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THEORETICAL REVIEW

Criteria for an Animal Model of Alcoholism

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LESTER, D. AND E. X. FREED. *Criteria for an animal model of alcoholism.* PHARMAC. BIOCHEM. BEHAV. 1(1) 103–107, 1973.–A correspondence between the various components of human alcoholism and their animal analogue has not yet been acheived; in some part, this failure resides with experimental attempts which obtain only surface equivalencies and which lack an underlying motivational structure. Seven criteria for an animal model are proposed including the oral ingestion of alcohol without food deprivation, substantial ingestion of alcohol with competing fluids available, drinking directed to the intoxicating effect of alcohol, the performance of work to obtain alcohol, the maintenance of intoxication over a long period and, finally, the production of physical dependence and, on withdrawal, the abstinence syndrome.

Alcoholism Animal model Psychological dependence Physical dependence

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THE REVIEW by Mello [14] recognizes that the ability to induce addiction to alcohol in a variety of animal species, as defined by the various features of the withdrawal syndrome consequent upon the prior intake of alcohol, by-passes those elements within and without the organism which initiate and then sustain alcohol drinking in a manner akin to that in the human alcoholic. Our purpose in this essay is to describe those criteria we believe need be met for the process of addiction in an animal to correspond to that in man and thus to become recognizable as a model of human alcoholism. Rational intervention to disrupt the process seems to us only possible to the extent that various components of the model are in or near a one-to-one relation.

Individual differences among alcoholics are legion and students of alcoholism thus have turned increasingly from uncontrolled naturalistic observations and investigations to laboratory studies. However, experiments inducing intoxication in alcoholics [16,22], while approximating drinking *au naturel*, still are hampered by lack of experimental control and are contingent upon subject selection, their results only partially generalizable.

As with a host of other human disorders, then, researchers have resorted to animal models and have pursued animal paradigms of human addiction to alcohol for years—unsuccessfully. The value of such a (successful) model is evident in the opportunity it provides to study the etiological parameters, symptoms, prevention and cure of a disorder in a variety of controlled situations not possible with humans either in a natural or laboratory setting. This paper discusses some criteria for an (elusive) animal model of alcoholism and assesses whether the challenge which these criteria pose has been or can be met. Pliny wrote that the Romans drew presages from rats and that to see a white rat was an augury of good fortune; although albino rats have been used *in extenso*, the fact that they are all about us remains still, unhappily, only an omen of our hopes.

There are many problems in the construction of an animal model; not the least of these is a semantic or conceptual one. Webster [27] provides 14 definitions or "senses" for the word "model". As used in science, for example, the applicable definition would be "a theoretical projection in detail of a possible system of relationships"; however, other definitions are also desirable. With animals, an exact resemblance to - a functional or structural design or pattern of - or an analogy to - human alcoholism would assuredly not be rejected. As conventionally conceived, an animal model is a miniature representation, perhaps altered in scope or scale, but not in its essence, which is brought into the laboratory. Accepting this, the researcher's task becomes clear: to be sufficiently conversant with the dimensions and parameters of the original so that they can

be appropriately duplicated, in this case not necessarily by reduction as much as by transference to another organism.

Lacking, however, is an exposition of the factors involved with human addicition to alcohol. It is evident that more than one variable is etiologically influential and that these multiple variables interact and operate in combination. A host of possible genetic, physiological, emotional, social and cultural influences have been described and it is not at all precluded that the behavior which is manifested as alcoholism finds expression in those individuals where the required constellation of environmental factors acts on a biologically predisposing matrix. Since social and cultural influences are not likely to be even tangentially duplicated in an animal model, it is the biological matrix upon which the burden falls for representation.

Should the biological contribution carry little weight in the constellation of forces producing alcoholism, it may well be that an animal model is unattainable. In fact, one is hard put to find more than the vaguest and most circumstantial of evidence in humans that there is a biological contribution, let alone being able to place a relative weight upon it. In this area, therefore, the criteria *in toto* we propose later in this paper (Table 1) may never be possible to meet, although some of its components (e.g., physical dependence and withdrawal) are obviously amenable to study and have received some measure of attention [14].

