A Biobehavioral Research Perspective on Alcohol Abuse and Alcoholism

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Synopsis

An empirical biobehavioral research approach to the conditions generally identified as alcohol abuse and alcoholism emphasizes the temporal ordering of participating biochemical, physiological, and behavioral events that provide an operational basis for characterizing the functional aspects of this complex disorder and identifying distinguishable features of the alcohol abuse and dependence process. The available evidence suggests that alcoholism is a condition determined by a host of continuous variables rather than an entity possessing static qualities that imply intractability. The challenge for biobehavioral research is to determine the details of how chronic and excessive alcohol drinking is generated as well as the conditions under which such overindulgence can be attenuated and prevented. Environmental context, for example, can dramatically alter the frequency and amount of alcohol intake. Such contextual malleability is suggested as an important key to at least some of the inconsistencies in the literature with regard to the conditions under which chronic and excessive alcohol intake occurs. Excessive and chronic alcohol ingestion would seem most parsimoniously viewed as a set of behaviors for which others might have been substituted, and intermittently do, rather than as a highly specific disorder or disease. Though current etiological, preventive, and therapeutic orientations emphasize the role of physical dependence and favor genetic influences as strong determinants of alcohol-related disorders, it is important to recognize that troubled drinking is malleable, waxing and then entering periods of remission, with alcohol drinking even in severely dependent individuals remaining susceptible to control by both antecedent and consequating environmental events.

IT IS THE PURPOSE of this article to provide a brief overview of the progress and prospects in developing biobehavioral research models of excessive alcohol ingestion and physiological dependence on ethanol. With regard to therapeutic and preventive measures, the modest insights gained from such biobehavioral research may help to answer perplexing questions that have been difficult to address directly in clinical settings. The thrust of this paper, then, is to indicate what laboratory biobehavioral research has to tell us about excessive alcohol ingestion and physiological dependence that may have new implications for the human conditions that are generally identified as alcohol abuse and alcoholism.

Basic Concepts and Definitions

Some definitional clarity has been gained recently in the analysis of drug abuse and dependence (of which alcohol problems must be regarded as a specific case) by dividing the vast arrray of events that characterize this area in general into two reasonably exclusive categories based upon explicit operational criteria (*1*). Such a division is possible by distinguishing events that occur *before* from events that occur *after* the actual intake of the substance. The defining operations of the "before" class would include (but are not necessarily limited to) proactive alcohol seeking and drinking behaviors associated with the consequences of excessive alcohol ingestion. The defining operations of the "after" class would focus upon the reactive biochemical, physiological, and behavioral changes associated with the consequences of excessive alcohol ingestion, as well as with the tolerance and abstinence effects after alcohol withdrawal following recurrent excessive alcohol ingestion. The temporal ordering of biochemical, physiological, and behavioral changes in relation to alcohol intake can thus provide an operational basis for analyzing the range of alcohol's functional characteristics and for identifying distinguishable features of its spectrum of action.

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The relevance and importance of this distinction between proactive "alcohol abuse" and reactive "alcohol dependence," that is, "alcoholism," resides in the fact that their defining properties are not coextensive, they do not invariably occur together, and the methods differ by which they are analyzed experimentally. The strength of proactive alcohol-seeking behaviors and abusive self-administration of alcohol can be maintained by use patterns with doses of alcohol that produce no significant tolerance or withdrawal (*2*, *3*). Conversely, tolerance and abstinence syndromes can be demonstrated under conditions that involve neither alcohol-seeking behaviors nor abusive alcohol self-administration (*4*).

Interactions between these proactive and reactive events of the alcohol scene are, of course, commonplace. Changes in alcohol-seeking and alcohol drinking can occur as sequelae to both the acute effects of alcohol and to the tolerance and withdrawal effects that follow more chronic and excessive alcohol ingestion (*5*). Conversely, the chemical and physiological changes that define "physical" dependence can as well be sequelae to the repeated excessive self-administration of alcohol (*6*). But the relative contributions of these distinguishable processes to alcohol-related problems can vary widely as a function of dose, environmental circumstances, and previous experience, including history of alcohol use (*7*).

