

NEUROCRITICAL CARE THROUGH HISTORY



# The Discovery of Acute Alcohol Withdrawal as a Cause of Delirium

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For heavy drinkers to come into a hospital carries risks, and worryingly, signs associated with imposed abstinence appear soon after admission. A considerable number could be transferred to intensive care units including neurointensive care units when the primary diagnosis was neurological. The Clinical Institute Withdrawal Assessment for Alcohol (CIWA) protocol to recognize and treat alcohol withdrawal is, in fact, one of the most common order sets (and so is IV thiamine). When we know a just admitted patient drinks excessively and for years—taking into account a continuously changing definition of ‘excessive’ over the last decades and cultural differences—we anticipate a delirium with or without seizures already within 24 h of admission.

A forgotten medical history is that for decades (and into 1950s), delirium was attributed to the direct effect of alcohol. The possibility that alcohol withdrawal plays an important role in the initiation of delirium was considered common knowledge in some circles around the turn of the century and by prominent psychiatrists Adolf Elholz, Wagner von Jauregg, and Hare [1]. Sudden distaste for alcohol had been recognized as an early sign, and much had been made of this statement in Kinnier Wilson’s leading textbook of Neurology in the 1940s, which also noted that abstinence was not a factor [2]. This surprised the Europeans, who had no difficulties linking delirium to sudden alcohol abstinence. In the USA, it remained a controversy due to contrasting observations. Bellevue Hospital’s psychiatric ward in New York (with ward designations of “quiet,” “semi-disturbed,” and “disturbed”) reviewed data in thousands of patients and found little related to sobriety [3]. Boston City Hospital,

however, confirmed alcohol withdrawal in their series of 101 cases with delirium and, in all, with falling blood alcohol levels [4]. Proof delirium tremens was due to abstinence would come from a prospective study. Isler and colleagues embarked on a controversial study in which prisoners were given as much whiskey as they wanted for a defined interval, after which it was suddenly stopped. This study with “informed” consent found alcohol did not cause delirium but rather the lack thereof.

The study was carried out in a “closed ward within an institution devoted entirely to the treatment of drug addiction” [5]. Volunteers were all former heroin or other opioid addicts serving sentences for “violation of the Harrison Narcotic Act.” The study reported that “the dangers inherent in the procedure were explained to them.” The psychiatric diagnosis in all 10 volunteers was a “character disorder” or “inadequate personality.” None had a prior history of seizures. The experiment consisted of three periods: preliminary or control period followed by a period of chronic intoxication and, finally, a period of abstinence. The abstinence period was divided into a 2-week withdrawal phase followed by a 3-month recovery phase. Dietary supplements, including IM injections of multivitamins and thiamine, were provided. All volunteers underwent a prior alcohol-metabolism study, which resulted in further adjustment of alcohol content in those with rapid clearance of alcohol. There was close laboratory monitoring of a number of parameters including alcohol breath analysis and EEGs while intoxicated. Volunteers were given 1.5 ml of 95% alcohol per kg diluted with two volumes of cold tap water and taken within 20 min. Under study supervision, seven volunteers (*Maurice, Red, Bob, Tom, Al, Jack and Charley*) drank these volumes every 2 h from 6 AM to midnight. (Increased amounts in the first 4 to 5 days were allowed to attain a “moderate degree of intoxication” and decreased amounts if nausea occurred.) In three volunteers with higher metabolism rates (*Junior, Slim* and

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*Tony*), the amount of alcohol was adjusted upwards with additional midnight drinks. Intoxication was graded as mild (garrulousness and laughter), moderate (slurring of speech, gait weaving), and marked (hostility, reeling gait, difficulty rising from a sitting position). No patient progressed to coma as a sign of severe intoxication. Significant variability in behavior while intoxicated was seen. Some became excessively noisy and boastful; others were elated, exhibitionistic, and “engaging in horseplay.” Others wished to fight. All volunteers remained mildly to moderately intoxicated with some reaching marked intoxication spikes. EEG recordings mostly showed slowing of alpha frequency and increased theta.

In three volunteers (*Maurice, Bob, Red*), the abstinence period ranged from 7 to 16 days and they became tremulous, perspired excessively, and demanded a drink, but the clinical picture did not go beyond a severe hangover with recovery in 3 days.

