# CHRONIC CENTRAL NERVOUS SYSTEM TOXICITY OF ALCOHOL

6562

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A recent review of the literature on the pharmacology of alcohol by Wallgren & Barry states that "strikingly little experimental work has been devoted to the neurological complications of alcoholism" (1). This reviewer agrees, and believes that some of the solutions to this enormous public health problem may be developed by scientific investigations at all levels of biological organization, ranging from the behavioral. electrophysiological, and morphological, to the molecular level. There are at least two identifiable reasons for the neglect of this area of investigation: uncritical acceptance of clinical impressions not scientifically validated, and appreciable methodological difficulties. The objective of this review is to examine critically the validity and relevance of the available information and to emphasize information gaps strategically important for an understanding of the neurological diseases associated with excessive chronic alcohol consumption.

A major problem is whether ethanol per se produces chronic neurotoxic effects, as the title of this review implies. Until recently most, if not all, diseases encountered in chronic alcoholics were attributed to concomitant malnutrition rather than alcohol. A priori these pathogenic factors are not mutually exclusive and may interact with each other to cause the disease. At one end of the spectrum are certain disorders clearly nutritional in origin, that are encountered in malnourished alcoholics, e.g., Wernicke's syndrome is caused by thiamine deficiency (2). At the other end of the spectrum are the withdrawal syndromes that are definitely
(3, 4). The mere occurrence of a particular disorder in a population of malnourished alcoholics does not permit one to decide whether alcohol, as such, or malnutrition, or an interaction of both is the cause. Coexistence does not prove a cause-effect relationship. The chronic toxicology of ethanol has been considered to be the "toxicology" of malnutrition, not based on experimental evidence, but on *post hoc ergo propter hoc* reasoning. As this review attempts to demonstrate, more research will be necessary to delineate the relative contribution of malnutrition or ethanol, or both, to the causation of diseases occurring in chronic alcoholics.

This controversy is of more than academic interest because only approximately 5% of the problem drinkers are of the "skid row" variety (5). The great majority of persons in our society who drink alcohol to the extent that it interferes with

their physical or mental health are gainfully employed and are what Hartroft (6) called "executive drinkers." They often take vitamins and derive a large proportion of their nonethanol calories from protein. Presumably, many of them are not malnourished. The question is whether they are susceptible to certain direct toxic effects of ethanol or acetaldehyde, its only specific metabolite.

If the chronic ingestion of alcoholic beverages per se has certain toxic effects, it is possible to attribute these to ingredients—the so-called "congeners"—other than ethanol (7, 8). However, hepatic cirrhosis occurs in consumers of all types of alcoholic beverages (9, 10), and some studies in rats have failed to show that different alcoholic beverages differ in their effects on growth rate, organ weights and histology, liver function tests, and tests of neuromuscular coordination (11). Clearly, more research is needed in this area.

The evaluation of chronic drug toxicity in laboratory animals usually presents no problems. However, in the case of ethanol, two facts have made such an evaluation particularly difficult. First, long-term administration of ethanol is practical only by the oral route, and even in low concentrations ethanol is aversive to animals (12).Therefore, it has been difficult to administer ethanol to animals in amounts comparable to those consumed by alcoholic patients. The classical method of feeding animals aqueous solutions of ethanol as the only drinking fluid is inadequate (13). The amounts of ethanol consumed are relatively small (14), and intoxication, withdrawal signs, or fatty infiltration of the liver are not observed (15). In free choice experiments the amount of ethanol consumed is even less; therefore, the relevance of this animal model to alcoholism in humans has been questioned. However with liquid diets 35–38% of total caloric intake can be obtained from ethanol and withdrawal syndromes can be induced in mice (16–19). Second, ethanol is a source of calories (6.9 cal/g). Any experimental design attempting to control for nutritional effects must employ pair-feeding with diets containing other nutrients, such as carbohydrates or fat, in amounts isocaloric with ethanol. If control animals, drinking water and eating ad libitum, consume the same amount of calories as the animals drinking aqueous ethanol solutions, they will also have eaten more protein, vitamins, etc. Therefore, pathological changes in the ethanol-drinking animals may be secondary to their lesser intake of nutrients, rather than to ethanol. The same difficulties in interpretation apply to studies and clinical observations in man. It was not until nutritionally controlled investigations were carried out that it was recognized that ethanol per se can induce fatty infiltration of the liver, in animals and humans in spite of good nutrition (20–22). The conclusions of many investigations must be considered tentative because adequate nutritional controls have not been incorporated into the experimental design.

