ALCOHOL WITHDRAWAL

Internal Medicine Grand Rounds

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INTRODUCTION

Alcoholism and various secondary withdrawal syndromes are well known to all internists. While attitudes and drinking patterns vary considerably between various cultural groups, the pathophysiological presentation of alcoholics can be reduced to general considerations. The purpose of this Grand Rounds is first to consider absorption and metabolism of alcohol, second to discuss the metabolic effects of alcohol, and finally to review the various alcohol related withdrawal syndromes.

ABSORPTION AND METABOLISM OF ALCOHOL

Ethyl alcohol is a small organic molecule which is highly soluble in water. It is permeable across most epithelial membranes, especially gastrointestinal tract, and therefore it is absorbed from the gastrointestinal tract by simple passive diffusive mechanisms, Figure 1. No metabolically active mechanisms have been identified. Once alcohol is absorbed from the gastrointestinal tract in an unchanged form it is rapidly distributed throughout body water.

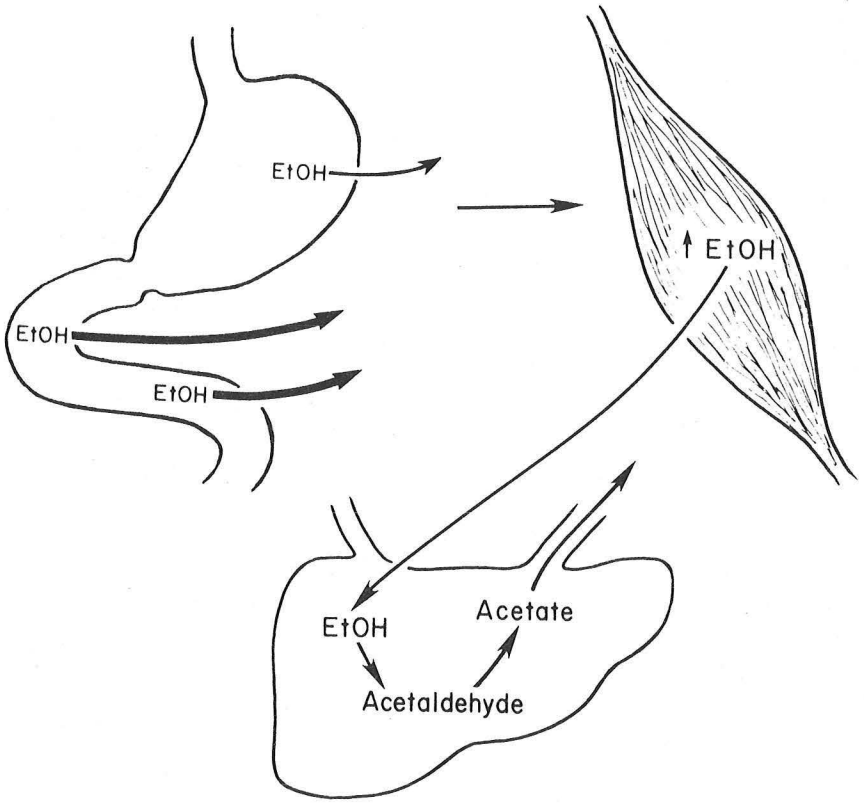

FIGURE 1. Absorption, distribution and metabolic fate of alcohol. Muscle depicts any organ as alcohol distributes throughout total body water. The rate of equilibration of alcohol in various tissues is a function of its blood flow and mass and its permeability to ethanol.

