**Making Organisms Model Human Behavior: Situated Models in North-American Alcohol Research, 1950-onwards**

*Final version accepted for publication in April 2013. Forthcoming in Science in Context.*

Sabina Leonelli*, Senior Lecturer, Department of Sociology and Philosophy, University of Exeter, St Germans Road, EX4 4PJ Exeter, UK, s.leonelli@exeter.ac.uk

Rachel A. Ankeny, Associate Professor, School of History & Politics, University of Adelaide, Napier 423, Adelaide 5005 SA, Australia, rachel.ankeny@adelaide.edu.au

Nicole C. Nelson, Postdoctoral Fellow, Department of Social Studies of Medicine, McGill University, 3647 Peel Room 207, Montreal QC, H3A 1X1, Canada, nicole.nelson@gmail.com

Edmund Ramsden, Research Fellow, Centre for the History of Science, Technology and Medicine, Faculty of Life Sciences, University of Manchester, Simon Building, Manchester, M13 9PL, UK edmundramsden@manchester.ac.uk

*Corresponding author

**Argument:** We examine the criteria used to validate the use of nonhuman organisms in North-American alcohol addiction research from the 1950s to the present day. We argue that this field, where the similarities between behaviors in humans and non-humans are particularly difficult to assess, has addressed questions of model validity by transforming the situatedness of non-human organisms into an experimental tool. We demonstrate that model validity does not hinge on the standardization of one type of organism in isolation, as often the case with genetic model organisms. Rather, organisms are viewed as necessarily *situated*: they cannot be understood as a model for human behavior in isolation from their environmental conditions. Hence the environment itself is standardized as part of the modeling process; and model validity is assessed with reference to the environmental conditions under which organisms are studied.

**Making Organisms Model Human Behavior: Situated Models in North-American Alcohol Research, 1950-onwards**

## 1. Introduction

In the history, philosophy, and social studies of biology, there has been extensive scholarship on the choice and use of organisms in 20th century research practices. Key themes have included the careful choice of organism in the first place, depending on the problems of interest and the available or preferred practices that allow the question of interest to be answered (e.g., Burian 1993; Ankeny 1997; de Chadarevian 1998; Todes 2001; Weber 2005; Rheinberger 2010). Another strand has addressed the critical role of the standardization of organisms as research tools through selective breeding and related processes (e.g., Clarke & Fujimura 1992; Kohler 1994; Logan 2002; Rader 2004; Leonelli 2007, 2008) and the related need to develop conditions for raising and maintaining animals in disease-free states (Kirk 2010, 2012). Key to the success of many such processes has been working on species characterized by a low number of genes, like *Caenorhabditis elegans* or *Arabidopsis thaliana*. These so-called 'model organisms' dominated biomedical research programs in the latter half of the 20th century (NIH 2012; NCBI 2012; Gest 1995; Davis 2004). They have been extensively studied in the hope that data and theories thus generated will be applicable to other organisms (Ankeny & Leonelli 2011).

Many accounts of the use of and rationale for experimental organisms in 20th century have focused on a particular subset of these investigations (Ankeny 2010),

namely the use of model organisms to explore and articulate what it is hoped will be generalizable underlying mechanisms (what elsewhere have been termed 'genetic model organisms,' see Spradling et al. 2006). Genetics, in the form of the degree of genetic conservation and homology between the experimental organism and the target species, provided the main measure of the likelihood of projectability from these organisms to other, more complex ones (and ultimately to humans).[1] The questions of (1) what criteria need to be fulfilled for an experimental animal model to be 'representative' (particularly of the human) and (2) how the potential scope of this representation can be assessed (that is, how extensively the results of research with any particular experimental organism can be projected onto a wider group of organisms), have been answered largely by examining genetic and molecular approaches to biology.[2] Thus much of the existing historical, philosophical and sociological scholarship on experimental organisms has emphasized their role in investigating how genetic materials inform development, and has used this approach as the basis for analyzing the potential for such organisms to represent other species (even if this was often done in the context of a critique of genetic determinism).

The relationship between the environment and genetics, however, has been a key ongoing consideration for those seeking to produce experimental animals, particularly in the early 20th century where there was an emphasis on generating 'pure lines' to reduce variability and maximize experimental control (see Rheinberger & Müller-Wille 2010). By the 1950s, amidst increased attention to the relationship between genetics and the environment, some practitioners questioned the emphasis on pure

lines, and the 'ideal' genotype became the one most capable of ensuring that the organism's phenotype would develop uniformly in response to environmental change (Kirk 2010). In other areas of 20th century biomedical research, notably those associated with the behavioral sciences, experimental organisms have been extensively used without limiting the focus to standardization via genetics but with a richer view of genetics and the environment in interrelation.

In this paper, we examine the criteria used within one such field, alcohol addiction research, to validate the experimental organism used and assess the extent to which it can represent processes that occur in humans. As we illustrate, debates about the validity of using animals to study alcoholism do not hinge on the genetic features and standardization procedures for one type of organism in isolation, as is often the case with genetic model organisms. Instead model validity is assessed with reference to the features of *both* the organism itself *and* the environment and experimental settings within which it is being studied.[3] As a result, environmental features become themselves part of the standardization process, thus serving as an experimental tool to increase the reliability and representational validity of the model as a whole. One philosophical issue brought out by this material is the need to carefully distinguish between the notion of 'experimental organism' and the idea of a 'model' for a phenomenon.[4]

Alcohol addiction researchers in 20th century North America have been very vocal in reflecting on and policing the choice and use of experimental organisms, and thus this field provides fertile empirical ground for examining the assumptions and validation strategies underlying experimental uses of organisms as models for humans.

The contemporary North American alcohol research community has two key characteristics that are important for our analytic purposes. First, it is interdisciplinary, encompassing experts in animal behavior, physiology, genetics, molecular biology, psychiatry, psychology, pharmacology, sociology, ecology, and more recently neuroscience—hence providing an excellent exemplification of behavioral science in its broadest, most inclusive sense. Second, it is a well-demarcated research area, where strong collaborations are built beyond disciplinary boundaries and researchers from different backgrounds regularly share results in conference venues, societies (e.g. the Research Society on Alcoholism) and journals (e.g., *Quarterly Studies on Alcohol*, now *Journal of Studies on Alcohol and Drugs* and *Alcoholism: Clinical and Experimental Research*). This cohesion around the common problem of alcoholism has been facilitated by sustained attention and governmental support for the field since the early 1950s, with several major research institutes created for the purpose of studying the effects of alcohol on humans. For example, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the United States created a $50 million dollar special fund in 2002 specifically to draw together researchers from different specialties and using different experimental organisms to study the biology of excessive drinking (NIH News 2002a).

The study of alcohol addiction is also characterized by a long history of discussions about what makes a valid model for alcoholism. Researchers find themselves struggling with questions that, explicitly or implicitly, plague any experimental uses of non-human animals to represent humans: which components of

addiction can be understood through biological and genetic study, and which are specific to human cultural situations? Can animals experience a 'craving' for alcohol, as human alcoholics report? Is alcohol drinking part of the 'natural' behavioral repertoire for many non-human animals, and if not, does it make any sense to conduct research on animals?[5] To answer these questions, researchers have elaborated explicit criteria for standardizing organisms and their behaviors, as part and parcel of a complex experimental set-up, to have projectable results. As we shall show, in the latter half of the 20th century North American alcohol researchers articulated the idea that close attention must be paid to the experimental set-up of which the organism is part, not merely by constructing a tractable standard setting which becomes a neutral background condition, but by constructing a model that represents the organisms themselves and their environment, as well as human traits such as volition, taste, and preferences. Thus to construct a model of human behavior, an experimental set-up must be created that represents the environment in which humans live as well as the behavioral characteristics of humans as social animals.

In what follows, we do not aim to fully unravel the history of any one research program on alcohol addiction, or to discuss relations to addiction research in a broader sense. Instead, we consider this relatively long and rich period of alcohol research in order to investigate how contributors to this field have reflected on their methodological assumptions in their published work; analyze the development of such discussions over time; and use this analysis as grounds for a philosophical reflection on the epistemic role of experimental organisms in research on human behavior. Our analysis is based

on published scientific papers that engage in public justification of the validity of specific experimental set-ups. These published defenses of research criteria are valuable sources insofar as they constitute explicit attempts by scientists to consider their methods and to explain and defend them to their peers. Relying on validity arguments in publications thus enables a rich evidence base that spans 60 years up to the present and is relatively consistent in its format. This methodological choice is innovative with respect to most historiographical work on the use of experimental organisms in science (including our own), which tends to focus on the practices fostered in specific labs and thus uses sources such as archival materials and ethnographic observations.[6] In this paper, we deliberately chose to move our analytic focus away from specific cases of addiction research, so as to evaluate general trends in the field over a relatively long period of time.