Toxicity of ethanol has been implicated in diseases of the heart (23), hematopoietic system (24, 25), the liver (20, 21), and muscle (26). It would be surprising if a pharmacological agent, like ethanol, with such profound acute effects on the brain and marked direct chronic toxic effects upon other tissues, did not also have the potential for producing chronic toxic effects on the brain. Clinical evidence of brain impairment may be manifest in altered morphology, electrophysiology, or

measures of intellect. There are many processes that may interfere with learning and memory. They range from gross anatomical lesions, localized (Wernicke's syndrome) or diffuse (various degenerative diseases of the brain), to purely chemical disorders (hypothyroidism).

## Clinical Studies

Clinicians have long recognized that chronic, excessive alcohol ingestion is accompanied by intellectual deterioration and psychotic behavior (27–30). Various pathological changes in the brain have been described, many of which are not specific for alcoholism and cannot be easily distinguished from changes associated with other degenerative organic brain syndromes, aging, traumatic subarachnoid hemorrhages (31), or hypoglycemia (32). It was a major advance when Victor, Adams & associates demonstrated conclusively that one commonly observed acute syndrome, first described by Wernicke, was caused by thiamine deficiency and was reversible if thiamine was administered early in the course of the illness (2). Isbell & associates (4) demonstrated that certain psychoses were caused by the withdrawal of ethanol, rather than by direct ethanol toxicity or malnutrition. Encephalopathies resulting from alcoholic liver disease and its surgical therapy were recognized (33).

Clinical studies attempting to demonstrate a direct toxic effect of ethanol on the brain are beset with great difficulties. There are no simple biochemical tests available comparable to liver function tests. Intellectual deterioration must be measured by serial, longitudinal, psychometric testing procedures and compared with appropriate control populations. Delicate anatomical changes cannot be assessed by serial needle biopsies but can only be inferred by relatively crude, radiological air-contrast studies, cerebral blood-flow measurements, or autopsy material with its inherent technical difficulties, such as autolysis and changes caused by terminal illness. It is possible that metabolic impairment of brain function is not accompanied by gross morphological changes. Electrophysiological assessment of brain function is essentially restricted to recordings from scalp leads, which may demonstrate changes only in extreme cases of deterioration. Defects in learning and memory and their anatomical or electrophysiological correlates may be compounded by aging (34, 35), atherosclerosis, or other associated illnesses (36). For instance, mild hypoxia and hypertension in the elderly have been demonstrated to be associated with a reversible decline of performance in intelligence tests (37, 38). Pathological deviations in any of the parameters examined may be nonspecific and indistinguishable from those caused by other conditions. As yet, there are no leads from animal experiments that can be applied to investigations in man. Because of these difficulties, the evidence to be reviewed for a direct toxic effect of ethanol on the brain is fragmentary and inconclusive, but suggestive.

*Psychometric investigations.*—Psychometric investigations of chronic alcoholic patients compare alcoholics with control populations matched by age, sex, and

education. They demonstrate varying degrees of impaired intellectual function in the alcoholics on a spectrum, ranging from subtle impairment to severe Korsakoff's syndome. This impairment is generally attributed to organic brain damage (39–49). These studies give no or only anecdotal information regarding the nutritional history and status of the subjects, but several of them (39–47) specifically excluded subjects with history of findings of neurological impairment (like Wernicke's syndrome) or obvious severe organic brain syndromes (like Korsakoff's syndrome). This, together with the finding that the degree of impairment is correlated positively with the amount and duration of alcohol consumption (39, 40), suggests that chronic alcohol consumption alone may impair brain function, in addition to thiamine deficiency associated with Wernicke's syndrome.