The Alcoholism Subcommittee of the Expert Committee on Mental Health of the World Health Organization adopted a definition [28], encompassing traditional criteria, for alcohol addiction: "Drug addiction is a state of periodic or chronic intoxication, detrimental to the individual and to society, produced by the repeated consumption of drug (natural or synthetic). Its characteristics include: (1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means; (2) a tendency to increase the dose; and, (3) a psychic (psychological) and sometimes physical dependence on the effects of the drug". Mendelson and Mello [9] proposed additional behavioral criteria of addiction in animals: that they would work (emit operant responses) for alcohol, show a preference for it in, presumably, a choice situation in the home cage, and might also tolerate punishment in order to obtain alcohol. These physiological and psychological requisites for alcohol addiction have not yet occurred together in any animal experiment.

The three most recent reviews of research on alcoholism draw the same conclusions: "In spite of widespread recognition of this research need, and many attempts to accomplish it, little evidence has been reported on the development of addictive voluntary alcohol consumption in laboratory animals. Failure to induce addictive drinking has been emphasized in reviews...." [25]. "As far as we are aware, nothing equivalent to a pathological appetite (for alcohol) has been observed in experimental animals" [11]. "To date, there is little evidence that either condition (drinking alcohol volitionally in an amount which has a pharmacological effect or dependence on alcohol) arises in rats or other species, at least based on the results of the self-selection of alcohol following continued exposure..." [21].

Generally, the effects of alcohol in rats, mice and monkeys, as in man, correspond to the rate at which alcohol is ingested over time. Thus the oral intake of alcohol usually increases somewhat the longer it is available in a suitable form in the animals' environment; tolerance to the effects of alcohol is acquired; withdrawal symptoms become more likely the more prominent the prior central effects of alcohol. These consequences of alcohol ingestion indicate only that alcohol, when chosen - or administered - in requisite amounts exhibits the characteristics of an agent with an addiction liability substantially less than that of heroin. It does not inform us how one can, to begin with, induce an animal to volitionally ingest ethanol, in the fashion and dosage required.

Some of the specific criteria of addiction in animals thus are really the sequels of addiction. We differ from this type of circularity by believing that the intake of alcohol must come about by directed behavior and the expenditure of energy by the animal to obtain alcohol. When the laboratory rat drinks alcohol in competition with response tendencies to behave in other ways, this behavior emphasizes the compulsive component of alcoholism, the alcohol-seeking behavior being a measure of the animal's motivation for alcohol. Motivational aspects of alcoholism, which we regard as the most significant criterion for an animal model, have received the least attention from investigators, perhaps because they represent the most elusive requirement to attain. Given alcohol-directed behavior of an animal over a period of time, the remaining components of addiction will follow if substantial blood alcohol levels are maintained over a sufficient integrated intoxication time.

The basic issue in orchestrating an animal model of alcoholism is the initiation of alcohol-seeking behavior specifically directed to alcohol's pharmacodynamic utility. A plethora of anecdotal, clinical and research evidence argues for the fact that alcohol ingestion is a strongly reinforcing behavior in man, based on the positive central nervous system benefits which alcohol confers. In some individuals, it becomes a compulsive need, resistant to change, and a dominant theme of life. The behavior seems to subserve a host of motivations generically conceptualized as tension reducing [3]. A man knows that alcohol gives a lift, is an intoxicant and tranquilizer, and exercises an anxiety-attenuating influence upon his behavior even before his first drink---because he has read about it or seen its action portrayed in movies or on television. This foreknowledge of the alcohol lore precedes actual experience with it and undoubtedly plays a prominent role in the genesis of ultimate alcohol-seeking behavior in man. It contributes to the positive reinforcement which accrues when, one day, the individual does drink alcohol and experiences first hand alcohol's palliative, ameliorative or other properties. A discomforting feeling, depressive mood, or disquieting internal state such as conflict is modified favorably or attenuated as a consequence of drinking alcohol. Learning occurs and in similar future circumstances, one can understand how the individual might resort again to alcohol. To what extent the effects of alcohol are preconditioned by genetic or cultural susceptibility or are psychopharmacological and primarily induced by alcohol per se or to what degree they represent a psychodynamic expectation by the drinker are questions remaining to be answered. In any event, the fact seems to be that the act of drinking becomes a powerful reinforcer for some individuals.