This conceptual framework for encompassing alcohol abuse and "alcoholism" provides an empirical approach to clarifying the semantic and taxonomic confusion perpetuated by the interchangeable use of terms like "addiction" and "dependence" as referents for a bewildering range of phenomena and experiential pseudo phenomena (*8*). The terms themselves, persistently reified as substantive noun "things" in subject predicate relationships with other "things" ("causing" as well as being "caused by" these other "things"), are seldom accorded appropriate conceptual status as constructs emerging from observed interactions between specifiable antecedents (biological and social) and definable consequences (biochemical, physiological, and behavioral). Within this context, biobehavioral research can provide a basis for defining these constructs more operationally and for specifying the conditions under which a unifying conceptual framework can be developed for treating and preventing the prominent health hazards involved.

Biobehavioral Perspective

The proactive events associated with alcohol seeking and excessive alcohol ingestion are of primary interest and concern from a biobehavioral perspective. Those who deal therapeutically with alcohol problems know the complexity of etiologic and maintaining factors as well as the web of social myths that surround the condition. These myths and expectations exacerbate clinical problems by perpetuating notions and explanations of alcoholism that endow terms such as "addiction," "loss-of-control," and "abstinence avoidance" with undeserved explanatory powers (*9–13*). One advantage of laboratory research models is that animal behavior is culture-free in that it is not directly determined by human cultural prescriptions. It is relatively culture-free, that is, unless investigators read into models the results that bits of cultural mythology call for.

Animal model delineation should not be merely a ritual behavior of scientists to confirm culturally based beliefs about the nature of "alcoholism." If that is what is chosen, then a model has little information to yield. One would have already decided what "alcoholism" is, and the models would furnish only an acceptable biomedical context in which to couch these beliefs so that we could get on with the business of re-stating what we already held to be the case: perhaps that alcoholism is a genetically determined behavior that specially and compulsively locks on to the ethanol molecule, primarily for reasons of individually flawed biochemistry, and inevitably leads to loss-of-control drinking for which the only cure is total and permanent abstinence. If we were certain of all

these facts, then we would hardly need the models, for they would only produce tedious and expensive demonstrations. The purpose of a model is not to confirm our beliefs about how something works, but rather to find out if our notions are tenable, and if so, what further consequences flow from the model.

Construction of a laboratory animal model would be facilitated if there were general agreement as to the definition of a case of human "alcoholism." "The main criteria of alcoholism seem to be present in populations as continuous distributions rather than as discontinuous, isolatable entities (*14*). The bulk of the evidence suggests that the more appropriate analogy might be with hypertension rather than with coronary thrombosis or with osteoporosis rather than with pathological fracture" (*14*). The lesson to be drawn is that we will probably fare better by clarifying the variables that institute and maintain ethanol overindulgence and the range of behavioral antecedents and biomedical consequences than in trying to produce a miniature version of the definitionally vague "alcoholic." The strategy of producing several kinds of renovascular hypertension in animals has unravelled many of the variables that produce and maintain this condition, even though none of the animal laboratory models are entirely similar to human renovascular hypertension.

If we approach "alcoholism" as an entity possessing static qualities, implying an essentially intractable status, then we naturally expect to mimic this in animal models that are deemed successful. But no model has demonstrated anything like a compulsively "hooked" alcoholic animal with loss of control. The existence of such an unremittingly static entity in humans has been questioned on several grounds: the alcohol consumption of a population is distributed unimodally (not bimodally); troubled drinking is malleable, waxing and then entering periods of remission; drinking, even in severe alcohol dependence, remains susceptible to control by both antecedent and consequating environmental events (*8*, *15–17*).

It is time to see if our experimental arrangements uphold commonly received notions of what sustains overindulgence or, what is more likely, if we will be induced to revise some of our opinions. If "alcoholism" is like hypertension, then it is a condition determined by the interaction of a host of continuous variables, and we need to determine the details of how excessive drinking is generated, as well as what useful attenuators can be applied for therapeutic and preventive ends.

