Morphine and Ethanol Physical Dependence: A Critique of a Hypothesis

Many biochemical hypotheses have been advanced to explain ethanol dependence (*1*). One of the most recent (*2*) ignores the most solidly established features of ethanol and morphine physical dependence, and Davis and Walsh strain at the literature to find support for their concept.

They state that "Because of the resemblance of symptoms occurring on withdrawal of either alcohol or the opiates, it seems possible that the addictions may be similar and that the real distinctions between the two drugs could be only the length of time and dosage required for development of dependence. The differences, therefore, may be purely quantitative rather than qualitative." On this basis, they postulate that "alcoholism is a true addiction which may involve specific biochemical events leading to the formation of the morphine-type alkaloids." They also present biochemical data which they assert support the view that an endogenous morphine-like alkaloid is produced by the interaction of acetaldehyde, a metabolite of ethanol, with one of the biogenic amines, dopamine.

Drug abuse is being recognized increasingly as a major medical and sociological problem. As a result, research on drug dependence, having been long neglected, is becoming scientifically respectable. Since it is preferentially supported, many investigators from disciplines other than pharmacology are being attracted to the field. Because so little is known of intimate mechanisms of physical dependence, this is highly desirable. Sound biochemical and physiological studies are badly needed. However, unless the hypotheses and interpretations based upon such studies are consonant with known pharmacological facts they can have no validity. It is believed to be worthwhile to review the fundamental and well-established facts concerning alcohol and morphine physical dependence specifically as they relate to the views of Davis and Walsh.

Long-term administration of alcohol or morphine induces a state of latent hyperexcitability in the central nervous system which is manifest only when the drug is withdrawn (*3*). In the case of morphine this hyperexcitable state is also rapidly unmasked by the morphine antagonists. Since different cell groups are involved in the two types of physical dependence, the clinical syndromes of morphine and alcohol abstinence may be clearly and easily differentiated and characterized (*4*). Furthermore, these two distinct types of physical dependence can be reproduced without fail in man and other mammals (*3*).

Ethanol exerts primarily psychomotor effects, with specific manifestations in intellectual function, emotional responses, integrated behavior, and motor control. A major portion of the signs of alcohol abstinence resembles the effects produced by convulsant drugs—severe motor hyperreflexia, generalized tremors, and grand mal convulsions. There is also a psychosis-like state with disorders of cognition and hallucinations. In contrast, morphine displays a mosaic of highly specific effects on a wide variety of neural systems. Morphine not only has psychomotor effects which are quite different than those of ethanol, but, in addition, it relieves pain, depresses respiration, and alters greatly the central and peripheral regulation of autonomic functions. In morphine abstinence, there is also a mosaic of behavioral, somatic, and autonomic signs which constitute a unique syndrome that is only reproduced in dependence to narcotic analgesics. There is no disorder of thought or perception, and convulsions are extremely rare.

Alcohol-barbiturate physical dependence is characterized by an all-or-none dose-response relation as well as a specific time-response effect. For example, a heavy social drinker can consume 50 to 60 percent as much alcohol in a 24-hour period as the alcoholic without developing physical dependence. Since it is usually consumed within a few hours, the brain is relatively free of alcohol during the greater part of the 24-hour period. The situation in the monkey is quite analogous. Strong physical dependence can be developed (delirium and convulsions on withdrawal) within 14 days by intravenous or oral administration of 8 g of alcohol per kilogram distributed over a 24-hour period, producing alcohol concentrations in the blood of 250 to 300 mg/100 ml (*5*). In the monkey, no physical dependence develops in many months if at all, if 4 to 5 g of alcohol is administered within a 3-hour period once daily, an amount which induces profound intoxication and comparable temporary peak alcohol concentrations in the blood (*6*). In contrast, the intensity of morphine dependence in the monkey is dose related over a range of 100 to 10,000 μg/kg given every 6 hours without interruption for 30 days (*3*). Furthermore, a single large dose, 40 mg/kg hypodermically once in 24 hours for 60 days, induces very strong physical dependence (*3*). A comparable situation exists in man.

