, their hands abruptly falling to the floor. Present-day viewers told me that one would very seldom see a monkey intoxicated so severely these days, because researchers work with smaller doses and get the same effects without having to worry about such gross effects.

Research methodologies have evolved with changes in the technical apparatus. Behavioral pharmacology laboratories are currently set up to examine the propositions of behavioral economics and choice models (Hursh 1991). Early studies simply allowed animals to self-administer extremely high doses in order to establish the pattern and schedule of ingestion and to determine the effects and consequences of that pattern. The seizures, convulsions, and self-injurious behaviors seen in the relatively crude studies are no longer produced. Although the FDA drug approval process required lethal dose (LD-50) studies in animal models, such studies were performed by toxicologists, not by substance abuse researchers. Those who study addiction have moved on to more nuanced approaches that allow them to get at the drug effects that result from chronic use, which are far more subtle than death. Such approaches rely on the reliable reproduction of drug dependence in animals, which is based on the laboratory logic of concordance.

Over the years since animal self-administration models became more precise, they have also become more predictive of "abuse potential" or "addiction liability" among human beings. Pharmacologists have discovered and documented animal preference for the same drugs that humans use in socially problematic ways. The establishment of correlations between human and animal drug consumption, "liking" or preference, and effects became more compelling. Once validated, that laboratory logic has given way to a preoccupation with the persistence of drug-seeking behavior in the face of negative consequences. These topics are taken up again in chapter 7 of this book, which situates behavioral pharmacology as the pivot point between older theories of conditioning and newer theories drawn from neuroscience and genetics. The research infrastructure developed by Seevers at the University of Michigan successfully marshaled enough resources and social status to continue (although

its existence came under pressure in the 1960s and 1970s as animal research became more controversial).

Interestingly, Seevers was a proponent of gathering "minimal animal data" and guarding against overgeneralization from animal studies to human beings. He did not seek to expand the domain of animal research but instead argued against the waste of animals inherent in what he saw as "slavish adherence" to the large-scale studies that were becoming customary practice in the pharmaceutical industry by the early 1960s.[22] Limitations on animal research are closely linked to the expansion of clinical research on human subjects: Seevers's ethical stance toward the minimization of animal research was based on his belief that studies should be performed in humans as soon as feasible. He argued that drugs of low toxicity in humans produced undetectable effects in animals unless they were administered in amounts "far in excess of those ordinarily used in human therapy." Seevers claimed that "human disease counterparts are rarely available for study in animals," although it was his lifelong goal to provide one (1960, 6). Thus he advocated the earliest possible clinical trials once toxicity in animals was determined to be low. This ethic of the minimal use of animals lost out in the regulatory emphasis on large-scale studies set into FDA policy by the 1962 amendments. However, Seevers's performance of ethicality was partly due to his belief in the partiality of knowledge claims based on animal research: there were limits to what could be learned about addiction through animal models.

Compared to the broader shifts within experimental therapeutics, biology, and pharmacology, the addiction research arena was a tiny enclave. However, the animal models produced by addiction researchers have enjoyed remarkable tenacity. Believing monkey studies of morphine-like compounds predicted qualitative responses in humans, Seevers nevertheless recognized the technical and philosophical difficulties of translating research methods and findings across species. He noted that "direct extrapolation or interpolation of results from one species to another is not only impossible but entirely misleading" (Seevers 1960, 6). At times, he even identified differences in drug effects between species of monkeys (Committee on Drug Addiction and Narcotics 1953). The scientific limitations lay with the difficulty of correlating pharmacological and psychological variables to explain drug-induced behavior or drug seeking (Seevers 1960, 6). Hitting squarely up against desire, Seevers turned to experimental psychology and behavioral analysis, fields that were in the process of evolving "drug self-administration" techniques based on a different set of laboratory logics than those of classical pharmacology. The results of the

testing program were "usually so unspectacular, so difficult of attainment, and so unrewarding in a scientific sense" that good scientists were uninterested in them (Seevers 1960, 9). For the monkey colony to yield on its scientific promise, a new set of laboratory logics would have to arise that used the "junkie monkeys" to mimic human self-medication and drug seeking. By the time that behavioral pharmacology arose to make use of the research platform constructed by Seevers, there were new cultural conversations and an emerging sense of the ethics of both animal and clinical research. These are related in the ensuing chapters; chapter 7 resumes the story of the "junkie monkeys."

Archives sometimes come to life in ways that serendipitously animate aspects of the historical moments they enshrine, as does a film made sometime in the early 1960s by the University of Michigan audiovisual department, *Morphine Physical Dependence in the Monkey*.[23] Rather than a data film geared toward the research community, this film was meant to convey seriousness of purpose to a wider—even public—audience. This film is an aesthetically pleasing documentary with high production values, set in a fashionable living room in which Seevers presides over a coffee table littered with artifacts, including opium pipes, books, and a small Japanese statue. Joining him are four men in suits: Nathan B. Eddy, who had been the linchpin of the NRC committee for thirty years and was perhaps the world's leading pharmacologist of the opioid drugs; University of Michigan pharmacologists Sam Irwin and Gerry Deneau; and Duncan McCarthy, a Parke-Davis executive closely associated with the University of Michigan Department of Pharmacology. When the conversation turns to individual susceptibility to drug dependence, Irwin explains that millions of people undergo anesthesia without developing "emotional ties" with the drugs administered. Eddy explains that physical dependence cannot be reduced to tolerance, in response to which Seevers jokes, "Have we spent all our lives just fooling around?" Irwin and Deneau proceed to explain the research question being studied in the monkey: How are psychogenic dependence, individual susceptibility, or "emotional ties" related to or different from physiological tolerance? They chart out the rationale for using monkeys, who behave in ways "much easier for us to interpret" and "more similar to man" than other animal models, such as the rat or dog.