*Electroencephalography.*—As in psychometric studies, age-matched controls appear to be essential for the detection of more subtle EEG abnormalities because the EEG changes with normal aging, even in the absence of mental deterioration (although with wide individual variations) (35, 50). These relatively slight EEG changes with aging are not correlated with psychometric performance. In contrast, the mentally deteriorated aged (50) and patients suffering from presenile dementia (51) have a higher incidence of diffuse and temporal lobe slow-wave abnormalities. But no EEG changes are demonstrable in some deteriorated patients, even when organic, cortical brain damage is proven histologically (51). The effect of chronic alcohol ingestion upon the EEG is still controversial. One study found a "10.5% incidence of abnormality comparable to that usually found in a normal control population" (52), but matched controls were not studied. The patients received a variety of medications while the EEG's were recorded, and no correlation between neurological status and state of withdrawal was reported. The duration and amount of alcohol ingestion in these patients was moderate in that only 68% of the patients admitted to problem drinking longer than five years. Other investigators reported a statistically significant increase of "sleep rhythms" in alcoholics, as compared to patients hospitalized for other psychiatric disorders (53). Other uncontrolled studies found unspecified "abnormal EEG's" in 79% (54), 31% (55), or a variable incidence, depending upon criteria of quality, frequency, and incidence of alpha rhythm (56). Involvement of central brain structures in Wernicke's syndrome may not affect the cortical EEG at all (27). Even though information derived from the standard scalp lead EEG may be limited, modern methods of computerized EEG analysis should be applied to controlled studies of chronic alcoholism, preferably by investigating patient populations longitudinally over prolonged periods of time (57).

*Cerebral blood flow.*—Cerebral blood flow and oxygen and glucose consumption were shown to be reduced in 11 chronic alcoholic patients diagnosed as having Wernicke's and Korsakoff's syndrome, in comparison with controls of

similar age (58). Similar reductions of overall cerebral blood flow were found in patients with presenile and senile dementia, and the degree of impairment was well correlated with the severity of mental impairment (59). The decrease of blood flow was most marked in the gray portion of the cerebral hemispheres, particularly in the temporofrontal regions. Approximately one-half of these patients had enlarged ventricles, demonstrated by pneumoencephalography. The frequent occurrence of generalized and localized cerebral cortical and subcortical atrophy, as determined by pneumoencephalography in alcoholic patient populations with dementia, has been emphasized in the French literature (30). The role of malnutrition, associated disease, and aging cannot be adequately determined in these reports. In other reports of cerebral atrophy in chronic alcoholics, these conditions appear to have been excluded (47, 60, 61), and alcohol per se was considered to have caused the cerebral atrophy. Echoencephalography demonstrated statistically highly significant enlargement of the third ventricle in 98 alcoholics when compared with age-matched controls (62). This difference in ventricle size was particularly marked in the younger age groups. Patients with a history or evidence of head trauma and cerebral diseases, including Wernicke's syndrome, were excluded from this study. Some authors (63) concluded from their data that chronic ethanol consumption may aggravate the cortical atrophy of senile dementia. The elegant methods of regional blood-flow measurements (59) may help to clarify the role of cerebral cortical involvement in chronic alcoholic patients.

*Anatomical studies.*—Wernicke's syndrome is characterized essentially by ophthalmoplegia, nystagmus, ataxia, and confusion associated with microscopic lesions in thalamus, hypothalamus, mesencephalon, and brainstem as reviewed by Victor, Adams, & Collins (27). There is good evidence that this syndrome is secondary to thiamine deficiency because it is observed in thiamine deficiency states that are not associated with alcoholism, and thiamine therapy may reverse the signs if administered early in the course of the disease (2). The classical Wernicke's syndrome is acute and potentially lethal; therefore, its incidence in malnourished alcoholics autopsied in general hospitals should be relatively high. More chronic, atypical cases of "Wernicke's syndrome" (defined morphologically) have been described (64, 65).

Korsakoff's syndrome consists of various degrees of impaired remote, and recent memory in the presence of a clear sensorium. Some patients with extreme forms of "Minutengedaechtnis" are not able to retain even the simplest type of information, given without intervening distractions, for more than a few minutes. This results in the inability to retain recent information long enough to learn. There is some impairment of perceptual and conceptual (integrative) functions and a diminution of patient's initiative and attention occasionally associated with confabulation. As has been reviewed by several authors (27, 28, 64, 66), histological changes in chronic alcoholic patients may be extensive, involving not only the central structures affected in Wernicke's syndrome, but cerebellum, frontal

lobe, and portions of temporal and parietal lobes of the cortex as well. It has been pointed out by Victor, Adams & Collins (27) that relatively small lesions in the central structures may result in impairment of memory; whereas anatomical lesions in the cerebral cortex have to be more extensive to interfere with cognitive and mnestic functions. The contribution of the cortical morphological changes to the intellectual impairment of alcoholic patients remains to be assessed.