Specific cross dependence and cross tolerance with morphine occur with ten or more chemical classes of substances with different molecular configurations. Because all these substances react with similar receptor sites, they possess morphine-like properties, and withdrawal precipitates a morphine-like abstinence syndrome. This type of specific cross dependence has been observed in this laboratory, without exception, in over 700 morphine-like compounds which have been examined in the monkey during the last 20 years. With ethanol a similar situation exists with many drugs having comparable pharmacological properties. For example, barbiturates, many sedative-hypnotics, and other hydrocarbons that affect relatively similar mechanisms as does ethanol, exert specific mutual cross dependence and cross tolerance with ethanol (*7*).

It is critical to this discussion to recognize that no specific mutual cross dependence or cross tolerance exists between morphine-like drugs and the ethanol-barbiturate-hydrocarbon class of substances.

Specific cross dependence should be distinguished clearly from nonspecific obliteration of signs of abstinence. Any psychoactive drug capable of producing marked central nervous system depression or anesthesia will obtund abstinence signs and symptoms of morphine or alcohol just as it will control hyperactivity of the central nervous system from hyperkinetic states of disease origin—epilepsy, tetanus, stimulant drug poisoning, and so forth. The fact that opiate addicts may consume large quantities of alcohol if nothing else is available, as Davis and Walsh cite in support of their concept, should be viewed in relation to these facts. More importantly, morphine users prefer barbiturates, amphetamines, cocaine, and many other substitutes over alcohol which is usually a last choice.

The nature and magnitude of tolerance development to alcohol and morphine are entirely different. The lethal dose of alcohol may under certain conditions be elevated less than

twofold by long-term administration. In contrast, humans, under controlled conditions, have taken 4000 mg of morphine intravenously in 24 hours, and this was not the limit. The short-term lethal dose in man is probably between 50 to 100 mg of morphine. Tolerance developed to morphine is, therefore, in the order of 25- to 100-fold.

Any hypotheses based on biochemical conversion to another pharmacologically active substance must account for the short-term as well as the long-term actions of the drug. Thus, if the concept of Davis and Walsh was tenable, the morphine antagonists (nalorphine, naloxone, and so forth) would antagonize short-term alcohol intoxication as they do specifically for morphine-like drugs. Furthermore, barbiturates and all of the dozens of sedative hypnotics (meprobamate and chloral, for example) which show specific cross dependence with alcohol must logically produce physical dependence by being converted metabolically to a morphine-like alkaloid. The known facts would require also that they be antagonized acutely with morphine antagonists. Finally, morphine antagonists would precipitate abstinence of the morphine-type in man and animals physically dependent on alcohol, barbiturates, and the sedative-hypnotics.

Certain other comments appear to be pertinent. If a sufficient quantity of a morphine-like alkaloid was produced from ethanol to account for its pharmacological effects and the development of physical dependence, current biochemical methodology is adequate to identify the material unless it had a potency of the order of the oripavines. Davis and Walsh postulate that "THP [tetrahydropapaveroline] may have . . . addiction liability of its own." It is a simple matter to determine whether this is true (*8*). But even if physical-dependence capacity were to be demonstrated for THP it would offer no support for the hypothesis.

Many questions arise which relate to the acetaldehyde postulation. One will suffice. Why do disulfiram (Antabuse) and calcium carbimide, which arrest the oxidation of alcohol at acetaldehyde, produce such specific toxicity which is not morphine-like, when administered in the presence of alcohol, if the brain is capable of converting acetaldehyde to a morphine-like alkaloid?

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Although several statements in our report may imply that all of the manifestations of ethanol dependence and morphine dependence should be synonymous, this is not our intention. The proposal should more appropriately be directed to defining a possible biochemical concomitant of alcoholism which could provide a common link between the addiction produced by ethanol and the narcotic alkaloids. It should not purport that all the phenomena of alcohol dependence can be thusly explained. Any identity or similarity of these addictions would have its origin in specific interactions of structurally related addictive compounds with biological "substrates" subserving the phenomena of addiction and the complex processes involved in creating the addictive state.