But how does the laboratory rat learn about alcohol? What does it detect when it drinks an alcohol solution? Besides taste, the rat usually learns that alcohol has caloric value---a large body of experiments attests to this. Whether

the *sine qua non* of the central effects of alcohol are appreciated by the rat and connected to the previous ingestion of alcohol seems a quite different matter; temporal contiguity between drinking and awareness of central effects seems sufficiently long to preclude such an association. The search for the rat's response specifically to alcohol would have little meaning if alcohol possessed no important pharmacodynamic attributes—indeed, there would be no problem. But alcohol does have important central actions which any animal model must take into account, and until it can be shown that the rat drinks alcohol for the same kind of central reinforcement that man seeks, then so-called animal models are merely phylogenetic analogues which bear only a superficial resemblance to man's alcoholism.

Thus, some attempts at studying animals' drinking behavior only simulate or mimic human drinking. If an animal model is feasible (and some doubt that animal and human personalitites can be equated [23]), then it should be one in which the internal phenomenal states of the laboratory animal closely approximate those of the alcoholic. In a simulation, on the other hand, some parallels can be drawn but only from an external frame of reference. It is no difficult feat to achieve high blood alcohol concentrations in rats constrained to drink alcohol by fluid or food deprivation, but where the alcoholic drinks from strong inner motivations, the rat is constrained to do so by equally compelling external manipulations alien to man. The net result for both organisms is the excessive consumption of alcohol without a model of functional relationships having been attained. Similarly, the seemingly compulsive, prolonged and intoxicating ingestion of alcohol by rats under schedule-induced polydipsia imitates the compulsive drinking of the binge alcoholic: from a motivational point of view, these behaviors are hardly generically related.

A wealth of literature demonstrates how alcohol affects experimental neurosis and conflict when it is administered in an acute preparation and even when animals exhibit adaptation and tolerance to its chronic administration. Absent, however, are demonstrations that animals select alcohol to attenuate tension states. In a few attempts [7,20], there has been failure to induce rats to emit operant responses for alcohol or to drink alcohol in response to stress. In the former study, it was apparent that rats more readily drank greater volumes of alcohol when it was freely available (as the only fluid choice) than when its availability was contingent upon appropriate operant behavior. Others [1,4] reported that stressed rats drank alcohol in a choice situation, and operant performance for alcohol reinforcement has been found in rats [15]. In a more recent study with monkeys, however, Mello and Mendelson [17] were unable to produce addictive-type drinking in a stressful avoidance paradigm.

An overview, then, suggests that (a) alcohol can - and does - reduce tension when its administration is controlled by the experimenter, but (b) animals have not learned this, or (c) that alcohol self-selection by animals may not be based upon this need [12]. This last is an important drawback to research involving animal models of experimental psychopathology because an underlying hypothesis for such paradigms has always been that conflict, stress and anxiety should result in increased alcohol intake. Lester [12] summarized the problem as follows: "If stress and anxiety are involved in the mechanism of addiction, then the ingestion of alcohol to reduce these states seems eminently reasonable. In the absence of any showing that enough alcohol has been ingested to produce such a reduction, however, the nexus of alcohol ingestion and degree of stress is nebulous. Experiments directed to the production of various levels of stress or anxiety and the conmitant measurement of alcohol selection might well illuminate this relationship."

Such experiments have not been performed. Some barriers to their accomplishment in the service of a viable animal model of alcoholism are determination of what constitutes a necessary and sufficient psychological or behavioral stressor, and a methodology for adequately acquainting animals *a priori* with alcohol's tension reducing properties à la human social learning without at the same time producing learned taste aversion.

As we have already noted, the ingestion of large amounts of alcohol by mouth is easily attained (14 Table 1); thus rats on polydipsic schedules, where the fluid is only an alcohol solution, have ingested voluminous and intoxicating quantities of alcohol; even when a choice is offered in this situation, the alcohol solution is usually preferred (unpublished observations). But one of the bases for this immoderate intake of alcohol is the control exerted by alcohol's energetic characteristic: alcohol provides calories. In studies of alcohol polydipsia, alcohol intake remains high and fairly stable over five levels of pellet nutrition ranging from 100 to zero per cent, whereas water intake declines sharply over this same range [8]. Similarly, when the intermittent food reward of a polydipsic schedule is halted, the ingestion of alcohol, but not of equi-intoxicating, noncaloric acetone, continues [9].