A number of factors have been shown to influence the rate of gastrointestinal absorption of alcohol. The most important of these factors is the concentration gradient of alcohol from gastrointestinal tract to the blood. The concentration gradient of ethanol in turn is a function of its rate of intake and rate of blood flow at the site of absorption. Thus it is not surprising that a rapid single ingestion of a given amount of alcohol leads to higher blood levels than does the ingestion of the same amount of alcohol in small doses which is spread out over a longer period of time. Decrease in alcohol absorption has been associated with those states with decreased splanchnic circulation such as has been noted to occur with decreased body temperature, during heavy physical exercise and with various anticholinergic and sympathomimetic drugs. It has also been well established that the various congeners (molecules of similar chemical structure as ethyl alcohol) may affect the rate of absorption of ethyl alcohol. The concentration of these congeners varies widely among various alcoholic beverages being the lowest in distilled spirits such as vodka and rising progressively in concentration in the more complex tasting alcoholic beverages such as wines and cognac, Table I. While the congeners generally decrease the rate of alcohol absorption from the gastrointestinal tract, they themselves may have toxic or irritant properties which may modify the pharmacological action of alcohol or contribute to the hangover syndrome. It also is well known that alcohol absorption is inhibited by various foods with rate of inhibition being most pronounced with diets which are high in protein and being least with foods with high carbohydrate content.

TABLE I
Congener Content of Alcoholic Beverages
(g per 100 litres at 50% alcohol)
(From Carrol, Q.J. Stud. Alcohol, 1970)

	Vodka	Gin	Whisky	Cognac
acetaldehyde	0.44	0.33	1.71	7.14
ethyl formate	0.50	0.40	1.11	3.93
ethyl acetate	0	0.06	14.70	53.58
methanol	0.49	2.33	2.82	14.76
n-propanol	0	0.06	2.19	16.67
i-butanol	1.35	1.17	5.56	39.60
i-amyl alcohol	0.52	0	18.45	116.60
TOTAL	3.30	4.35	46.54	252.28

Excretion, like absorption, is a passive process. Urinary excretion rates of ethanol are not much different from that of urea. Additionally, some ethanol is excreted in expired air and sweat. However, these excretory routes are of minimal significance in the overall removal rate of alcohol.

The principle route of ethyl alcohol removal from the body is by oxidation of ethanol to acetaldehyde in the liver as facilitated by alcohol dehydrogenase. The present evidence indicates that previously postulated contribution of microsomal ethanol oxidizing system or catalase do not have a physiologically significant role in oxidation of ethanol. Once acetaldehyde is formed by the liver it is doubtful that this acetaldehyde escapes into the systemic circulation in significant amounts from normal livers but rather it is converted to acetate and ultimately metabolized. A normal human metabolizes approximately 150 mg of alcohol per kg of body weight per hour which is equivalent to an average of approximately one ounce of 90 proof spirits or 12 ounces of beer in a 70 kg person.

Although the hepatic oxidation of ethyl alcohol occurs at a relatively constant rate, a number of factors have been identified which alter the rate of its metabolism. From the clinical viewpoint perhaps the most important factor which increases the rate of alcohol metabolism is the past history of alcohol intake. It has been well shown that chronic alcohol consumption can accelerate the rate of alcohol metabolism by at least a factor of two. Other factors which have been reported to accelerate the metabolism of ethanol include insulin, epinephrine, cortisone, thyroxin, oral contraceptives, barbituates, triiodothyronine and fructrose. Unfortunately none of these agents have been of value in clinical settings. In fact, the use of fructose has been associated with potentially harmful lactic acidoses and hyperuricemia. Decreased rates of ethanol metabolism have been noted in immature livers and alcoholics with cirrhosis. A number of recent studies have focused on the possibility that biochemical basis exists to explain increased incidences of drunkenness in various different races or ethnic groups. The basis of this hypothesis has been that a number of different alcohol dehydrogenase isoenzymes have been shown to exist. However, studies on various races have not convincingly supported this view since when absolute rates of alcohol metabolism per unit of body weight are calculated there do not appear to be significant differences between various races.

METABOLIC EFFECTS OF ALCOHOL

Hypoglycemia. Many, if not most, patients who are admitted to the hospital with alcoholism have lower than normal blood sugars. However, true hypoglycemia (<50 mg%) is more rare, but is recognized with greater frequency as familiarity with this syndrome becomes more widespread. It is more common in a malnourished alcoholic but may also be a finding in a weekend binge drinker. It is now well appreciated that an intoxicated patient may be comatose due to hypoglycemia and not to excessively high blood ethanol concentrations. Thus this possibility must be considered and acutely treated when a comatose alcoholic is brought in for evaluation.