As we illustrate, this analysis reveals that the arguments and criteria used by researchers to justify the validity of their models shift considerably through time. Further, on the basis of this material we defend the view that, within alcohol addiction research with non-human animals, assessing the validity of an experimental set-up involves an evaluation of both the biological features of the experimental organism being used and of the contexts in which those features are instantiated (e.g., the environment in which the organism develops or the ways in which animals are introduced to alcohol). Indeed, the environment itself is standardized as part of the modeling process; and model validity is assessed with reference to the environment in which organisms are studied. The experimental organism is thus viewed as necessarily *situated*: it is constantly

responding to environmental stimuli and the material conditions in which it finds itself, and cannot be understood as a model for human behavior in isolation from its environment. Hence clear criteria must exist for the environmental conditions under which an experimental set-up can be argued to represent humans. Our analysis illustrates how a field like alcohol research, where the similarities between addiction behaviors in humans and in non-humans are particularly difficult to assess, has addressed questions of model validity by transforming the situatedness of non-human organisms into an experimental tool.

## 2. Experimental organisms in American Alcohol Research

From the time of the first coherent definitions of alcoholism as a disease, termed "alcoholic insanity" or "neurosis" in the 19th century, experiments on non-human animals have been critical to its analysis. Up to the end of the 19th century, and following the delineation of the symptomology of "chronic alcoholism" by the Swedish physician Magnus Huss (1849), studies focused on the effects of high and sustained doses of alcohol on the body and mind (e.g., Stewart 1898; Lewis 1899). These early experiments were carried out predominantly in France, Russia, and Germany on a variety of organisms, including dogs (e.g., Magnan 1876) and fowl (Bernard 1856). At the turn of the century, the bulk of research activities in this area moved to the United States, where dogs, rabbits, pigs, guinea pigs, monkeys, cats, birds, and wild rats were used, as well as the "white rat" which was employed for the first time in the laboratory of Clifton Fremont Hodge of Clark University (1903; see also Stewart 1898; Miles 1930; Logan 1999). Hodge carried out a series of studies in which animals were force-fed

alcohol to study its effects on digestion and secretion, growth, and development, resistance to infection, toxicity, nutrition, and general physical pathology. Animal studies were critical to the debate between the temperance movement and its critics, over the effects of alcohol on the body: “the great complexity of the human organism… has made the definite interpretation of the human experiment impossible. The method of physiological science is to reduce the problem to simplest terms in every way possible” (Hodge 1903, 359-60).[7] Importantly, non-human animals were not considered to be simpler solely by virtue of their physiological adaptations. Hodge also noted that the “conditions of life” of the animals could be controlled in the laboratory, though the degree of control he exerted was limited, especially by later laboratory standards. Hodge’s animals lived in a semi-naturalistic setting to ensure their physical and psychological health, and the animals were given “complete freedom” to wander in a sunny quarter-acre yard, so much so that one kitten was killed by a dog, and a dog run over by a car (Hodge 1903). The set-up of an experimental environment granting such a degree of freedom to the animals was significant in terms of the validity of data obtained through these studies: according to Hodge, freedom of movement would remove the possibility that distress would confound the research results.

With the advent of Prohibition in the 1920s, interest in alcohol research waned in the US and the American Association for the Cure of Inebriety was disbanded along with its *Journal of Inebriety* (Blocker 1989). With the failure of Prohibition and its repeal in 1933, interest in alcohol abuse returned, with a more specific focus on the causes of alcoholism. In 1939, the Research Council on Problems of Alcohol was established,

evolving into the Center of Alcohol Studies at Yale, directed by Elvin Morton Jellinek. This was the focal point of alcohol research and published of the *Journal of Quarterly Studies on Alcohol*. Active in the treatment of alcoholics through the Yale Plan Clinics and closely tied to Alcoholics Anonymous, Jellinek (1942, 1960) vigorously promoted what was seen as the "new approach to alcoholism". He defined five "species" of alcoholism (1960), two of which were diseased due to physical dependency. The disease could be diagnosed by symptoms of tolerance and withdrawal, but most critical was the complete loss of control, in spite of immense physical, psychological, financial, and social consequences. Choice, will, and volition were overridden by an overwhelming desire for drink (Jellenik 1960, 45). This vision of alcoholism as a disease proved popular because it removed stigma: alcoholism was not due to weakness of will or temperament, but an illness to be understood by science and treated by medicine (Schneider 1978, Conrad and Schneider 1980).[8]

For Jellinek, the study of alcoholism was fundamentally interdisciplinary. While empirical verification of various clinically-anticipated effects of alcohol as well as range of physiological functions had been well established, when it came to the "motivation in the genesis of the alcohol habit", psychiatric speculation was rife while experiment offered a complete "*tabula rasa*" (Jellinek & McFarland 1940, 276). Jellinek reviewed the physiological contributions to this topic, noting in particular the work of the Johns Hopkins psychobiologist Curt Richter, as it provided possibilities for further psychological study. Richter's preferred experimental organism was the Norway rat, an animal that the laboratory scientist "could not possibly improve on" (Richter 1968). The

rat was rapidly becoming the generic animal model in psychology (Logan 1999). Richter initially used the albino rat to which he was introduced by John Broadus Watson, but he later rejected his mentor's use of this animal, privileging innate and spontaneous behavior over learning. He also rejected the tendency among biologists to associate the use of standardized cages with behaviorism: "The use of our cages makes it possible to put very definite questions to the rats, and to get definite answers… From the beginning… my interest focused entirely on what animals do on their own, that is, their innate behavior, not on what they can be taught to do" (1985, 377). In the 1930s, Richter devised a series of "cafeteria" experiments in which the animals were free to choose a variety of foods, believing that the "wisdom of the body" ensured the animal selected the correct nutritional requirements (Richter & Campbell 1940). This experimental set-up was particularly innovative in comparison to the reliance of earlier physiologists on force-feeding tubes and gastric fistula.

In the course of these studies, Richter discovered that rats also drank alcohol when it was provided in a "free choice" situation. The animals would accept beverages with alcohol volumes between 1-6% due to their caloric content (preferring a 5.1% concoction), but when offered the choice between alcoholic beverages and water, would take sip of the former before turning to the latter. Rats considered alcohol a food—they did not drink to get drunk. Richter also noted a great deal of variation among the animals, and a small minority of "alcoholics" (approximately 10%), which were more common among the wild rats, would drink larger volumes than others. He suggested this was the result of differing taste thresholds or perhaps endocrine deficiencies that

could be corrected through supplements (Richter 1926, 1957; Richter & Campbell 1940).[9] Richter's experimental set-up stimulated numerous studies of self-selection among individually caged rats which were used to identify various metabolic, endocrinal, nutritional, chemical, and later, behavioral genetic differences between "drinker" and "non-drinker" animals within and between different strains (Eriksson 1972, Eriksson et al. 1980).

Jellinek was, however, less than impressed with evidence of hereditary factors in the generation of addiction (Jellinek and Jolliffe 1940). Increasingly drawn towards the social and behavioral sciences, he was more intrigued by the potential of experimental psychology to identify the causes of drinking in the early stages of alcoholism before physical dependence took hold. Particularly important in this respect was the work of the psychiatrist Jules Masserman. Masserman was committed to psychoanalysis but felt that, focused as it was on clinical cases, it had not yet fulfilled its opportunity to broaden and extend its approach through closer associations with general and comparative psychology (Masserman 1943). For Masserman, psychoanalytical concepts such as "inner needs" and "motivational conflicts" could be legitimately applied to non-human animals; humans differed only with regards to the variety and versatility of their "technics of adaptation" (Masserman 1968). Devising a variety of conflicting situations (retrieving food at the risk of an air-blast), Masserman generated "neuroses" among cats. After injecting them with alcohol, found that their neurotic reactions to the laboratory environment was relieved. He lent his support to further studies by the clinical psychologist, John Conger (1951, 1956) who carried out similar experiments with rats.

Masserman and Conger argued that the animal laboratory provided support for arguments that drinking served to overcome fear, inhibition and phobia, thus highlighting the importance of the environment as a trigger for the disease. Thus, not only was the physical and psychical make-up of experimental organisms of critical importance, but the space in which they were located when setting up experiments.

While Masserman considered animal studies as a means of further establishing the credentials of psychoanalysis as a biologically-grounded medical science, with the growing influence of behaviorism in addiction research, attention shifted from the role of alcohol for relieving conflicting drives, to a focus on its positive reinforcing qualities. For instance, animals were kept in experimental chambers (typically referred to as 'Skinner Boxes') in which food would be delivered only when the animals drank a drug solution or pressed a bar that would deliver alcohol, morphine and cocaine (Keehn 1969, 1986; cf. Campbell 2007). Once this behavior was established and animals were conditions to request drugs, psychologists sought to identify the symptoms of physical dependence that sustained the use of intoxicating substances. Schedule-induced polydipsia, a particular method developed by the behaviorist psychologist John Falk, proved both influential and controversial. Falk (1961) discovered that an intermittent feeding schedule (one food pellet every few minutes) induced the rats to consume vast quantities of water. He then quickly applied this finding to alcohol research by using the intermittent feeding schedule as a method for inducing rats to consume large quantities of alcohol, thereby inducing intoxication (Falk et al. 1972, 1976; Lester 1961; Mello & Mendelson 1971).

### 3. Validating Experimental Models in Alcohol Research

This brief historical outline shows some of the variety of ways in which experimental organisms were enrolled into research programs to investigate the biological bases of drinking behavior. For early researchers, using experimental organisms to study alcoholism offered several advantages: the animal's environment could be controlled in ways that would be impossible in humans, as Hodge noted, and Richter similarly argued that using animals gave researchers unique opportunities to pose precise experimental questions. But using animals as experimental models for alcohol research also raised questions about the validity of these experiments; that is, about what constitutes a representative experimental set-up for human behavior.