Experimental Findings

There is now a substantial experimental literature confirming that laboratory animals, including rodents and primates, will self-administer alcohol both intravenously and orally (*3*, *18–20*). The conditions under which such self-administration can become chronic and excessive, however, are not simply derivable from the pharmacological properties of ethanol. Unlike cocaine, for example, which dramatically preempts the stream of behavior over a range of experimental conditions, alcohol self-administration (particularly via the oral route) has been difficult to establish in the animal laboratory without special induction procedures. Perhaps noxious taste factors are involved (as they certainly are in some humans, including most children) or the slow onset of pharmacological action by the oral route, but chronic alcohol overindulgence has rarely been modeled in laboratory animals. But then, most people do not overindulge chronically either, and the challenge of determining the conditions under which such excessive alcohol ingestion can be observed enhances the relevance of an experimental analysis. A promising lead in this regard is suggested by the experimental evidence that the environmental context in which drug-taking occurs can dramatically alter the reinforcing function of even the most abusable substances. This contextual malleability of a drug's reinforcing efficacy has recently been documented with both cocaine (*21*) and nicotine (*22*), revealing that both drugs can have either pronounced reinforcing or punishing effects depending upon environmental contingency conditions. Biobehavioral research findings strongly suggest that such contextual malleability may hold the key to some of the apparent inconsistencies in the experimental literature with regard to the conditions under which chronic and excessive alcohol intake may occur.

The conditions for producing an explosive increase in oral fluid intake with laboratory animals, for example, turn out to be not all that complex. A relatively minor constraint on the availability of some important commodity (for example, food) and an intermittent schedule of access to that commodity is sufficient. Although never deprived of water, animals receiving food pellets on the average of once every minute drank 10 times as much water in 3 hours as they did when receiving the same number of pellets all at once (*23*, *24*). They drank about half their body weight in 3 hours when on such an intermittent food schedule. This overindulgence, which continues for months during

daily intermittent feeding sessions, cannot be explained by any standard physiological, nutritional, or behavioral considerations (*25*).

This intermittent delivery of food has been demonstrated to increase the intake of a number of drugs taken orally in addition to alcohol: barbiturates, opiates, phencyclidine, and amphetamine (*26–30*). And excessive heroin, methadone, cannabis, and nicotine intake has been reported intravenously under such schedule-induced conditions (*31–33*). Alcohol was drunk excessively by a group of animals exposed continuously to an intermittent feeding schedule (*26*). The alcohol was preferred to water and other solutions, and chronically excessive intake under such intermittent feeding conditions resulted in severe physiological dependence (that is, abstinence syndrome following alcohol withdrawal). This model of excessive alcohol intake has been used to investigate several problems and consequences related to "alcoholism." Among these are tolerance, cross-tolerance, cross-abuse, physical dependence, motor function, ethanol elimination rates, water-electrolyte status, liver pathologic changes, brain changes in adult, and body weight reduction in fetally exposed animals (*26, 34–43*).

The excessive alcohol intake demonstrated in these experiments is in concordance with other kinds of excessive behavior that can be generated by the environmental context that determines schedule-induced behavior. For example, intermittent schedules of reinforcement for delivering food (or other commodities) can induce many kinds of excessive behavioral adjuncts including attack, pica, hyperactivity, inappropriate escape, elevated drug intake, and smoking (*44–50*). In general terms, while deprivation acts as a crucial facilitating condition, it is the episodic delivery of the valued, deprival commodity (food) in one domain that induces excessive behavior adjunctive to that domain. If we consider that both nature and society often provide an uneven flow of crucial commodities important to survival—food, territory, sex, social interactions—which all too often amounts to deprivation, then this can constitute intermittent scheduling with the possibility of generating excessive behavior.

The environmental conditions that give rise to schedule-induced behavior can apparently induce a variety of excesses, some productive (creative endeavors, workaholic overcommitment) and others characterized by social disturbances, violence, and drug abuse. The particular directions taken appear to depend upon current environmental opportunities and the individual's capacity and history to use an available commodity or activity. Environmental conditions that produce alcoholism can thus be seen as continuous with those producing other sorts of excessive behaviors and woes. Certainly, the diagnostically relevant determinants of alcoholism (degree of ethanol consumption and impaired job performance or social behaviors, or both) present as continuous population variables rather than as special and discrete disease entities. These considerations suggest that excessive and chronic alcohol ingestion represents a set of behaviors for which others might have substituted (and intermittently do), rather than as a highly specific disorder or disease state.