The anatomical aspects of memory are now better understood (36), but its biochemical basis is now only beginning to be elucidated (67). The possibility must be considered that chronic ethanol consumption may impair neuronal functions without gross morphological alterations. Toxic agents, such as lead and arsenic, have been reported to cause Korsakoff's syndrome (68, 69). Organic solvents, like toluene, may cause cerebral atrophy (70, 71). Endocrine disorders (72) may interfere with intellectual function at the biochemical level of organization with little or no gross morphological correlates. At least 39 metabolic disorders may cause mental impairment in the absence of localizing neurological signs (73).

Korsakoff's syndrome has been considered to be caused by thiamine deficiency (27) as a result of the following observations. First, the thiamine deficiency syndrome (Wernicke's) is frequently associated with Korsakoff's syndrome. Second, tumors or other lesions located in brain regions, usually involved in Wernicke's syndrome, may cause an amnestic syndrome similar to Korsakoff's. Third, in some patients there is an improvement of Korsakoff's syndrome that is concomitant with thiamine therapy. Treatment failures are common and are attributed to irreversible changes, too far advanced to respond to thiamine. This unitarian concept may be questioned on several grounds.

*First*, Korsakoff's syndrome is associated with both chronic alcohol consumption and malnutrition. It is impossible to decide a priori which of the two conditions is the cause of Korsakoff's syndrome. Damage from malnutrition and direct ethanol toxicity are not mutually exclusive. Both may contribute or interact to various degrees in causing mental impairment in a particular patient. Victor et al reviewed the nonethanol-related causes of malnutrition causing Wernicke's syndrome (27). This reviewer has not been able to find reports of any documented cases of permanent Korsakoff's syndrome (with disturbed memory persisting for more than two to three months) in patients where Wernicke's syndrome was induced by malnutrition alone in the absence of alcohol consumption. This suggests the possibility that ethanol itself may play a role in the pathogenesis of Korsakoff's syndrome. The absence of documented permanent mental disability is striking in large numbers of prisoners of war with long-standing malnutrition, which had resulted in severe neurological disorders, including peripheral neuritis, retrobulbar neuritis, deafness, ataxia, Wernicke's syndrome, laryngeal palsy, and spastic paraplegia (74–78). Denny-Brown (79) describes the severe neurological syndromes occurring in large numbers of patients suffering from thiamine deficiency, endemic in the Orient. He attributed the distinct rarity of Wernicke's syndrome, even in lethal cases, to a lesser degree of thiamine deficiency, in comparison with those cases related to alcoholism. This reviewer could find only

one case of permanent mental impairment which may have been induced by nonethanol-related malnutrition (80). This patient was a criminal psychopath, imprisoned much of his life, who developed Wernicke's syndrome following a hunger strike. "Air encephalography revealed severe cortical, and slight ventricular, atrophy." Four weeks after the acute onset, psychometric testing (81) revealed features characteristic of Korsakoff's syndrome. Six months later "no important improvement in his mental state" was found, but repeated psychometric testing was not reported. Approximately one year later this patient died in chronic uremia. Autopsy revealed a histological picture that was "in accordance with the diagnosis of Wernicke's encephalopathy" and "slight degenerative changes in the cerebral cortex due to aging." It is apparent that several factors may have been responsible for this patient's mental impairment.

*Second*, the cerebral cortex showed histological and gross evidence of degeneration (57% in Victor's series) in series reported by Victor et al (27), as well as in other series of alcohol-related Wernicke's syndrome.

*Third*, Korsakoff's syndrome has even been described in alcoholic patients when histological lesions were confined to the cerebral cortex (82). Cortical degenerative changes have been found in alcoholics without evidence of history of malnutrition in comparison with age-matched controls (66). Some authors, however, find only minor changes in the cerebral cortex with major changes in the central gray structures in patients with clinical Korsakoff's syndrome (83). But there is no doubt that cortical damage alone may result in severe intellectual impairment as seen in presenile dementia, Pick's disease, and Alzheimer's disease.