One of the main questions of validity in this field concerns whether animals can be used to understand the "uniquely human" phenomenon of alcohol addiction. There is considerable evidence supporting the idea that alcoholism is peculiar to humans: animals, even when interested in using some alcohol, do not show a tendency towards consuming large amounts of it (in ways that the WHO would define as 'abusive and damaging', 1955). Mice and rats, the favorite experimental organisms of late 20$^{th}$ century biomedical research, are particularly reluctant to drink alcohol when given a choice between alcohol and water, as Richter's early work on the innate feeding behavior of rats showed. Later experiments such as Gerald McClearn and David Rodgers' two bottle choice experiments (where they gave animals bottles of alcohol and water and measure how much they drank from each) showed that only a few strains of mice will drink alcohol in large quantities and some strains of mice will refuse to drink

alcohol entirely (McClearn & Rodgers 1959). More recent experiments have shown that even strains of mice that do seem to drink alcohol in large quantities (such as the C57BL, the standard strain with the highest affinity for alcohol) do not appear to consume it in a way that results in consistently high blood alcohol levels (Dole & Gentry 1984). Alcohol addiction in experimental animals thus is largely understood as induced, inasmuch as the behavior and preferences of animals have to be transformed in order for them to serve as experimental models for human alcoholism. Even in the few cases where researchers find evidence which supports the portrayal of alcohol addiction as innate for some types of animals, interest in human alcoholism is what drives research interests, not scientific interest in understanding alcohol's effects on non-human animals for its own sake.[10]

If alcoholism in experimental animals was understood to be largely the results of inducements rather than innate preferences, what kinds of inducements should be considered legitimate for modeling human alcoholism? This question was strenuously debated in the field from the mid 1960s through the 1980s, and various strands of these debates continue into the present day. The use of behaviorist techniques in the 1960s generated some of the most severe criticisms. Scientists were concerned with the validity of experimental set-ups such as Falk's schedule-induced polydipsia technique, and about the standards for what counted as a valid model for alcoholism more generally (cf. Broadhurst 1963). Critics suggested that in many experimental set-ups the animals were in fact choosing alcohol for its caloric properties or due to the sugary taste of many of the solutions (Freed & Lester 1970). Some researchers also found that even

after inducing rats, mice, and monkeys to consuming alcohol over considerable periods of time, the animals did not choose alcohol when placed in free-choice situations, nor did they display the symptoms of physical dependence (Freund 1969; Ogata et al. 1972; Mello 1973; Mello & Mendelson 1971). More generally, critics questioned the degree to which animals were acting "voluntarily". In the behaviorist's laboratory, animals were trained to drink, and thus did not choose alcohol because of its intoxicating quantities as was the case among humans.

A series of papers published by behavioral pharmacologists throughout this period (Lester 1966; Lester & Freed 1972, 1973; Cicero 1979, 1980) argued that it was perfectly acceptable to use non-volitional techniques to explore various aspects of alcoholism such as physical dependence (Cicero et al. 1971). But terms such as "animal" or "addiction model" needed to "be parsimoniously reserved for animal behavior which stringently meets both psychological and physiological criteria" (Lester & Freed 1973, 106). A 1979 paper by Theodore Cicero articulated several criteria that an animal model should meet in order to be considered a valid model of alcoholism, such as: animals had to self-administer alcohol by the oral route and consume it in quantities that would result in pharmacologically significant blood alcohol levels; alcohol should be consumed for its pharmacological properties and not for its taste or caloric properties; animals should be willing to work for alcohol; and tolerance and dependence must emerge as a result, measured by reduced effects of alcohol consumption and acute withdrawal symptoms. These criteria became a touchstone for later debates in the field about model validity, with researchers attempting to assert the utility of particular animal

models by arguing that they fulfilled all of Cicero's criteria (Bell et al. 2006, Rodd et al. 2004) and suggesting new additions to the list, such as a new criterion specifying that animal models should also show evidence of relapse (McBride & Li 1998).

**4. Situating animals in valid experimental contexts**

What is most notable for our purposes here is that, despite the heavy focus in this field on using animals to understand the biology of alcoholism (especially genetic factors that predispose individuals to heavy drinking or the neurobiological mechanisms that underlie drinking behaviors), the validity of the experimental models depends to a large extent on the behaviors of the animals and the settings in which those behaviors are elicited, rather than the biology of the organism alone. Cicero's requirement that an animal must "orally self-administer alcohol," for example, suggests that it is not just the rodent itself that models alcoholism, but a rodent situated in certain environments and experimental situations that allows it to become a model for the human. This criterion suggests that other methods for administering alcohol to animals—letting animals breathe in alcohol vapor, forcing them to drink alcohol by mixing it with their food or water, or even injecting it directly into their bodies—can be used to understand some aspects of the biology of alcoholism, but fall short of becoming representative for behavioral features of alcoholism such as craving.

The different positions taken by researchers in the field with regards to the implications of various manipulations to get experimental animals to drink demonstrate how the experimental setting is simultaneously a resource for overcoming experimental

problems (such as rodents' aversion to alcohol) and a site for drawing parallels to the human and assessing the validity of the model. In another controversial experimental design developed in the 1980s by Herman Samson, animals were trained to press a lever in a conditioning box to get drops of a sweet solution, and then the sugar in the solution was gradually reduced while the alcohol was gradually increased until the animals are drinking unsweetened alcohol (Samson 1986). When trained in this way, even animals that had been selectively bred for low alcohol preference would drink a moderate amount, a result that the researchers argued demonstrated the powerful effect of the environment on drinking behaviors (Samson et al. 1989). The "sucrose fading" procedure was effective for getting rodents to drink significant amounts of alcohol, but activated discussions in the field once again about taste, learned behaviors, and the motivation to drink alcohol. Using a sugary solution to make alcohol initially more palatable to rodents seemed to contravene Cicero's requirement that true animal models of alcoholism should consume alcohol freely and only for its pharmacological effects, and some in the research community argued that adding sugar into the experimental situation was adding an unnecessary complication that "preclude[d] seeing animals learning to work for alcohol in the absence of confounding factors" (Hyytia & Sinclair 1988: 161). Other researchers took the position that taste confounds were not just limited to models where sugar or food deprivation were involved, but were a potential problem in all experiments where animals had to ingest alcohol orally. Grahame and Cunningham (1997) argued that the high-drinking C57BL mouse strain might be drinking because the taste of unadulterated alcohol was less aversive to them

than to other strains, and suggested an alternative experimental design whereby mice could be trained to press a lever to have alcohol delivered directly into their stomachs via a pump. Other researchers argued that while the motivation to drink in various experimental designs was complicated by taste, the same could be said of drinking in humans. One group reported choosing the sucrose fading model because it offered a more "anthropomorphic" representation of drinking behaviors that bore a resemblance to the environmental conditions in which humans learn to drink. "Humans do not…usually initiate their drinking with pure ethanol," they argued, and "in contemporary times, 'wine coolers' or mixed drinks are used as a 'gateway' to drinking large amounts of ethanol" (Gauvin, Moore, & Holloway 1998, 38).

In these cases, establishing and using a particular set-up involves making decisions about the scope of representation (whether to model general features of alcoholism such as motivation to drink or specific features such as the moment relapse), and tradeoffs between representing some aspects of alcoholism over others. None of these experimental set-ups are considered by researchers to be "isomorphic to the human condition;" rather, researchers argue that they each reveal "some aspects of a complex process" of addiction and abuse, such as preference for alcohol, dependence, withdrawal, and relapse (McBride & Li, 1998: 339). The main question for researcher is, how much of the human condition should researchers aim to model, and which aspects are most crucial to represent? Some experimental set-ups aim for a biological resemblance to human drinking, targeting the development of their models towards particular physiological features such as a blood alcohol level of 0.08% (the legal limit

for drunk driving in humans) (Rhodes et al. 2005). Other researchers aim for behavioral similarities between animals and humans, placing less emphasis on the amount that rodents drink and more emphasis on whether experimental organisms appear to find alcohol motivating or rewarding (Green & Grahame 2008).

The ways in which researchers decide on these priorities is linked to their understandings of the ultimate purpose of experimenting on nonhuman organisms. The aim of developing animal models of alcoholism, after all, is to produce information that will facilitate better treatments or a better understanding of the etiology of human alcoholism. Some researchers argue that if the purpose of animal models is to develop new medications, then it is not necessary for experimental organisms to manifest all (or even any) of the symptoms of human alcoholism as long as the experimental set-up as a whole predicts which drugs will be effective in humans. For instance, NIAAA intramural researcher Mark Egli argues that researchers' efforts might be better directed towards developing "rapid, inexpensive tests which yield the same information as the more elaborate models, although they may be less obvious models of alcoholism" (Egli 2005, 315). Others argue that experimental designs where the physiology and behavior of the animals strongly resembles human drinking can be used to identify novel genes or signaling pathways involved in drinking, which may point the way towards new drug targets or susceptibility genes in humans (Tabakoff et al. 2009).