One characteristic of alcoholic drinking that should be considered by a research model is the volatility of the intake pattern. Chronic excess may be followed by relative moderation; bingeing may be succeeded by months of sobriety, only to slip into relapse. In human beings, it is not always clear why these changes occur, but an experimental model that can clarify the variables that turn on and off chronic excesses could illuminate volatility. By simple manipulation of the variables that produce and cut short schedule-induced excess, it has been easy to evoke such volatility (*51, 52*). But even in experiments where the external circumstances are held constant day-to-day, episodes of self-imposed abstinence have been noted in monkeys (*53*) and humans (*54*).

A venerable theory of "alcoholism" is that the development of a state of physical dependence is a major factor in that it explains chronically maintained excessive intake. Inasfar as schedule-induction is the only voluntary (unforced) oral ingestion model that produces physical dependence so severe that death ensues from withdrawal convulsions, it is an arrangement that has been of use in evaluating this notion. It should be clear that physical dependence cannot account for the genesis of overindulgence. Frank physical dependence in humans is an end-stage phenomenon that is present only after some years of severe overindulgence (*54*).

The role of physical dependence in alcohol self-administration has been extensively reviewed (*55, 56*), and it is now clear that the extraordinary focus on this aspect of the problem should perhaps be regarded as vestigial. Advances in an understanding of the factors that maintain self-administration have long since relegated physical dependence to a supporting role, albeit of potential significance. It remains a strong hypothesis, if not an act of faith, that physical dependence plays a central role in the

maintenance of the self-administration of alcohol. While emphasizing the efficacy of the schedule-induction method in the production of physical dependence on ethanol, it must be recognized that this attests only to the robust intake level and its long-term maintenance. The resulting dependence state may just be unequivocal "proof of the pudding" and not a systematically crucial endpoint for the analysis of alcohol overindulgence. No clear evidence exists that chronic, excessive intake is maintained by avoidance of the withdrawal syndrome associated with physiological dependence.

The conditions sufficient for the induction of chronic ethanol overindulgence can also give rise to a host of other adjunctive, exaggerated behaviors, depending upon the context. This places alcoholism within a general framework of other excessive and pathologic behaviors that are primarily environmentally driven. By manipulating a few situational variables, the overindulgence can be turned on, off, or otherwise modulated, perhaps aiding in the analysis of the volatility of the alcoholic drinking-pattern. The food-limitation condition of this model is viewed as homologous to other facilitating variables that act in human situations to transform an agent of only moderate abuse potential into a more powerful one. Finally, schedule-induced overindulging in animals remains under the control of the environmental events that determine the excessive intake, even after a long history of overdrinking. The eventual physical dependence (while it can play a role in fluid preference) does not indicate that ethanol captures the ingestive behavior motivationally to transcend the original inducing conditions.

Therapeutic Implications

The very fact that long-term ethanol overindulgence in laboratory experimental models can be cut short by very simple changes in the scheduling of environmental events sounds an optimistic note with respect to therapeutic intervention. This dramatic reversibility clearly indicates that an overindulgence pattern is by no means self-perpetuating, even though the rest of the drinking context remains unaltered. Some interventions may only require appropriate alternatives to ethanol. Even in the presence of severe dependence, for example, with schedule-induced animals having had a long history of choosing ethanol in preference to water, availability of an oral glucose or saccharin solution that is concentrated enough alleviates the alcohol overindulgence.

The high levels of voluntary ethanol intake as a result of schedule-induction have been used to evaluate the ethanol intake-blocking properties of a few pharmacological agents. Disulfiram can decrease the intake of ethanol, mainly through the inhibition of aldehyde dehydrogenase. Both disulfiram and EMD 15,700 (also an aldehyde dehydrogenase inhibitor) markedly decrease the 5 percent ethanol intake of animals chronically exposed to schedule-induction, but they have little effect on animals that have water to drink rather than ethanol (*57*). In spite of repeated drug injections, however, the attenuation of ethanol intake does not appear to outlast the pharmacological action of the blocker. Upon drug discontinuance, the animals quickly resume drinking the 5 percent ethanol solution at the usual rate. In other studies (*58*), the specificity of both disulfiram and calcium cyanamide in blocking schedule-induced ethanol overindulgence in a dose-dependent manner has been confirmed.