*Fourth*, not all patients with extensive anatomical involvement causing Wernicke's syndrome have Korsakoff's syndrome. Which of the diencephalic structures are most critical for memory formation is still debated (27).

*Fifth*, it is unexplained why thiamine therapy can reverse the pathogenetic process of the neurological manifestation of acute Wernicke's syndrome but often is ineffective in Korsakoff's syndrome, although the anatomical lesions and pathogenesis are presumed to be identical in the two.

*In summary*, this reviewer believes that the available morphological evidence favors the possibility that in some patients Korsakoff's syndrome may be caused exclusively by a constellation of localized diencephalic and mesencephalic lesions induced by thiamine deficiency. But there is no reason to believe that this is the only mechanism whereby chronic alcohol consumption may impair mental function. The contribution of cerebral cortical damage remains to be assessed at the behavioral, morphological, physiological (particularly synaptic transmission), and biochemical levels of organization. This assessment should not be restricted to the extreme forms of mental impairment that Korsakoff's syndrome represents, but should include cases of lesser degrees of dementia. The dramatic increase in mental hospital admissions of patients suffering from alcoholism (84) and the irreversible "chronic brain syndrome associated with alcohol intoxiaction" (85) should serve as a stimulus to expand this research to find means of prevention.

## ANIMAL STUDIES

As discussed in the preceding sections of this review, the long-term effects of ethanol ingestion may be analyzed at many levels of organization from the behavioral to the molecular. There is now good evidence that in the absence of malnutrition chronic ethanol consumption in mice impairs the rate of learning of a shuttle box paradigm (86). The degree of impairment increases with the duration of alcohol consumption from three to five months and is essentially irreversible (87). The acquisition of active avoidance (88) is also impaired in rats after chronic ethanol consumption. The results of these experiments support the concept that ethanol has a direct toxic effect on the brain.

Electrophysiological or electronmicroscopical correlates of *chronic* ethanol toxicity apparently have not been investigated in experimental animals. Recent biochemical investigations in young mice drinking aqueous solutions of alcohol demonstrated an impairment of incorporation of leucine-$^{14}$C into brain ribosomal protein and specifically into tRNA. This phenomenon was observed only after the mice had consumed ethanol for at least 24 days (89). It is possible that chronic ethanol consumption affects the synthesis of proteins, nucleic acids, or both, which are thought to be necessary for the acquisition, storage, and retrieval of information (90, 91). Brain acetylcholine concentrations measured by bioassay were reportedly lowered by 38% in rats drinking 15% aqueous ethanol solution for 22 weeks (92). In similar experiments coenzyme A, cholinesterase, and choline transacetylase were also lowered (93). It is not possible to determine from these reports if these effects were acute, occurred while blood ethanol concentrations were elevated or during ethanol withdrawal, persisted after acute withdrawal, or were secondary to nutritional factors. Gamma aminobutyric acid concentrations in brains of rats drinking 15% aqueous ethanol solutions for 23 days were unchanged from controls when the animals were sacrificed while blood ethanol concentrations were elevated (94). Ethanol administered to mice in liquid diets for 14 days, increased the rate of 5-hydroxytryptamine biosynthesis (measured after pargyline MAO inhibition) without changing the baseline steady state concentration (95). Tryptophane hydroxylase activity was increased concomitantly. The results were attributed to ethanol-induced pituitary-adrenal stimulation, as tryptophane hydroxylase is stimulated by adrenal corticoids, and the ethanol-treated mice had elevated corticosterone blood concentrations. The animals were sacrificed during ethanol consumption while blood ethanol levels were still elevated. Therefore, the reported findings are probably not secondary to withdrawal. It is not known how long these changes persist after withdrawal or if they can be induced by exogenous corticosteroids alone.

Biochemical changes in the brain resulting from chronic ethanol ingestion could be secondary to effects on cell metabolism, organelle membranes, cell-wall membranes (including blood-brain barrier) (96), electrophysiological processes such as localized (withdrawal) seizure activity, or gross hypoxic changes induced by intermittent sludging of erythrocytes in capillaries (97). At present,

only a few isolated facts about chronic alcohol toxicity are known. Therefore, no rational prophylaxis or therapy can be developed. It is also apparent that the development of a coherent biological concept of chronic ethanol toxicity could make a major contribution to the understanding of the molecular aspects of learning and memory.



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