Finally, researchers' considerations of the contexts in which drinking behaviors are elicited and their implications for model validity can extend also to the animals' home cage environments. In some cases, the ways in which animals are housed aim at

controlling away rather than explicitly utilizing environmental context. For example, since stress is believed to impact on drinking behavior, some researchers use only mice bred in local facilities to avoid the stress caused by shipping them from a commercial supplier, or compare mice locally-bred with mice with shipped mice in their experimental design (for an example of this design, see Mulligan et al. 2008); and animal researchers in behavioral fields routinely control for many of these aspects of the laboratory environment, such as noise and light levels, food, and even the person conducting the experiment (Chesler et al. 2002). In other cases, the home environment and early experience of animals are explicitly used as variables to model the conditions under which humans come to drink excessively. Masserman and Conger's early work on how stressful events change patterns of drinking in experimental organisms remains a topic of study in behavioral research today, with researchers investigating how stressful events early or late in life change patterns of drinking in both rodents and non-human primates (Sillaber et al. 2002, Chester et al. 2004, Fahlke et al. 2006). Another line of research that extends back to the 1960s uses the home cage environment as a variable to explore how living in environments that have been "enriched" with shelters, bedding materials, exercise wheels, and other objects rather than standard cage environments impacts behavior and development (Ramsden 2011). Researchers have used these enriched set-ups to study, for example, how the rearing environment modulates the behavioral consequences of exposing rodents to alcohol while *in utero* (Hannigan, Berman, & Zajac 1993). Some lines of research have even investigated the relationship of drinking and social behavior in animals, such as the influence of dominance

hierarchies on drinking patterns in rodents and especially in primates (Blanchard et al 1987, Peretti & Lewis 1969). Interest in the effect of social structure on drinking is high because of its obvious parallels to human drinking, although there are presently relatively few experimental programmes focusing on social structure and alcohol intake in rodents (Crabbe 2012).

## 6. Standardizing Genes, Organisms *and* Environments

The standardization of rodents as experimental organisms undoubtedly is a key component of the research strategy currently employed in the alcohol field. Enthusiasm for genetic and genomic approaches to studying behavior at the National Institutes of Health in the 1990s drove increased funding for research on addiction with animals, especially mice (Hyman 2006), and availability of standardized inbred mouse strains is considered crucial for research in the field (see e.g. Wahlsten et al. 2006, who compare results from two-bottle choice experiments conducted fifty years ago with contemporary results). Nevertheless, there are many instances in which alcohol researchers approach standardization as more than just a problem of creating a standard genetic organism. The large variability in alcohol-related traits in genetically heterogeneous populations of mice and rats has allowed researchers to use selective breeding techniques to develop genetic animal models to address questions about particular facets of alcoholism; such as the selectively bred "preferring" and "non-preferring" rats that are used as models of alcohol preference, and selectively bred lines of mice that are prone or resistant to having seizures during alcohol withdrawal. Further, researchers have critiqued the

tendency of the mouse research community to use only a few standard genetic mouse strains (such as the widely used C57 Black 6 strain, or the 129 strain which is particularly amenable to genetic manipulation), pointing out that although strains such as the high-drinking Black 6 have been extensively studied for addiction behaviors many strains of mice have never even been tested for alcohol preference (Yoneyama 2009).

Changing expectations in the mouse research community more broadly about the "complexity" of behavioral traits have given rise to different ways of thinking about the standardization of genes, organisms and environments. The Complex Trait Consortium, a interdisciplinary group of researchers from the mouse community, has argued that "existing and proposed mouse resources... are optimized to study the actions of isolated genetic loci on a fixed background," and that these standard organisms are "less effective for studying intact polygenic networks and interactions among genes, environments, pathogens and other factors" (Churchill et al. 2004, 1133). They proposed the development of new lines of inbred mice, made by breeding eight different strains, which would provide "a far broader representation of genetic variation in natural populations than current mapping resources" (JAX Notes 2003). Behavioral researchers have similarly argued that the approach of comparing a mutant to a standard model organism is unlikely to succeed in behavioral studies because of the small effects of individual genes and the presence of gene-gene interactions. Crawely et al. (1997) note that the simplest way to achieve genetic standardization in knockout experiments "is to derive and maintain mutations in an isogenic genetic background, a

standard practice in other model organisms such as yeast, *Drosophila*, and *C. elegans*;"[11] but they reject this strategy as an appropriate one for behavioral researchers to employ because "behavioral characteristics of certain isogenic strains could overshadow the effects of the targeted mutation" (108). Instead, they recommend choosing different strains for knockout studies depending on the trait studied; for example, selecting a high drinking mouse strain such as the C57 when studying a gene that is expected to reduce drinking in order to be able to see a behavioral change more clearly. Some researchers have even gone so far as to argue against the development of generic standards for housing rodents to be used in behavioral studies, contending that simply adopting a single standard across laboratories may be counterproductive because it could limit the range of environmental contexts in which experiments are performed and thus result in the black-boxing of housing arrangements when interpreting results (Würbel 2000, 2002). As one researcher puts it, the very idea of using organisms living in standard environments to model human behavior "fails to acknowledge the fundamental biological significance of the interactive nature of gene-environment relationships underlying most behavioral phenotypes" (Würbel 2002, 5). Richter, Garner, and Würbel (2009) argue that researchers should instead adopt the practice of systematically varying the environment in order to observe how behavior changes depending on the context.

Finally, researchers have made productive use of existing variations in both animal genomes and the laboratory environment. In the alcohol field, comparisons between different strains of mice have long been used as a way to provide insight into

the genetics of alcoholism, and researchers have even used the small genetic differences between substrains of C57 mice to identify candidate genes that influence alcohol consumption (Mulligan et al. 2008). In the Mouse Phenome Project, another interdisciplinary collaboration between mouse researchers from many fields, a database has been established to collect information on the results of common mouse experiments and the laboratory conditions under which they were performed, in order to look at the influence of the environment on genotype. By collecting information on existing variation in experimental protocols and laboratory environments, researchers hope to produce a dataset that can be used to investigate what environmental factors influence mouse behavior (Bogue & Grubb 2003).

**7. Conclusions: Situatedness as an Experimental Strategy**

We have shown how the use of experimental organisms in alcohol research has become more standardized with time. Early researchers were more willing to work with a diversity of types of organisms, and to alter the environment in a wide variety of ways. However the latter half of the 20$^{th}$ century brought convergence both in terms of the preference for particular types of experimental organisms (namely rodents) and about the need to pay close attention to the experimental set-up of which the organism is a part. Many researchers agreed that careful consideration about how the whole experiment was set up, and particularly the environmental conditions, was necessary to accurately observe these behaviors, to assess their potential implications for the phenomenon of interest, alcoholism, and to make claims about the projectibility of these findings onto humans.[12] How the environment was construed has shifted over time: for

instance, the idea of an ‘enriched environment’ was a critical concept for many of the later researchers, but has been used in a variety of different ways. Despite these variations, the way in which the environment comes to be standardized in this later period is importantly different from other uses of experimental organisms, notably (genetic) model organisms.

In many studies conducted with model organisms, the environment is treated as something to be standardized, controlled, and then ignored, as it is treated merely as the background conditions against which the phenomena of interest are instantiated. Environmental considerations can and often do surface when researchers are interpreting results obtained through the use of such models; but they are not incorporated into the model, and the significance of data acquired through this use of model organisms is precisely dependent on the isolation of the organism from the environment for the duration of experiments. By contrast, in research on alcoholism using experimental organisms in the second half of the 20$^{th}$ century, environmental factors are part of the phenomenon of interest. This depends on the researchers’ focus on the study of behavior, rather than on the genetic make-up of organisms per se: while it is possible to study processes of genetic regulation without reference to an organisms’ relation to a specific environment, behaviors cannot be investigated, let alone understood, without close attention to the conditions under which they are elicited (or not). Hence the experimental set-up is designed to facilitate the stabilization and replication of patterns which result from the organism being situated in a particular environmental context. The number of ‘ceteris paribus’ conditions (those that must be

held constant so that researchers can focus on the unique effects of a given factor in a complex experimental situation) becomes greater and more diverse with increased information about the environment, and in turn the experimental set-up can continue to be modified as necessary. The experimental organisms used in this field are thus only one component of what we term a 'situated' model, which is a product of considering the interaction between a given type of organism and the specific environment within which it is located. Claims about the representativeness of situated models can only be made with respect to both the organism and its immediate environment, operating in a constant feedback loop.