Where there has been a choice between water and an alcohol solution, female alcohol-addicted rats have taken as much as 9.9 g/kg/day for short periods [6] and C57B1 mice take as much as 20 g/kg/day for long periods [24]. Even here, where the ingestion of alcohol does not appear to have caloric deprivation as a motivating factor, the ingestion appears accidental and inadvertent: there seems little doubt that in the face of fluids competing on the basis of either calories or taste (sucrose, saccharin, fat), the alcohol solution, if drunk, would have been drunk in insubstantial quantity [13]. Self-selection of an alcohol solution where the choice lies only between water and an alcohol solution is restrictive, and in most instances seems to represent an effort to limit the applicability of any experimental findings. It is problematical whether such a methodology can provide any insights for an animal model. Unless fluids other than alcohol and water are present, fluids chosen because they offer competitive characteristics of taste, calories and pharmacodynamic effect (saccharin; sucrose; butanediol-1,3; acetone; methanol; etc), such insights for an animal model are not likely to result.

A recent paper seems to overcome some of these caveats. Cicero *et al.* [5] gave an experimental group of rats a 7% (v/v) alcohol solution as their sole fluid source for 133 days, beginning with weaning. After 7 days of intervening tests, and beginning on Day 162, two series of 7-day, 3–30% alcohol versus water preference–aversion tests were made, the second series with 0.005% saccharin as a third fluid choice. Data on only 1 of 4 animals in the experimental and control groups, each animal representative, are given. Although it appears that the presence of a 0.005% saccharin solution did not affect the intake of 3, 5, 7 and 10% alcohol solutions in the experimental rat, at higher concentrations of alcohol (15, 20 and 30%), alcohol

intake fell. Quite the reverse was the case with the control rat: in the presence of the saccharin solution, alcohol intake was less when 3, 5, 7, 10 and 15% solutions of alcohol could be ingested, but alcohol intake from 20 and 30% solutions increased. Unquestionably, part of the difficulty lies with the great variance in intake exhibited by animals on self-selection and data restricted to one animal per group can hardly be called definitive. But a greater objection is that the authors restricted their testing to only 0.005% saccharin. Why not 0.1%? Or a sucrose or acetone solution? These objections do not lessen the importance of the presence of alcohol immediately upon weaning for the later heightened intake of alcohol; confirmation of these observations and determination of the critical developmental period should have a high priority.

Other efforts in initiate alcohol drinking, whether by hypothalamic stimulation [2,26] or by intraventricular infusion [19] and whether confirmed or not [10] have also not directed themselves to the question of the specificity of the alcohol drinking, it purpose, or to its maintenance in the face of additional fluid choices.

In summary we suggest the criteria of Table 1 for an animal model.

TABLE 1

CRITERIA FOR AN ANIMAL MODEL OF ALCOHOLISM

1. Oral ingestion of alcohol without food deprivation.
2. Substantial ingestion of alcohol with competing fluids available.
3. Ingestion directed to the central intoxicating character of alcohol, substantiated by determination of circulating blood alcohol levels.
4. Work performed, even in the face of aversive consequences, to obtain alcohol.
5. Intoxication sustained over a long period.
6. Production of a withdrawal syndrome and physical dependence.
7. After abstinence, reacquisition of drinking to intoxication and reproducibility of the alcoholic process.

Our criteria, not necessarily completely definitive, envision a primary stage in which alcohol's positive reinforcing properties as a discomfort attenuator, mood elevator and anti-anxiety agent are emphasized and, we would hope, learned. Because of the temporal lag from drinking and swallowing to the time when central effects are experienced, experimental manipulation will be necessary to ensure temporal contiguity between the conditional stimulus, alcohol, and the unconditioned response, be it associated with termination of punishment, resolution of conflict or receipt of some other positive reinforcer. Repeated reinforcements over a fairly long time span will undoubtedly be needed.

The model will also require demonstration of sustained, substantial alcohol consumption by animals given competing fluid choices in the experimental situation with generalization of this behavior to their home cage. One would also expect generalization of alcohol drinking in response to other stressors or tension reduction designs; there has to be assurance that what has been conditioned is not merely an isolated and specific drug-situation interaction. And, finally, following upon the volitional intake of sufficient alcohol and its withdrawal, one would expect to note an abstinence syndrome.

One definition of model is "something perfect of its kind". While not advocating perfection, we do recommend that the phrases "animal model" and "addiction model" be parsimoniously reserved for animal behavior which stringently meets both psychological and physiological criteria. One of the many dictionary definitions of "model" concerns something worthy of imitation. The prevalence, seriousness and deleterious impact of human alcoholism renders it most unworthy, but by its very imperfection it merits modeling.

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