quence of prey-catching behavior (*16*). Similarly, stimulation of discrete brain sites in the freely moving cricket elicits different songs (*17*), and activation of certain neurons in the marine gastropod, *Tritonia diomedia*, elicits a complex escape pattern (*18*). These electrical stimulation experiments in lower vertebrates and invertebrates demonstrate that in the central nervous system there are motor programs with fixed neuronal circuits which, when stimulated, result in complex, well-coordinated motor patterns. It is probable that such "hard wired" behaviors exist in mammals. Our studies indicate that the microinjection of AVP into a discrete area of the hypothalamus of the hamster is able to trigger a complex, stereotypic motor pattern that exists normally in the animal's behavioral repertoire, and they suggest that AVP might function as a chemical messenger in the initiation of flank marking in the golden hamster.

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Factors in Ethanol Tolerance

The report by Wenger *et al.* (*1*) reiterates these investigators' important addition to the literature on alcohol tolerance (*2*), but the conclusions of the authors would lead one to believe that learning is the most important, if not the only, factor important for the development of ethanol tolerance. These conclusions ignore a large number of experiments with other techniques, such as liquid diets (*3*), in which ethanol was administered to animals in a manner such that learning could play but a minimal role in the development of tolerance. Yet, functional tolerance to ethanol's physiologic and behavioral effects was clearly demonstrated after such a method of ethanol administration.

Recent work in our laboratories (*4*) has, however, also demonstrated that the use of ethanol in paradigms which constitute conditioning can produce tolerance not only to the hypothermic, but also to the hypnotic effects of ethanol. The demonstration of this "conditioned" tolerance depends on testing the animals in the environment within which they are accustomed to receiving ethanol, and no tolerance can be demonstrated when animals are given ethanol in a novel environment. On the other hand, tolerance produced by feeding animals a liquid diet containing ethanol can be demonstrated within a wide variety of experimental environments. We have, therefore, used the terms "environment-dependent" and "environment-independent" tolerance to refer to forms of tolerance in which learning plays a major and a minor role, respectively (*4*), and we have presented evidence that development of the chronic, environment-independent form of alcohol tolerance requires the presence in the animal of higher levels of ethanol for continuous and extended periods of time compared to the levels of ethanol required for development of environment-dependent alcohol tolerance.

Whether environment-dependent and environment-independent forms of ethanol tolerance are simply dose-related, additive, manifestations of a singular physiological process is not, at present, clearly understood, but more is known in this area than is presented by Wenger *et al.* The pharmacologic manipulations which have been used to investigate learning and memory have been applied to studies of ethanol tolerance. Our studies, with neurotoxins and neurohypophyseal peptides (*5*) have shown certain similarities and some important differences in the way these agents affect the environment-independent form of alcohol tolerance and their effect on learning and memory. Our recent data on the effects of neurohypophyseal peptides or their analogs on development of environment-dependent and environment-independent alcohol tolerance further demonstrate differences in the effect of the peptides on these two forms of ethanol tolerance (*6*).

We would caution against an oversimplification of the alcohol tolerance phenomenon. Learning may be important in the development of some aspects of ethanol tolerance, but may not be important in all forms of ethanol tolerance. One should not ignore the fact that even within the categories of environment-independent and environment-dependent forms of tolerance, a further subdivision into dispositional (metabolic) and functional forms of ethanol tolerance is necessary (*7*).

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Our hypothesis that learning may be the predominant mechanism underlying tolerance to ethanol was based on our studies (*1, 2*) showing that rats exhibited tolerance to the disruptive effects of ethanol on treadmill performance only if, during training trials, they walked on the treadmill while intoxicated. Tabakoff, Melchior, and Hoffman state that not all instances of drug tolerance are caused by learning. We agree that drug tolerance may have multiple causes; however, in many of the commonly used experimental designs, including those used and cited by Tabakoff and his colleagues, learning appears to us to be the most parsimonious explanation.

Tabakoff *et al.* state that learning "could play but a minimal role in the development of tolerance" when animals are given ethanol as a necessary component of their sole source of food, a liquid diet (*3*). This procedure, as well as that in which ethanol vapor is a part of the atmosphere in which animals live (*4*), presents an unusual situation as regards a possible influence of learning. Most experiments indicating that learning has a major role in the development of drug tolerance are done with procedures that maximize the likelihood of revealing a learning effect. In these studies, single, specific discriminative stimuli are always associated with drug administration or drug effect (or both), so that only the same stimuli are ultimately capable of eliciting the expression of tolerance. This is true in both our own (*1, 2, 5*) conditioning experiments and those of Melchior and Tabakoff (*6*). However, in the liquid diet and ethanol inhalation experiments, the drug is taken into the body continually and therefore elicits its physiological and behavioral effects continually and in the presence of all possible environmental situations available to the animal. Neither a particular time of the day nor a particular stimulus signals the drug's effects. It is therefore unlikely that specific environmental stimuli will become reliable predictors of a drug's effects in such situations. However, since the physiological effects of ethanol are continually present, internal or interoceptive stimuli may come to assume a greater than normal control of compensatory responses that may be responsible for tolerance; that is, in the absence of predictive exteroceptive stimuli, interoceptive stimuli invariably associated with the effects of ethanol in the body may in time control the expression of tolerance. It is therefore not surprising that tolerance in such situations "can be demonstrated in a wide variety of (exteroceptive) experimental environments," as Ritzmann and Tabakoff (*3*) found, because the interoceptive stimuli were present in all of their test situations. Learning is therefore a possible explanation of tolerance to ethanol acquired in the liquid diet and ethanol vapor experiments.

The fundamentally different mechanism by which the expression of tolerance is elicited in procedures requiring a continual intake of ethanol may also account for its differential sensitivity to neurotoxins and neurohypophyseal peptides, as found by Tabakoff and his colleagues (*7*). Ettenberg *et al.* (*8*) reported that neurohypophyseal peptides may have differential effects on different types of learning.

In order to describe the apparent diversity of causes and types of tolerance, Melchior and Tabakoff (*6*) suggested that tolerance should be classified as environment-dependent or environment-independent. We believe that such a distinction may mask the more important issue concerning the development of tolerance. We believe that the specific experience one has while intoxicated is the critical factor. Ethanol administration does not in itself necessarily lead to the development of tolerance. Our studies (*1, 2, 5*) and those of others (*6, 9*) have shown that, for tolerance to develop, animals must experience the functionally disruptive effects of ethanol in a context that permits learning to occur. Blocking the functional effects of ethanol blocks the development of tolerance to these effects. Conversely, allowing animals to experience some of the effects of ethanol through nonpharmacological treatments allows animals that have no previous experience with drugs to develop tolerance to these effects (*2, 10*). Thus, the critical factor appears to be the opportunity to experience the functional effects of the drug (*11*) in a context that permits learning to occur (*10*).

There are undoubtedly changes that occur in the body as a simple function of drug exposure. Indeed, Tabakoff and his co-workers have long been in the forefront in demonstrating such changes at the cellular level (*12*). What is not clear, however, is whether the cellular changes are related to the expression of tolerance to ethanol by the intact organism. Tolerance at the physiological and behavioral levels may be quite different. When adequate control procedures are used in experiments on behavioral and physiological tolerance, learning appears to be the predominant causal mechanism.

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