We are here pointing to the concept of situatedness as itself an experimental tool, a strategy explicitly used by researchers to address the ever-thorny question of how to 'control' for environmental factors – by including them in the model, rather than treating them as a side issue or background condition to be black-boxed and ignored (as is typically the case in standardization procedures or the processes associated with the development of disease-free colonies). Our notion of situatedness is targeted to a precise philosophical characterization of the epistemic status and functioning of models in alcohol research. As such, it is specific and innovative in the context of contemporary scholarship on the use of non-human organisms in science. At the same time, it draws from the numerous, broader discussions of situatedness developed within science and technology studies since the late 1980s, and particularly Donna Haraway's seminal arguments about the need to assess the content and social significance of scientific knowledge through a detailed understanding of the specific processes and material

conditions through which such knowledge is produced (Haraway 1988, 1997). Haraway defines ‘situatedness’ as the capacity to locate knowledge claims and practices, as well as the people who embody them, within what she calls “the webs of differential positioning” (1988, 590) – the multiple ways in which humans can split and perceive the world that they inhabit. We want to bring Haraway’s intuition to bear on notions of modeling hitherto underelaborated within the history and the philosophy of science, thereby extending it to encompass not only the ways in which scientists position their scientific tools (including the organisms they use as models), but also the ways in which scientists explicitly configure these tools as localized gateways for developing generalizations from and comparisons between experimental datasets. Our view of situatedness thus also shares in the spirit and methods of Adele Clarke’s ‘situational analysis’, particularly in her use of historical and sociological research to contextualize the use of organisms in biomedical research, which led her to argue that an important marker of 20th century biology was the shift from ‘an organism- or species-based problem structure to an analytic, problem-based problem structure’ (1998, p. 46).

We have analyzed the historical circumstances in which certain types of model for alcohol research have come to be standardized and validated. Researchers have developed a set of recommendations for how a non-human organism should be made to interact with its experimental environment, but the resulting standards, which aim to establish the validity of the model across different locations and times, do not guarantee that knowledge obtained through use of such models will be universally reliable and trustworthy with regard to its applicability to alcohol addiction in humans. Inferences as

to whether the organism itself can reliably stand for human beings, and whether the experimental setting bears any relation to the social situations in which a putatively similar human behavior would be instantiated, remain open-ended: researchers draw different conclusions about what counts as a useful model for understanding human alcoholism depending on the specific criteria they wish to foreground. Indeed, by explicitly including environmental aspects in multiple, overlapping experimental models, alcohol researchers may be viewed as refraining from making firm commitments to a specific view of the social. Of course, their choice of environmental parameters is influenced by their interest in specific social behaviors associated with alcohol intake and/or addiction; and yet, by making these choices into explicit experimental parameters, they open up their research to critique and diverging interpretations of precisely those assumptions.

Our philosophical reading of this modeling strategy is that it provides an excellent solution to what is possibly the thorniest issue confronted by alcohol researchers. These scientists want to be able to discriminate between alternative ways of using non-human organisms to model human behaviors. They are aware that such an evaluation depends in part on how human behavior is conceptualized in the first place; and yet, at the same time, they know that making firm commitments to what causes alcoholism and the extent to which it depends on environmental factors is controversial, premature and arguably defeating the whole point of their research, which aims to answer exactly this question. We argue that the use of a situated model, as we characterized it in the previous section, makes it possible for researchers to avoid this vicious circle. This is

because a situated model can be seen as reliable without prescribing the extent to which knowledge inferred from its use can be applied to humans. The model remains a model of human behavior, but exactly what it represents of human behavior is left to the interpretation of specific observers. What makes the model reliable is, rather, the way in which several elements of the experimental set-up – including the choice of organism, the characteristics of the cages in which it is kept and the actions it is required or allowed to perform - are considered in relation to each other and to the social, scientific and technical assumptions and constraints that guide those choices. Through these processes of model development, the model acquires validity as well as becoming precise enough to exclude a whole range of experimental set-ups from being viewed as reliable or even meaningful for the scientific investigation of addiction.

Thus, as illustrated in the last part of the history detailed above, experimental animal models for alcoholism (particularly using standardized, 'off the shelf' strains of mice) become standard without becoming general: researchers recognize that their results are projectable to humans only under very specific conditions, and specific strains or populations of mice are identified as representative only of specific populations of humans or specific aspects of drinking behavior (e.g., bingers as compared to chronic drinkers, preference for alcohol versus dependence) rather than generally. Thus in this period, geneticization is happening, but not by ignoring environmental and population variability, as is typical in the contemporary context in many other areas of research which rely on model organisms. Alcohol addiction researchers are making deliberate choices to insert and track parameters reflecting both

environmental and population variability, so as to be able to ‘control’ both under experimental conditions in order to make experiments likely to result in projectable results. Recognition of variability is incorporated into the research methods in this field, but it is difficult to map results obtained through model organisms (namely by ’standardizing out’ the environment or the organisms’ features) back onto what these models are supposed to represent. Hence for these researchers, experimental organisms are unavoidably situated: the material conditions in which animals are kept and within which experiments are performed have clear impacts on their physiology and behaviors and thus on the projectibility of claims from these non-human animals to humans.

Of course it is not surprising that the manipulation of the experimental environment is so critical within the behavioral sciences, as behaviors cannot be elicited in isolation. Maintaining a fluid boundary between what counts as a product of ‘nature’ versus ‘nurture’ is imperative in these fields, where what constitutes an ‘innate’ (i.e., inheritable) trait versus a ‘cultural’ trait is much more difficult to determine than in molecular science which privileges the genetic or inheritable (see e.g. Degler 1991; Rose 1997). Nevertheless, the importance of viewing experimental organisms as situated, and the different degrees to which this insight is valued and actively adopted within different biological fields, have been vastly underestimated in the current historical and philosophical literatures on various experimental organisms. This paper has attempted to go beyond the ‘genetic bias’ (see Ankeny 2010) and examine a case in which genetics is only one factor in the standardization and use of experimental

organisms. In so doing, we hope to pave the way for new dialogues in history, philosophy, and social studies of biological practices.

**References**

Alexander, Bruce K., Robert B. Coambs, and Patricia F. Hadaway. 1978. “The Effect of Housing and Gender on Morphine Self-Administration in Rats.” *Psychopharmacology* 58:175–79. doi:10.1007/BF00426903

Ankeny, Rachel A. 1997. “The Conqueror Worm: An Historical and Philosophical Examination of the Use of the Nematode *C. elegans* as a Model Organism.” PhD diss., University of Pittsburgh.

Ankeny, Rachel A. 2001a. “Model Organisms as Models: Understanding the ‘Lingua Franca’ of the Human Genome Project.” *Philosophy of Science* 68:S251–61.

Ankeny, Rachel A. 2001b. “The Natural History of *C. elegans* Research.” *Nature Reviews Genetics* 2:474–8. doi:10.1038/35076538

Ankeny, Rachel A. 2010. “Historiographic Considerations on Model Organisms: Or, How the Mureaucracy May Be Limiting Our Understanding of Contemporary Genetics and Genomics.” *History and Philosophy of the Life Sciences* 32:91–104.

Ankeny, Rachel A. and Sabina Leonelli. 2011. “What’s So Special about Model Organisms?” *Studies in the History & Philosophy of Science* 42:313–23.

Bell, Richard L., Zachary A. Rodd, Lawrence Lumeng, James M. Murphy, and William J. McBride. 2006. “The Alcohol-Preferring P Rat and Animal Models of Excessive Alcohol Drinking.” *Addiction Biology* 11:270–88.

Bernard, Claude [1865] 1927. *An Introduction to the Study of Experimental Medicine*. Translated by Henry Copley Creene. New York: Macmillan.

Billings, John S., ed. 1903. *Physiological Aspects of the Liquor Problem: Investigations Made by and under the Direction of W. O. Atwater, J. S. Billings, H. P. Bowditch, R. H. Chittenden and W. H. Welch*. Boston & New York: Houghton, Mifflin & Co.

Blocker, Jack S., Jr. 1989. *American Temperance Movements: Cycles of Reform*. Boston: Twayne.

Bogue, Molly A., and Stephen C. Grubb. 2004. “The Mouse Phenome Project.” *Genetica* 122:71–4.

Broadhurst, Peter L. 1963. *The Science of Animal Behaviour*. Harmondsworth: Penguin Books.

Burian, Richard M. 1993. “How the Choice of Experimental Organism Matters: Epistemological Reflections on an Aspect of Biological Practice.” *Journal of the History of Biology* 26:351–67.

Bynum, William F. 1990. “‘*C’est un malade’:* Animal Models and Concepts of Human Diseases.” *Journal of the History of Medicine* 45:397–413.

Campbell, Nancy D. 2007. *Discovering Addiction: The Science and Politics of Substance Abuse Research*. Ann Arbor: University of Michigan Press.

Chesler, Elissa J., Sonya G. Wilson, William R. Lariviere, Sandra L. Rodriguez-Zas, and Jeffrey S. Mogil. 2002. “Identification and Ranking of Genetic and Laboratory Environment Factors Influencing a Behavioral Trait, Thermal Nociception, via Computational Analysis of a Large Data Archive.” *Neuroscience & Biobehavioral Reviews* 26:907–23.

Chester, Julia A., Annette M. Blose, Mark Zweifel, and Janice C Froehlich. 2004. “Effects of Stress on Alcohol Consumption in Rats Selectively Bred for High or Low Alcohol Drinking.” *Alcoholism: Clinical and Experimental Research* 28:385–393.

Churchill, Gary A., David C. Airey, Hooman Allayee, Joe M. Angel, Alan D. Attie, Jackson Beatty, William D. Beavis, et al. 2004. “The Collaborative Cross, a Community Resource for the Genetic Analysis of Complex Traits.” *Nature Genetics* 36:1133–7.

Cicero, Theodore J. 1979. “Critique of Animal Analogues of Alcoholism.” In *Biochemistry and Pharmacology of Ethanol,* vol. 2, edited by Edward Majchrowicz and Ernest P. Noble, 533–60. New York: Plenum.