Symptoms of alcohol withdrawal in the remaining 7 volunteers occurred at varying times. Tremors appeared early in most patients and were sufficiently severe to hamper buttoning clothes. The patients described vivid visual hallucinations including a “disembodied head that was shrunken,” reminiscent of heads prepared by a South American Indian tribe; a frog man; a dwarf; attack dogs; and other aggressive animals such as egg-shaped insects. Others visualized a bed flying through a dark tunnel, a man peeping around a corner, an approaching ‘Sicilian’ killing gang, and a snake with two hands. Acoustic hallucinations included human voices outside windows, ringing telephones, and a man screaming as if he was being killed.

Neurologically, there were markedly dilated pupils and hyperactive reflexes but no clonus or Babinski signs. *Charley* had 7 seizures as early as 12 h after discontinuation and was subsequently treated with barbiturates. His convalescence was characterized by disorientation, amnesia, and confabulation. EEG in patients showed random spikes and bursts of slow waves during abstinence but only 2 patients had clinical seizures. A full physical and psychiatric examination 3 months after this experiment showed no psychiatric or neurologic remaining adverse effects.

### **A Larger Story**

The study found a severe withdrawal delirium after days of continuous drinking and sudden discontinuation. Marked tremulousness came first, and several had acoustic and visual hallucinations. The study may have settled the issue but the results did not surprise Maurice Victor and Raymond Adams, US experts on the neuropsychiatry of alcoholism. In their comprehensive article written 2 years before the prison study titled

“The Effects of Alcohol on the Nervous System,” they described a spectrum of syndromes in chronic alcoholics and made a compelling argument for the notion that delirium tremens and related syndromes are due to partial or total withdrawal of alcohol, which was supported by extensive clinical experience and blood alcohol level estimations [4]. They endowed the resulting syndrome with the cumbersome but precise compound designation of “the tremulous, hallucinatory, epileptic, delirious state,” the most severe expression of which was delirium tremens, often shortened to its initials DT, which became more commonly known as “the DTs.” Victor concluded: “The one indispensable factor in the genesis of delirium tremens and kindred disorders is the relative or absolute withdrawal of alcohol following a period of chronic intoxication.” Victor had already pointed out the acoustic hallucinations of telephones ringing, threatening accusatory human voices but all with preserved orientation and alertness. Acoustic hallucinations would last up to 6 days [6].

We now know more about a presumed mechanism. Recent studies [7] have shown that ethanol selectively inhibits NMDA (N-Methyl-D-aspartate) receptors that transmit the excitatory effects of the neurotransmitter glutamate. The depressive effect of alcohol on NMDARs (N-Methyl-D-aspartate receptors) results in compensatory up-regulation of these receptors and consequent brain hyper-excitability that emerges upon the withdrawal of alcohol [8].

For centuries, the effect of alcohol and the brain remained poorly understood including a number of significant misunderstandings. Death from cerebral edema (the so-called alcoholic “wet” brain) was considered a clinical entity and resulted in therapies such as dehydration and CSF diversion through lumbar punctures [2]. It took some time for textbooks to catch up and recommend the exact opposite (i.e., to provide hydration). The brains in patients who died were remarkable for lack of findings if the patient had no major prior nutritional deficit. Raymond Adams recalls that he found nothing in the cortex, basal ganglia and thalamus [9].