Recently, the imidazobenzodiazepine Ro 15–4513 has been reported to block the anticonflict activity of low doses of ethanol, as well as the behavioral intoxication observed with larger ethanol doses (*59*). Since concern has been expressed that if the drug attenuated drunkenness it could encourage, rather than discourage, overindulgence (*60*), studies have been undertaken to evaluate its relative effects on both ethanol and water schedule-induced overindulgence. The drug decreased the intakes of both the ethanol and water groups equivalently, indicating perhaps that there is little danger that Ro 15–4513 will trigger uncontrolled bingeing.

Preventive Implications

Using the laboratory experimental models of excessive and chronic ingestion of alcohol to evaluate possible prevention strategies represents an important research challenge since the overindulgence can be so predictable, severe, and durable. Virtually all animals exposed to the experimental conditions develop chronic and excessive alcohol ingestion, and they belong to normal, unselected populations with presumably no bias toward the development of alcoholism. In human beings, as well, prevention efforts are aimed at populations thought to be at hazard for the development of alcoholism, but owing to genetic as well as environmental factors. The problem amounts almost to the attempted block of a fated identity. Alcoholism is one of the few diseases which one "becomes," suggesting a behavioral etiology. In our culture we

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"have" heart attacks and are "victims" of cancer, but "become" neither of these diseases (*61*).

While alcohol overindulgence is a highly probable response to the appropriate experimental conditions, the question does arise as to whether its development can be blocked by some other adjunctive behavior. In a recent study using the schedule induction model, a running wheel was present for the first 3 months as an adjunctive behavior alternative. When water was then made concurrently available, overdrinking was not only retarded, but upon a change to 5 percent ethanol *overindulgence failed to develop*. Animals drank only at known control levels. McMillan (*62*) found that when either water or 5 percent ethanol solution was available, making a running wheel available had either no effect or a minor one on schedule-induced drinking. However, when a choice between the two fluids was available (5 percent ethanol was much preferred over water), running-wheel availability decreased consumption of 5 percent ethanol and increased water consumption. It would appear that an alternative activity other than an ingestive one can interfere with established ethanol overindulgence. Adding the availability of a 0.9 percent NaCl solution alternative to an established 3-hour schedule-induced 5 percent ethanol overindulgence also results in a stable, marked reduction in daily ethanol ingestion (*63*). Of even greater interest is the finding that a history of schedule-induced 0.9 percent NaCl solution overindulgence greatly interfered with attaining later 5 percent ethanol overindulgence. Much of this latter research begins to suggest that such laboratory models of ethanol overindulgence at least might be dependent on the initial conditions of the experiment.

Two groups of animals, for example, were given differential fluid polydipsia histories (*64*). One had a history of choosing between 5 percent ethanol and 0.7 percent glucose (dilute, mildly acceptable), in standard daily 3-hour schedule-induction sessions, while the other similarly treated group chose between 5 percent ethanol and 5 percent glucose (highly acceptable). Both groups then had 5 percent ethanol in both tubes for 1 month and overindulged in the usual manner. The crucial evaluation was done by gradually increasing the glucose concentrations of one of the fluids over weeks from 0.7 percent to 5 percent glucose for both groups. This was to ascertain whether a distant history of having experienced a highly acceptable glucose solution would induce animals to give up the 5 percent ethanol overindulgence choice more readily than in the case of the group which had experienced only the rather dilute glucose, even though they were both given equivalent current choice opportunities. The answer was clear. As the glucose concentration was increased, animals with histories of 5 percent glucose gave up drinking 5 percent ethanol more readily than those with 0.7 percent glucose histories. The history of having experienced a highly preferred glucose solution militated against continuing to drink 5 percent ethanol, even when it was presently paired with a glucose concentration of relatively low acceptability. Perhaps a history of having experienced a potent reinforcing agent helps to ameliorate abusive overindulgence even when an attenuated version of the reinforcing agent becomes available.