Cicero, Theodore J. 1980. “Animal Models of Alcoholism?” In *Animal Models in Alcohol Research* edited by Kalervo Eriksson, John D. Sinclair, and Kalervo Kiianmaa. London: Academic Press.

Cicero, Theodore J., Stuart R. Snider, Vernon J. Perez, and Larry W. Swanson. 1971. "Physical Dependence on and Tolerance to Alcohol in the Rat." *Physiology and Behavior* 6:191–8.

Clarke, Adele E. 1998. *Disciplining Reproduction: Modernity, American Life Sciences and the "Problems of Sex".* Berkeley, CA: University of California Press.

Clarke, Adele E. and Joan H. Fujimura (eds.). 1992. *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences.* Princeton, NJ: Princeton University Press.

Clause, Bonnie T. 1993. "The Wistar Rat as a Right Choice: Establishing Mammalian Standards and the Ideal of a Standardized Mammal." *Journal of the History of Biology* 26:329–49.

Conger, John J. 1951. "The Effects of Alcohol on Conflict Behavior in the Albino Rat." *Quarterly Journal of Studies on Alcohol* 12:1–29.

Conger, John J. 1956. "Alcoholism: Theory, Problem, and Challenge." *Quarterly Journal of Studies on Alcohol* 17:296–305.

Conger, John J. 1958. "Perception, Learning, and Emotion: The Role of Alcohol". The Annals of the Political Academy of Political and Social Science 315: 31-9.

Conrad, Peter 1999. "A Mirage of Genes." *Sociology of Health & Illness* 21:228–41.

Conrad, Peter, and Joseph W. Schneider. 1980. *Deviance and Medicalization: From Badness to Sickness*. St. Louis, MO: Mosby.

Crabbe, John C., Douglas Wahlsten, and Bruce C. Dudek. 1999. “Genetics of Mouse Behavior: Interactions with Laboratory Environment.” *Science* 284:1670–72.

Crawley, Jacqueline N. 1996. “Unusual Behavioral Phenotypes in Inbred Mouse Strains.” *Trends in Neuroscience* 19:181–2.

Crawley, Jacqueline N. 2007. *What’s Wrong with My Mouse: Behavioral Phenotyping of Transgenic and Knockout Mice*, 2nd ed. Hoboken, NJ: Wiley.

Crawley, Jacqueline N., John K. Belknap, Allan Collins, John C. Crabbe, Wayne Frankel, Norman Henderson, Robert J. Hitzemann, et al. 1997. “Behavioral Phenotypes of Inbred Mouse Strains: Implications and Recommendations for Molecular Studies.” *Psychopharmacology* 132:107–24.

Crist, Eileen. 1999. *Images of Animals: Anthropomorphism and the Animal Mind.* Philadelphia: Temple University Press.

Davis, Rowland H. 2004. “The Age of Model Organisms.” *Nature Reviews Genetics* 5:69–76.

de Chadarevian, Soraya. 1998. “Of Worms and Programmes: *Caenorhabditis elegans* and the Study of Development.” *Studies in History and Philosophy of Biological and Biomedical Sciences* 29:81–105.

Degeling, Chris. 2010. “Cutting a Bone to Heal a Ligament: Idealized Animals and

Orthopaedics." *Medicine Studies* 2:101–19. Degeling, Chris, and Jane Johnson. Forthcoming. "Evaluating Animal Models: Some Taxonomic Worries." *The Journal of Medicine and Philosophy*. <<CHECK REF?>>

Egli, Mark. 2005. "Can Experimental Paradigms and Animal Models Be Used to Discover Clinically Effective Medications for Alcoholism?" *Addiction Biology* 10:309–19.

Ellison, Gaylord. 1987. "Stress and Alcohol Intake: The Socio-Pharmacological Approach." *Physiology & Behavior* 40:387–92.

Endersby, Jim. 2007. *A Guinea Pig's History of Biology.* London: Random House.

Engber, Daniel. 2011. "The Trouble with Black-6." *Slate,* November 17. http://www.slate.com/articles/health_and_science/the_mouse_trap/2011/11/black_6_lab_mice_and_the_history_of_biomedical_research.html.

Eriksson, Kalervo, 1972. "Behavioral and Physiological Differences among Rat Strains Specially Selected for Their Alcohol Consumption." *Annals of the New York Academy of Sciences* 197:32–41. Eriksson, Kalervo., John D. Sinclair, and Kalervo Kiianmaa, eds. 1980. *Animal Models in Alcohol Research* London: Academic Press.

Fahlke, Claudia, Joseph G. Lorenz, Jeffrey Long, Maribeth Champoux, Stephen J. Suomi, and J. Dee Higley. 2006. "Rearing Experiences and Stress-Induced Plasma Cortisol as Early Risk Factors for Excessive Alcohol Consumption in Nonhuman Primates." *Alcoholism: Clinical and Experimental Research* 24:644–50.

Falk, John L. 1961. "Production of Polydipsia in Normal Rats by an Intermittent Food Schedule." *Science* 133:195–6.

Falk, John L. 1971. “The Nature and Determinants of Adjunctive Behavior.” *Physiology & Behavior* 6: 577–88. Falk, John L. 1983. “Drug Dependence: Myth or Motive?” *Pharmacology Biochemistry & Behavior* 19:385–91

Falk, John L., Herman H. Samson, and Gail Winger. 1972. “Behavioral Maintenance of High Concentrations of Blood Ethanol and Physical Dependence in the Rat.” *Science* 177:811–3.

Falk, John L., Herman H. Samson, and Gail Winger. 1976. “Polydipsia-Induced Alcohol Dependency in Rats.” *Science* 192:492.

Freed, Earl X., and David Lester. 1970. “Schedule-Induced Consumption of Ethanol: Calories or Chemotherapy?” *Physiology & Behavior* 5:555–60.

Freund, Gerhard. 1969. “Alcohol and Withdrawal Syndrome in Mice.” *Archives of Neurology*, 21:315–20.

Friese, Carrie, and Adele E. Clarke. 2011. “Transposing Bodies of Knowledge and Technique: Animal Models at Work in Reproductive Sciences.” *Social Studies of Science*, 42:31–52.

Froehlich. 2004. “Effects of Stress on Alcohol Consumption in Rats Selectively Bred for High or Low Alcohol Drinking.” *Alcoholism: Clinical and Experimental Research* 28:385–93.

Gauvin, David V., Kyle R. Moore, and Frank A. Holloway. 1993. “Do Rat Strain Differences in Ethanol Consumption Reflect Differences in Ethanol Sensitivity or the Preparedness to Learn?” *Alcohol* 10:37–43

Gest, Howard. 1995. “*Arabidopsis* to Zebrafish: A Commentary on “Rosetta Stone” Model Systems in the Biological Sciences.” *Perspectives in Biology and Medicine* 39:77–85.

Grahame Nicholas J., and Christopher L. Cunningham. 1997. “Intravenous Ethanol Self-Administration in C57BL/6J and DBA/2J Mice.” *Alcohol: Clinical and Experimental Research* 21:56–62.

Green Alexis S., and Nicholas J. Grahame. 2008. “Ethanol Drinking in Rodents: Is Free-Choice Drinking Related to the Reinforcing Effects of Ethanol?” *Alcohol* 42:1–11.

Guerrini, Anita. 2003. *Experimenting with Humans and Animals: From Galen to Animal Rights*. Baltimore, MD: The Johns Hopkins University Press.

Hannigan, John H., Robert F. Berman, and Carol S. Zajac. 1993. “Environmental Enrichment and the Behavioral Effects of Prenatal Exposure to Alcohol in Rats.” *Neurotoxicology and Teratology* 154:261–6.

Haraway, Donna. 1988. “Situated Knowledges: the Science Question in Feminism and the Privilege of Partial Perspective”. *Feminist Studies*, 14:575–99.

Haraway, Donna. 1997. *Modest_Witness@Second_Millennium.FemaleMan©_Meets_OncoMouse™: Feminism and Technoscience*. New York: Routledge.

Hodge, C.F. 1903. “The Influence of Alcohol on Growth and Development.” In *Physiological Aspects of the Liquor Problem*, edited by W. O. Atwater, John S. Billings, H. P. Bowditch, R. H. Chittenden, and W. H. Welch, 359–75. Boston: Houghton Mifflin.

Holmes, Frederic L. 1993. “The Old Martyr of Science: The Frog in Experimental Physiology.” *Journal of the History of Biology* 26:311–28.

Huss, Magnus. 1849. *Alcoholismus Chronicus eller Chronisk Alkoholsjukdom. Ett Bidrag till Dyskrasiernas Kannedom*. Stockholm: Afdel.

Hyman, Steven E. 2006. “Using Genetics to Understand Human Behavior: Promises and Risks.” In *Wrestling with Behavioral Genetics: Science, Ethics, and Public Conversation,* edited by Erik Parens, Audrey R. Chapman, and Nancy Press, N., 109–30. Baltimore, MD: Johns Hopkins University Press.

Jackson Laboratory. 2003. “JAX Notes. Issue 492, Winter 2003,” accessed August 29, 2012, http://jaxmice.jax.org/jaxnotes/archive/492a.html.