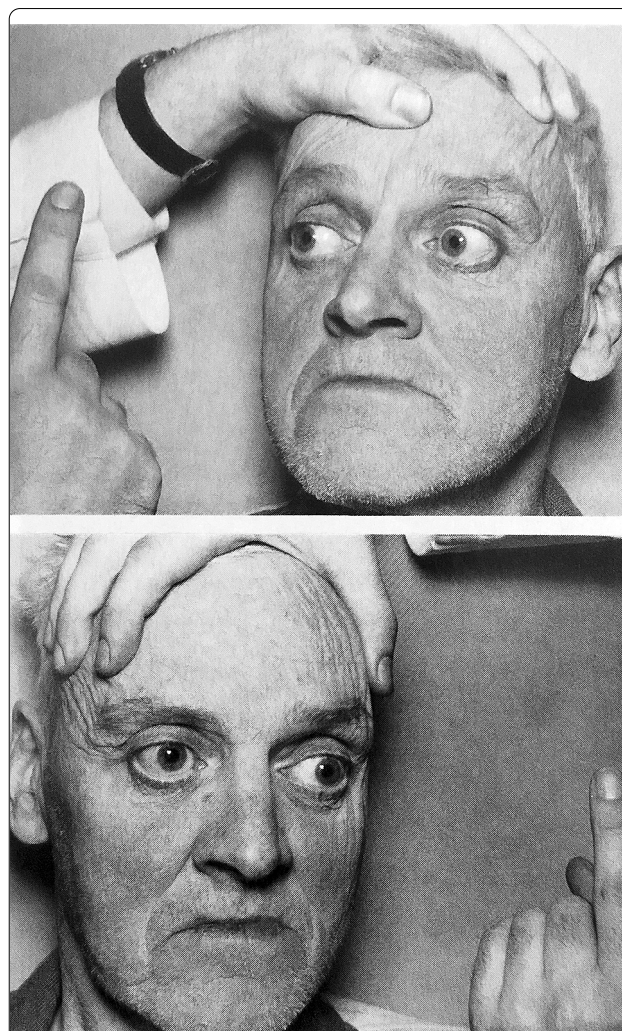
Equally importantly was the discovery that patients admitted in an alcohol-related delirious state actually could have specific and localized structural brain lesions. Victor and Adams importantly recognized that Wernicke’s disease and Korsakov’s amnesic psychoses overlapped in some patients recovering from alcohol abstinence—and they saw it in an estimated 3% of their neurologic consultations for disorders associated with alcoholism. (This compared well with the incidence of Wernicke–Korsakoff syndrome in a number of autopsy series). These neurologic findings had been independently described by Carl Wernicke and Sergei Korsakoff in the late 1880’s. The discovery

of a nutritional etiology had to wait to 1930's and was first recognized in hyperemesis gravidarum which also tells us the syndrome is not exclusively seen with alcohol use disorder. The fact that Wernicke-Korsakoff syndrome is now rarely seen in thiamine-deficient, long-term, critically ill patients (estimated one in 5) is remarkable unless the syndrome is hidden underneath the more common states of confusion; patients who do not know where they are and do not know why they are there. In Victor and Adams' series [10], with over 200 cases and over 80 autopsies, confirmed the presence of structural injuries (more often medial thalamic lesions than in the mammillary bodies) in patients with Wernicke-Korsakoff syndrome who displayed these clinical findings (Fig. 1). The current and often routine practice of IV thiamine may have reduced the incidence of the disorder but patients may still present with alcohol delirium, marked amnesia, confabulations, ataxia and ophthalmoparesis.

Appropriately, in hindsight, one should question the ethics of conducting this study in incarcerated persons [11, 12]. Before the 1970s, incarcerated persons were (disproportionately) exposed to the side effects associated with medical research. Currently, participants in federally funded studies in the USA are afforded special protections. One of the current criteria is whether the research is intended or deemed likely to improve the health or well-being of participants. Clearly, this study would not have been approved by current oversight or monitoring committees. Furthermore, providing alcohol to persons already known to have severe additional problems brought them into a constant state of intoxication. This is further supported by the investigator observations that some, while the study was in preparation, expressed a strong desire to begin (and in fact could not wait to begin).

Delirium tremens is another critical illness that can develop in any patient admitted to an intensive care unit. Alcohol withdrawal delirium is a serious medical disorder with both psychiatric and neurologic manifestations. It can be fatal. It is no joke although it seems it is for the brewers of *Delirium Tremens*<sup>®</sup> who won a gold medal during the 1997 World Beer Championships in Chicago.

Alcohol withdrawal delirium became suddenly a major issue during the SARS-CoV-2 pandemic with some US states allowing liquor stores to remain open during the initial spring lockdown so that emergency departments were not overwhelmed treating patients bereft of alcohol. Similarly, increased DT was seen in India when liquor stores were closed. Emergency rooms had to cope with twice the usual number of severe withdrawal cases which included seizures in 17% of cases [13]. We should not forget the irony exposed with this pandemic—liquor stores



**Fig. 1** Delirium tremens may be associated with nutritional deficiencies causing Wernicke-Korsakoff psychosis, amnesia and ophthalmoparesis. Example shows it may simulate an internuclear ophthalmoparesis with characteristic bilateral adduction paralysis but with full abduction with tracking. Characteristically it improves in a matter of hours after IV thiamine (Victor et al. *used with permission*)

deemed "essential services." For medical historians, there is no better recent proof of the major side effects of sudden alcohol abstinence.

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#### Conflicts of Interest

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