The monkeys play a role in this film that resembles that of domestic pets rather than laboratory animals. They are encircled by flimsy, circular wire cages quite unlike the boxes in which they were actually housed. The animals stretch, doze, yawn, and cry, becoming more and more obviously exhausted and pathetic as withdrawal proceeds inexorably. Deneau narrates their progress,

stating at the crucial moment that "one never fails to be impressed by the rapidity with which morphine reverses the course" of the withdrawal. Indeed, the sick animal responds almost immediately by returning to a state of comfort before the viewer's eyes. Eddy intones, "Since results in the monkey are very like man, producers and legal people accept them as unequivocal evidence of what would happen in man." Surprisingly, he states, "A nonaddicting analgesic would *not* solve our problem with drug abuse by any means"—an admission indicating that the NRC project had run up against a limit marked by the presence of human desire and social context. As Eddy elaborated later, physical dependence was inadequate to explain the drive that underlay drug-seeking behaviors in monkeys and men.

The protobehavioral primate laboratory described in this chapter was to later serve as an entrée for a full-blown behavioral logic of drug self-administration by animals, a logic that transformed the field in the 1960s. Nascent behaviorist principles underlay the laboratory logic of the physiological investigations by Seevers and his fellows. However, they did not possess a vocabulary for the scientific analysis of behavior other than the discredited lexicon of psychoanalysis. Preoccupied with studying physiological dependence, they built a pharmacological research infrastructure that became instrumental for behavioral pharmacologists to come (Balster and Bigelow 2003; Schuster 1976). Interestingly, Seevers recognized the potential of behavioral models of drug self-administration even as they proved threatening or unpersuasive to other pharmacologists. "Seevers was smart enough to know that psychology was going to have something to say about these things" (Woods 2005). When it came to drugs beyond his self-defined purview, Seevers recognized the limits of the laboratory logics of substitution but did not yet see how to move toward establishing concordance.

One of the limitations that Seevers hit up against was how to define "addiction" as a scientific object capable of holding together heterogeneous elements. "It has become impossible in practice, and is scientifically unsound, to maintain a single definition for all forms of drug addiction and/or habituation. A feature common to these conditions as well as to drug abuse in general is dependence, psychic or physical or both, of the individual on a chemical agent"—thus began a 1965 article by Eddy, Halbach, Isbell, and Seevers, "Drug Dependence: Its Significance and Characteristics," which was written by a powerful scientific coalition seeking to shift the older, protoscientific terminology toward a newer scientific terminology of "drug dependence of this or that type."[24] Applying the term *dependence* to habitual drug use represented a scientific consensus and a lasting conceptual shift in the field.[25] The Committee

on Drug Addiction and Narcotics concurred with the semantic shift on July 1, 1965, by voting to change its name to the more scientifically credible Committee on Problems of Drug Dependence.

Despite the rising fortunes of pharmacology, Seevers remained concerned about his field's status. He wrote: "Today pharmacology no longer needs to be sharply circumscribed to find its place in the scheme of things. In this era of molecular biology defining pharmacology to encompass the action of all chemicals on all living matter is accepted with little debate" (1969b, 210). At the time, some pharmacologists felt that molecular biology might subsume their discipline and become "the only thing that really counts" (Seevers 1969b, 211). Seevers was critical of the gap between the promises of molecular pharmacology and "application of pharmacologic knowledge to human therapeutics or the public health" (1969b, 213). His concerns were twofold: that those who did not use biochemical approaches would be relegated to second-class citizenship and that knowledge of molecular approaches did not truly qualify one as a pharmacologist (1969b, 212–13). Indeed, he argued against exalting molecular pharmacology, because other pharmacological approaches were equally likely to contribute to public health. Bringing perspective to public health problems involving drugs or chemicals was, in Seevers's view, the unique domain of pharmacology, given the problems of alcoholism, drug dependence, air and stream pollution, and the ubiquitous presence of pesticides, food additives, and over-the-counter drugs (1969b, 216). Producing useful and usable knowledge for the sake of these public health problems was the overarching goal at the heart of this research enterprise.

The "junkie monkeys" of Michigan were maintained on morphine as a means by which to render them useful to the project of categorizing drug effects and classifying the elements of drug dependence. The monkey colony was brought into being for this purpose, and its existence allowed researchers to begin raising questions about the underlying structure of addiction. The "junkie monkeys" thereby invoke the ethical specters typically associated with utilitarianism and the instrumental use of animals as research subjects. These specters have increasingly come to haunt the pharmacological research enterprise, which relies on intact organisms even in the age of molecular pharmacology. They loom especially large when scientific work on intact animals must be coupled with research on human beings, as is necessary for research on drug dependence. The next few chapters look further into the thought collectives that became central to the social organization of the clinical research infrastructure, which relied on prisoner patients rather than "junkie monkeys" for "research material."