Jellinek, E. Morton, ed. 1942. *Alcohol Addiction and Chronic Alcoholism*. New Haven, CT: Yale University Press.

Jellinek, E. Morton. 1960. *The Disease Concept of Alcoholism*. New Haven, CT: Hillhouse.

Jellinek, E. Morton, and Ross A. McFarland. 1940. “Analysis of Psychological Experiments on the Effects of Alcohol.” *Quarterly Journal of Studies in Alcohol* 1:272–371.

Jellinek, E. Morton, and N. Jolliffe. 1940. “Effects of Alcohol on the Individual.” *Quarterly Journal of Studies in Alcohol* 1: 110-181.

Keehn, J. D. 1969. “‘Voluntary’ Consumption of Alcohol by Rats.” *Quarterly Journal of Studies on Alcohol* 30:320–9.

Keehn, J. D. 1986. *Animal Models for Psychiatry*. London: Routledge & Kegan.

Kirk, Robert G. W. 2010. “A Brave New Animal for a Brave New World: The British Laboratory Animal Bureau and the Constitution of International Standards of Laboratory Animal Production and Use, circa 1947–1968.” *Isis* 101:62–94.

Kirk, Robert G. W. 2012. “’Standardization Through Mechanization’: Germ-Free Life and the Engineering of the Ideal Laboratory Animal.” *Technology and Culture*, 53: 61–93.

Kohler, Robert E. 1994. *Lords of the Fly: Drosophila Genetics and the Experimental Life*. Chicago: University of Chicago Press.

La Follette, Hugh, and Niall Shanks. 1997. *Brute Science: The Dilemmas of Animal Experimentation.* New York: Routledge.

Leonelli, Sabina. 2007. “Growing Weed, Producing Knowledge. An Epistemic History of *Arabidopsis thaliana*.” *History and Philosophy of the Life Sciences* 29:55–87.

Leonelli, Sabina. 2008. “Performing Abstraction: Two Ways of Modeling *Arabidopsis thaliana*.” *Biology and Philosophy* 23:509–28.

Lester, David. 1961. “Self-Maintenance of Intoxication in the Rat.” *Quarterly Journal of Studies in Alcohol* 22:223–31.

Lester, David. 1966. “Self-Selection of Alcohol by Animals, Human Variation, and the Etiology of Alcoholism: A Critical Review.” *Quarterly Journal of Studies in Alcohol* 27:395–438.

Lester, David. and Earl X. Freed. 1972. “A Rat Model of Alcoholism?” *Annals of the New York Academy of Sciences* 197:54–9.Lester, D. and E.X. Freed. 1973. “Criteria for an Animal Model of Alcoholism.” *Pharmacology Biochemistry & Behavior* 1:103–7.Levine, Harry G. 1983. “The Committee of Fifty and the Origins of Alcohol Control.” *The Journal of Drug Issues* Winter:95–116.

Lewens, Tim. 2004. *Organisms and Artifacts: Design in Nature and Elsewhere*. Cambridge, MA: MIT Press.

Lewis, W. Bevan. 1899. *A Text-Book of Mental Diseases with Special Reference to the Pathological Aspects of Insanity.* Philadelphia: P. Blakiston’s Son.

Logan, Cheryl A. 1999. “The Altered Rationale for the Choice of a Standard Animal in Experimental Psychology: Henry H. Donaldson, Adolf Meyer, and ‘the’ Albino Rat.” *History of Psychology* 2:32–4.

Logan, Cheryl A. 2002. “Before There Were Standards: The Role of Test Animals in the Production of Scientific Generality in Physiology.” *Journal of the History of Biology* 35:329–63.

Löwy, Ilana. 1992. “From Guinea Pigs to Man: The Development of Haffkine’s Anticholera Vaccine.” *Journal of the History of Medicine and Allied Sciences* 47:270–309. Magnan, V. 1876. *On Alcoholism: The Various Forms of Alcoholic Delirium and Their Treatment*, translated by W. S. Greenfield. London: Lewis.

Mardones, Jorge. 1951. “On the Relationship between Deficiency of B Vitamins and Alcohol Intake in Rats.” *Quarterly Journal of Studies on Alcohol* 12:563–75.

Masserman, Jules H. 1943. Behavior and neurosis: An experimental psychoanalytic approach to psychobiologic principles. Chicago, University of Chicago Press.

Masserman, Jules H. 1968. Animal and Human. New York: Grune and Stratton.

Masserman, Jules H., and K. S. Yum. 1946. “An Analysis of the Influence of Alcohol on Experimental Neuroses in Cats.” *Psychosomatic Medicine* 8:36–52.

McBride, William J., and Ting Kai Li. 1998. “Animal Models of Alcoholism: Neurobiology of High Alcohol-Drinking Behavior in Rodents.” *Critical Reviews in Neurobiology* 12:339–69.

McClearn, Gerald E. and David A. Rodgers. 1959. “Differences in Alcohol Preference among Inbred Strains of Mice.” *Quarterly Journal of Studies in Alcohol* 20:691–5.

Mello, Nancy K. 1973. “A Review of Methods to Induce Alcohol Addiction in Animals.” *Pharmacology Biochemistry & Behavior* 1:89–101.

Mello, Nancy K. and Jack H. Mendelson. 1971. “Evaluation of a Polydipsia Technique to Induce Alcohol Consumption in Monkeys.” *Physiology & Behavior* 7:827–36.

Miles, Walter R. 1930. “On the History of Research with Rats and Mazes: A Collection of Notes.” *Journal of General Psychology* 3:324–37.

Mitman, Gregg, and Anne Fausto-Sterling. 1992. “Whatever Happened to *Planaria?* C. M. Child and the Physiology of Inheritance.” In *The Right Tools for the Job: At Work in Twentieth-Century Life Sciences,* edited by Adele E. Clarke and Joan H. Fujimura, 172–97. Princeton, NJ: Princeton University Press.

Morse, Robert M., and Daniel K. Flavin. 1992. “The Definition of Alcoholism.” *Journal of the American Medical Association* 268:1012–14.

Mulligan, M.K., I. Ponomarev, S. L. Boehm II, J. A. Owen, P. S. Levin, A. E. Berman, Y. A. Blednov, et al. 2008. “Alcohol Trait and Transcriptional Genomic Analysis of C57BL/6 Substrains.” *Genes, Brain and Behavior* 7:677–89.NCBI (National Center for Biotechnology Information). 2012 “Model Organisms Guide,” accessed August 26 2012. http://www.ncbi.nlm.nih.gov/About/model/mammal.html.

Nelson, Nicole C. 2011. “Capturing Complexity: Experimental Systems and Epistemic Scaffolds in Animal Behavior Genetics.*”* PhD diss., Cornell University.

Nelson, Nicole C. 2013. “Modeling Mouse, Human and Discipline: Epistemic Scaffolds in Animal Behavior Genetics.” *Social Studies of Science* 43(1): 3-29.

NIH (National Institutes of Health). 2012. “Model Organisms for Biomedical Research,” accessed August 26 2012. http://www.nih.gov/science/models/.

NIH News. 2002a. “NIAAA Steps Up Search for Brain Mechanisms of Alcohol Abuse, Alcoholism.” Press release, March 8. http://www.niaaa.nih.gov/news-events/news-releases/niaaa-steps-search-brain-mechanisms-alcohol-abuse-alcoholism.

NIH News. 2002b. “Ting-Kai Li, M.D. Named New Director of NIH’s Alcohol Research Institute.” Press release, September 10. http://www.nih.gov/news/pr/sep2002/niaaa-10.htm.

Ogata, Hiroshi, Fumilo Ogata, Jack H. Mendelson, and Nancy K. Mello. 1972. “A Comparison of Techniques to Induce Alcohol Dependence in the Mouse.” *Journal of Pharmacology and Experimental Therapeutics* 180:216–30.

Pauly, Philip J. 1994. “Is Liquor Intoxicating? Scientists, Prohibition, and the Normalization of Drinking.” *American Journal of Public Health* 84:305–13.

Rader, Karen A. 2004. *Making Mice: Standardizing Animals for American Biomedical Research, 1900–1955*. Princeton, NJ: Princeton University Press.

Ramsden, Edmund. 2011a. “From Rodent Utopia to Urban Hell: Population, Pathology, and the Crowded Rats of NIMH.” *Isis* 102:659–88.

Ramsden, Edmund. 2011b. “Model Organisms and Model Environments: A Rodent Laboratory in Science, Medicine and Society.” *Medical History* 55:365-368.

Rheinberger, Hans-Jörg. 2010. *An Epistemology of the Concrete: Twentieth-Century Histories of Life.* Chapel Hill, NC: Duke University Press.

Rheinberger, Hans-Jörg, and Müller-Wille, Staffan W. 2010. “Gene.” In *Stanford Encyclopedia of Philosophy,* Spring 2010 ed. Stanford University. http://plato.stanford.edu/entries/gene/

Rhodes, Justin S., Karyn Best, John K. Belknap, Deborah A. Finn, and John C. Crabbe. 2005. “Evaluation of a Simple Model of Ethanol Drinking to Intoxication in C57BL/6J Mice.” *Physiology and Behavior* 84:53–63.Richter, Curt P. 1926. “A Study of the Effect of Moderate Doses of Alcohol on the Growth and Behavior of the Rat.” *Journal of Experimental Zoology* 44:397–418.