Based on the hypothesized metabolic sequence which was described, it would be expected that alcohol-induced aberrations of endogenous dopamine metabolism might occur within neuronal elements where dopamine is synthesized, stored, released, and functions as a neurotransmitter. Since dopamine is localized in high concentrations in specific brain areas, notably the infundibular and extrapyramidal regions (*1*), it would be anticipated that any ethanol-mediated alteration in the metabolism of endogenous dopamine would be confined to these areas. Similarly, from a pharmacodynamic standpoint, any intrinsic activity of aberrant metabolites would necessarily have functional manifestations of a restricted and discrete nature.

This modification in dopamine metabolism may be unrelated to the attendant physical sequela characteristic of ethanol withdrawal. Nevertheless, because this biochemical event should be confined to specific neuronal sites, if any manifestations were attributable to it, they would be difficult to predict at the present time. Consequently, the possible endogenous formation of amine-derived alkaloids would not necessarily be a determinant for the majority of characteristics of ethanol withdrawal, including convulsions and delerium. These phenomena, as well as the depressant and intoxicating properties of ethanol, are likely related to other direct actions of the drug rather than to the indirect biochemical sequence proposed. For example, respiratory alkalosis and hypomagnesemia have been correlated with decrements in blood alcohol concentrations and with manifestation of certain withdrawal symptomatology in man (*2*). In this case, therefore, the withdrawal symptoms may be a reversal of the pharmacological actions of ethanol in depressing the respiratory center. The rapid development of physical signs of abstinence in mice previously exposed to ethanol vapor and treated with an alcohol dehydrogenase inhibitor, pyrazole, further attests to a more direct action of ethanol for these effects (*3*). Thus, the physical consequences, if any, of an endogenously formed addictive alkaloid in localized brain areas, would be superimposed on the multiple and diverse effects of ethanol. As a result, the use of narcotic antagonists for the demonstration and identification of "abstinence" symptoms which could be related to formation of such an alkaloid would be difficult to achieve. Induction of abstinence signs, especially if they are of a finite character, by naloxone administration could be "nonspecifically" suppressed when blood ethanol concentrations are elevated. Conversely, if naloxone were administered in the presence of falling ethanol concentrations or after its disappearance, the major contributions of the ensuing withdrawal signs directly attributable to the ethanol molecule could completely mask or at least prevent distinction of such a discrete symptomatology. Another, more germane consideration is the question of whether narcotic antagonists would reach the specific site where endogenous alkaloids would be synthesized or would exert their activity.

Furthermore, this hypothesis would not require that the entire abstinence syndrome characteristic of narcotic analgesics should be mimicked either on discontinuation of alcohol or adminis-

tration of morphine antagonists to alcohol-dependent animals. Exogenously administered narcotic analgesics interact with many target organ systems and flood the entire nervous system. Consequently, withdrawal of a narcotic after long-term administration exhibits a broad panorama of signs. In contrast, it is reasonable to assume that the isolated and localized "withdrawal" of an endogenously formed alkaloid would not exhibit the same "mosaic" of symptoms that occur on cessation of narcotic analgesics or administration of narcotic antagonists. In addition, specific cross dependence between narcotic analgesics and alcohol is likewise unnecessary. As Seevers correctly points out, any efficacy of either of these two drug types in obtunding the abstinence syndrome of the other would probably be related to their nonspecific central nervous system depressant effects. Similarly, the meager degree of tolerance which develops to alcohol as compared with the narcotic analgesics—that is, the inability to markedly elevate the lethal dose of alcohol—could be due to a lack of tolerance development to the pharmacological effects of ethanol on the cardiovascular and respiratory centers. Thus the amount of alcohol that can be ingested and the maximum blood concentration that can be achieved is limited by the pharmacological actions of alcohol on certain vital functions. Lack of cross dependence and cross tolerance between alcohol and the narcotic analgesics, therefore, does not negate the possibility that these two chemically distinct drug types may share some common denominator which could be related to their abuse potential. It also follows from these considerations that there is neither any reason for postulating that specific cross dependence or cross tolerance, or both, between alcohol and other sedative-hypnotic drugs would necessarily involve this type of biochemical sequence; nor that physical dependence produced by these other drugs need be based on a similar pharmacological interaction with neuroamines. Specific symptoms of physical dependence, as well as the relatively low-grade tolerance which develops with sedative-hypnotic drugs, must also be considered in light of the inherent and generalized depressant effects of these molecules.