Summary and Conclusions

An empirical biobehavioral research approach to the conditions generally identified as alcohol abuse and "alcoholism" suggests that the temporal ordering of biochemical, physiological, and behavioral events can provide an operational basis for characterizing the functional aspects of this complex disorder and for identifying distinguishable features of the alcohol abuse and dependence process. Within this interrelational framework, determinants are conceptualized and analyzed in the context of observed interactions among a host of continuous variables, both antecedent and consequent, with a focus on the conditions under which chronic and excessive alcohol drinking is generated and maintained, as well as modified therapeutically and prevented (*65,66*).

The available evidence suggests that "alcoholism" is a condition determined by a host of continuous variables rather than an entity possessing static qualities that imply intractability. The challenge for biobehavioral research is to determine how chronic and excessive alcohol drinking is generated, as well as the conditions under which such overindulgence can be attenuated and prevented. Recent experimental evidence has documented the fact that environmental context can dramatically alter the frequency and amount of drug taking even with the most abusable substances. Such contextual malleability is suggested as an important key to at least some inconsistencies in the literature with regard to the conditions under which chronic and excessive intake can be demonstrated in laboratory experimental models of alcoholism.

It has now been convincingly demonstrated, for example, that alcohol and a number of other substances taken both orally and intravenously will be self-administered excessively and chronically when even relatively minor constraints are imposed on the availability of an important commodity (for example, food) by providing only intermittent access to that commodity. The excessive alcohol intake under these conditions is concordant with other kinds of excessive behavior generated by the episodic delivery of a valued, deprival commodity in one domain that induces excessive behavior adjunctive to that domain. The adjunctive excess appears to depend, in the particular case of ethanol, upon the environmental opportunity to drink alcohol and the individual's history and capacity in this regard. These findings suggest that excessive and chronic alcohol ingestion can be viewed as a set of behaviors for which others might have substituted (and intermittently do) rather than as a highly specific disorder or disease.

Despite its venerable status among the theories of "alcoholism," physical dependence has long been relegated to a supporting role, albeit one of potential significance. As a result of research advances in an understanding of the factors generating and maintaining alcohol self-administration, physical dependence has now been deposed from its former stardom in this regard. No clear evidence exists that chronic and excessive alcohol intake is maintained by avoidance of the withdrawal syndrome associated with physiological dependence.

Although currently fashionable etiological and preventive orientations favor genetic influences as strong determinants of alcohol-related disorders, the main criteria for "alcoholism" present in populations are continuous distributions rather than discontinuous isolable entities. The alcohol consumption of a population is distributed unimodally rather than bimodally as a dominant genetic influence would require. And of course, troubled drinking is malleable, waxing and then entering periods of remission. Alcohol drinking, even in severely dependent individuals, remains susceptible to control by both antecedent and consequating environmental events. Perhaps most importantly from a biobehavioral research perspective, while laboratory animal models have demonstrated genetic determinants of alcohol preference, additional factors aside from genetic make-up and exposure to alcohol are clearly necessary to catalyze excessive, chronic intake. No genetic model has selectively been bred for chronic and excessive alcohol intake, per se.

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Research on Alcohol Problems from the Perspective of Changes—1940 to 1990

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Synopsis

The nature of alcohol problems, knowledge about alcohol use and abuse, and public perceptions and responses have all undergone substantial change during the past half-century. This paper traces some interrelationships between changes in alcohol-specific knowledge and behavior and other relevant social forces. The importance of change in the derivation, utilization, and interpretation of this knowledge is emphasized. Special emphasis is also placed on changes that make the integration of research between the biological and behavioral sciences desirable and necessary.

ALTHOUGH HISTORY is technically defined as a branch of knowledge that records and explains past events by enabling us to trace processes of change and their impact, history can contribute substantially to our understanding of the present and our projections for the future. This observation certainly is true for the field of alcohol studies in the United States. The theme of this paper is change. This encompasses changes in knowledge about alcohol and in beliefs and assumptions about what we know and can expect to learn in the future; changes in the social contexts of drinking and in who drinks what, where, when, with whom, and why; changes in attitudes and values about drinking and alcohol problems; changes in the classification and labeling of problems; changes in the risks and liabilities of intoxication; changes in our perceptions of the social costs of alcohol problems; and changes in social responses.

The time frame for this review is the half-century