Richter, Curt P. 1957. “Production and Control of Alcohol Cravings in Rats.” In *Neuropharmacology, Transactions of the Third Conference, May 21, 22, and 23, 1956,* edited by Harold A. Abramson, 39–146. Madison, NJ: Josiah Macy, Jr. Foundation.

Richter, Curt P. 1968. “Experiences of a Reluctant Rat-Catcher: The Common Norway Rat—Friend or Enemy?” *Proceedings of the American Philosophical Society* 112:403–15.

Richter, Curt P. 1985. “It’s a Long Long Way to Tipperary, the Land of My Genes.” In *Leaders in the Study of Animal Behavior: Autobiographical Perspectives,* edited by Donald A. Dewsbury, 356–86. Lewisberg, PA: Bucknell University Press.

Richter, Curt P. and Kathryne H. Campbell. 1940. “Alcohol Taste Thresholds and Concentrations of Solution Preferred by Rats.” *Science* 91:507–8.

Richter, S. Helene, Joseph P. Garner, and Hanno Würbel. 2009. “Environmental Standardization: Cure or Cause of Poor Reproducibility in Animal Experiments?” *Nature Methods* 6:257–61.

Rodd, Zachary A., Richard L. Bell, Helen J.K. Sable, James M. Murphy, and William J. McBride. 2004. “Recent Advances in Animal Models of Alcohol Craving and Relapse.” *Pharmacology Biochemistry and Behavior* 79:439–50.

Rose, Steven. 1997. *Lifelines: Biology Beyond Determinism.* New York: Oxford University Press.

Samson, Herman H. 1986. “Initiation of Ethanol Reinforcement using a Sucrose-Substitution Procedure in Food and Water Sated Rats.” *Alcohol: Clinical and Experimental Research* 10:436–42.Samson, Herman H., Gerald A. Tolliver, Lawrence Lumeng and Ting Kai Li. 1989. “Ethanol Reinforcement in the Alcohol Nonpreferring Rat: Initiation Using Behavioral Techniques without Food Restriction.” *Alcohol: Clinical and Experimental Research* 13:378–85.

Schneider, Joseph W. 1978. “Deviant Drinking as Disease: Alcoholism as a Social Accomplishment.” *Social Problems* 25:361–72.

Sillaber, Inge, Gerhard Rammes, Stephan Zimmermann, Beatrice Mahal, Walter Zieglgänsberger, Wolfgang Wurst, Florian Holsboer, et al. 2002. “Enhanced and

Delayed Stress-Induced Alcohol Drinking in Mice Lacking Functional CRH1 Receptors." *Science* 296:931–3.

Spradling, Allan, Barry Ganetsky, Phil Hieter, Mark Johnston, Maynard Olson, Terry Orr-Weaver, Janet Rossant, et al. 2006. "New Roles for Model Genetic Organisms in Understanding and Treating Human Disease: Report from the 2006 Genetics Society of America Meeting." *Genetics* 172:2025–32.

Stewart, Colin C. 1898. "Variations in Daily Activity Produced by Alcohol and by Changes in Barometric Pressure and Diet, with a Description of Recording Methods." *American Journal of Physiology* 1:4–56.

Tabakoff, Boris, Laura Saba, Morton Printz, Pam Flodman, Coling Hodgkinson, David Goldman, George Koob, et al. 2009. "Genetical Genomic Determinants of Alcohol Consumption in Rats and Humans." *BMC Biology* 7:70.

Todes, Daniel P. 2001. *Pavlov's Physiology Factory: Experiment, Interpretation, Laboratory Enterprise.* Baltimore, MD: Johns Hopkins University Press.

Valverde, Mariana. 1998. *Diseases of the Will: Alcohol and the Dilemmas of Freedom*. Cambridge: Cambridge University Press.

Wahlsten, Douglas, Alexander Bachmanov, Deborah A. Finn, and John C. Crabbe. 2006. "Stability of Inbred Mouse Strain Differences in Behavior and Brain Size between Laboratories and Across Decades." *Proceedings of the National Academy of Sciences* 103:16364–9.

Weber, Marcel. 2005. *Philosophy of Experimental Biology.* Cambridge: Cambridge University Press.

Weiss, Friedbert, Marge T. Lorang, Floyd E. Bloom, and George F. Koob. 1993. “Oral Alcohol Self-Administration Stimulates Dopamine Release in the Rat Nucleus Accumbens: Genetic and Motivational Determinants.” Journal of Pharmacology and Experimental Therapeutics 267:250–8.

WHO (World Health Organization). 1955. *Alcohol and Alcoholism: Report of an Expert Committee*. Geneva: WHO.

Williams, Roger J. 1951. *Nutrition and Alcoholism*. Norman: University of Oklahoma Press.

Williams, Roger J., L. Joe Berry, and Ernest Beerstecher, Jr. 1949. “Individual Metabolic Patterns, Alcoholism, Genetotrophic Diseases.” *Proceedings of the National Academy of Sciences* 35:265–71.

Würbel, Hanno. 2000. “Behavior and the Standardization Fallacy.” *Nature Genetics* 26:263.

Würbel, Hanno. 2002. “Behavioral Phenotyping Enhanced: Beyond (Environmental) Standardization.” *Genes, Brain and Behavior* 1:3–8.

Yoneyama, Naomi, John C. Crabbe, Matthew M. Ford, Andrea Murillo, and Deborah A. Finn. 2008. “Voluntary Ethanol Consumption in 22 Inbred Mouse Strains.” *Alcohol* 42:149–60.

[1] The situation is further complicated by the fact that some organisms, such as the mouse, have been officially 'anointed' model organisms (e.g. by the National Institute of Health n.d.) and are widely used outside of research focused on genetics.

2 Exceptions which explore experimental organisms explicitly in other historical contexts include Bynum 1990; Löwy 1992; Guerrini 2003; Endersby 2007; Degeling 2010; and Friese & Clarke 2012. Philosophical explorations include La Follette & Shanks 1997; Degeling & Johnson forthcoming.

[3] It could be argued that most uses of genetic model organisms in some sense took the environment into account as an element that needed to be controlled, however in a very different manner from the ways in which addiction researchers incorporate environmental features into their modelling strategies. We thank one of our referees for encouraging us to make this point explicit.

[4] We use the term 'model' in the sense of mediator between theory and the world, as detailed in Morgan and Morrison (1999). While experimental organisms can and have been functioning as models for specific phenomena throughout the history of biology (see Ankeny & Leonelli 2011), in the cases that we discuss here the experimental organism is but one component of what counts as the model for the phenomenon of alcoholism: the experimental set-up, and the ways in which the environment is construed and controlled therein, also constitutes a key part of the model. We intend to examine the complex relations between these views and Hans-Joerg Rheinberger's analysis of experimental systems (e.g. 2010) in a separate paper.

5 These issues obviously raise extremely thorny questions about the role of volition in setting up experimental animal models for alcoholism, and a long tradition of volition and free will in animals being contested (e.g. Crist 1999). Volition is key in the concepts of alcoholism and addiction themselves (e.g., see Valverde 1998). See also Ramsden 2011.

[6] Note that all the authors of this paper have successfully used ethnographic research, observation in laboratories or oral histories to investigate scientific practices in specific biological and biomedical laboratories (e.g. Leonelli 2007 and 2008, Ankeny 2001a/b, Nelson 2013, Ramsden 2001a/b). We

therefore do not mean to disqualify the importance of these methods, but rather to perform a different type of analysis in this paper, which scrutinizes a long time-span and focuses particularly on the evolution of scientific arguments on model validity.

[7] Pauly (1994) identifies C. R. Stockard's studies of the negative effects of alcohol on guinea pigs as important to the temperance movement.

[8] From 1952, Jellinek served as a consultant to the WHO, ensuring that the Alcoholism Sub-Committee of the Expert Committee on Mental Health extended its purview beyond psychiatry to address pharmacology and physiology. His considerable influence is reflected in its 1954 description of alcoholism as a disease, involving "craving", "withdrawal", "loss of control", and "alcoholic amnesias" (WHO 1955).

9 These animal studies also were stimulated by the intense debate between temperance reformers and their critics. A research group known as the Committee of Fifty organized in 1893 to attack "so-called 'scientific' temperance instruction" in public schools (Billings et al., 1903, xvii; cf. Levine 1983). Their final report, published in 1903, did conclude that "excess is the cause of much disease, suffering, and poverty, and of many crimes" (xxii). Moderate drinking did little damage, however, and the claims of the temperance movement were "unscientific and undesirable" (xxi), concluded the report. Roger J. Williams' research similarly argued that variation in alcohol preferences in the white rat suggested that alcoholism was a genetotrophic disease (i.e., a nutritional problem which is genetic in origin) to be corrected by massive doses of vitamins (Williams 1951; Williams et al. 1949; cf. Mardones 1951).

[10] See Nelson 2013 for a discussion of how the use of biomedical animal models is justified through their relationship to human disorders.

[11] The reference in this quote is to *Drosophila melanogaster* and *Caernorhabditis elegans*.

12 The emphasis on modeling environments in research on rodents behavior has also been documented by Ramsden (2011b) in the case of John B. Calhoun's work on rat society.