Several of Seevers' comments may be misinterpretations and need clarification. The authors did not suggest nor imply that the formation of tetrahydropapaveroline (THP) would be even remotely related to the intoxicating properties of ethanol. The efficacy of narcotic antagonists in blocking the pharmacological effects of the morphine-type drugs is associated with structural specificity and affinity of the antagonist for "receptor sites" with which narcotic analgesics interact. Because the short-term intoxicating versus the addicting properties of ethanol are likely dualistic in their mechanisms and involve quite distinct molecular interactions, narcotic antagonists would not be expected to block or prevent alcohol intoxication. Contrary to the suggestion, the methodology required to resolve the effect of ethanol on endogenous dopamine metabolism within dopaminergic neurons in the central nervous system is not immediately at hand. Moreover, because of the localized nature and kinetics of this possible biochemical event, any endogenously formed alkaloid need not possess high intrinsic activity. Formation at or near the site of action would preclude such a requirement. Additionally, failure to demonstrate physical-dependence capacity for THP would not reflect on the validity of this proposal. Physiochemical characteristics as well as the biological disposition of peripherally administered THP could conceivably prevent its addiction capability from being evident. Similarly, lack of physical dependence on THP would not necessarily prove an absence of addiction liability. While physical dependence is a most useful pharmacological criterion to aid in predicting if a drug has addiction liability, it is not satisfactory for demonstration of all addictions. Finally, Seevers infers that alcohol or acetaldehyde is converted directly to a morphine-like alkaloid. This is not the hypothesis. The proposal is that the neuroamine, dopamine, and its deaminated product, 3,4-dihydroxyphenylacetaldehyde, condense to form THP; and that ethanol and acetaldehyde may facilitate this reaction in vivo as they do in vitro. While THP is the requisite intermediate in the biosynthesis of a variety of plant alkaloids, including the morphine-type, it should not be concluded that morphine per se is formed or that it is just around the corner.

We have demonstrated the augmentation of THP formation in vitro during the metabolism of ethanol and have pointed to the requisite role of this alkaloid in the biosynthesis of other plant alkaloids. The postulated endogenous formation of THP in the central nervous system as a consequence of excessive ethanol consumption could conceivably have a number of ramifications. In contrast to the inactivity of most biogenic amine metabolites, THP has diverse pharmacological actions (*4*). Although not emphasized in our report, it is also the natural biosynthetic precursor in plants of a vast complex of alkaloids including the papaverine, tetrahydroberberine, aporphine, and morphine-type alkaloids (*5*). Conversion of THP to these alkaloids involves specifically directed methylation, demethylation, and oxidative phenol coupling reactions. Even in plants, however, the enzymes or conditions which direct these conversions are not well understood. It remains to be determined, of course, whether THP is formed under pharmacological conditions within dopaminergic neurons in specific brain areas; if formed, whether THP could undergo metabolic transformations similar to those occurring in plants; and if endogenous generation of alkaloids does occur, whether it would have any relevance in alcoholism. Concrete experimental verification for these speculations is lacking at this point. However, the construct was offered to hopefully focus on a heretofore unrecognized possible biochemical concomitant to alcohol abuse. Considering the present limitations in knowledge of the complex mechanisms underlying alcoholism, the need for hypotheses may be as essential as the acquisition of more data.

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