The etiology of hypoglycemia has been most extensively examined in the classic series of papers published from Southwestern Medical School and reviewed in depth by Leonard Madison in his April 21, 1977 Grand Rounds. As noted earlier in Figures 1 and 2, ethanol is metabolized to acetate by alcohol dehydrogenase and acetaldehyde dehydrogenase which is specifically

coupled to NAD which acts as a hydrogen acceptor to form $NADH_2$. Of importance in this reaction is that it also regulates the ratio of pyruvate to lactate. Thus with increased generation of $NADH_2$ (as with alcohol metabolism) there is decreased amounts of pyruvate available (since pyruvate is converted to lactate) for conversion to oxaloacetate which ultimately is used for hepatic gluconeogenesis. Also there is decreased availability of amino acids and glutamate as precursor of hepatic gluconeogenesis due to unfavorable ratios of $NADH_2/NAD$ which would normally allow conversion of these substrates to citric acid cycle intermediates, Figure 3. There are other factors which contribute to decreased hepatic gluconeogenesis in alcoholism but they are beyond the scope of these grand rounds. Though it is attractive to postulate that all of alcoholic hypoglycemia is due to changes in $NADH_2/NAD$ ratios, it is becoming clear that $NADH_2/NAD$ ratio does not account for all of the observed decrease in blood glucose concentration. All of these non $NADH_2/NAD$ dependent factors have not yet been identified but it has been shown that acetate can decrease hepatic gluconeogenesis directly without implicating changes in $NADH_2/NAD$ ratios.

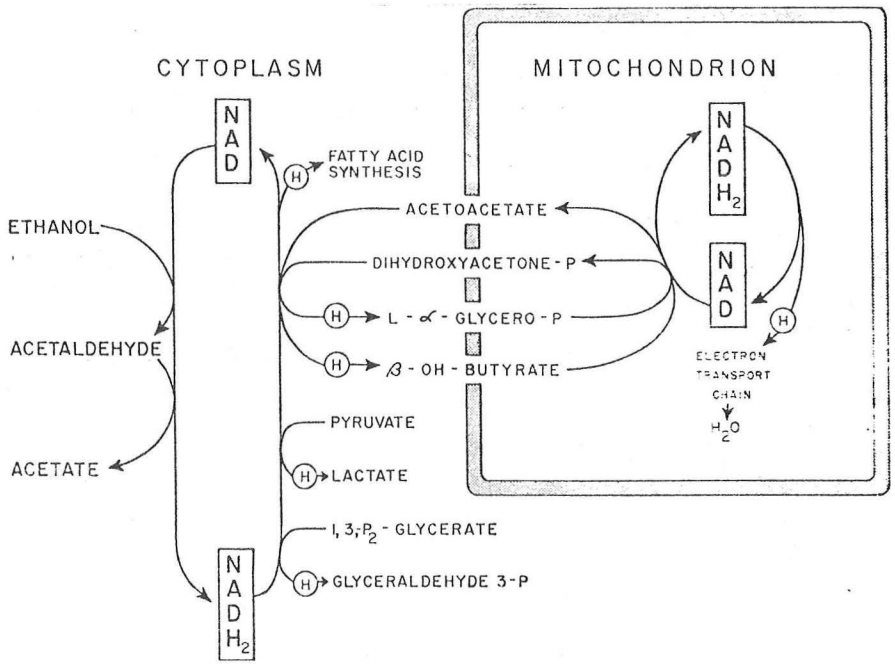

FIGURE 2 Reduction of NAD to $NADH_2$ during ethanol oxidation and the pathways for disposition of the ethanol-generated reducing equivalents. (From Madison, Adv. in Metab. Dis., 1968)

One of the potential non $NADH_2/NAD$ dependent processes which has been postulated to decrease blood glucose values during ethanol ingestion has been the suggestion that insulin secretion is augmented by alcohol. While earlier studies offered some support for this concept the later and more carefully conducted studies clearly demonstrate in a fasted state (typical of alcoholic admitted to the hospital) that ethanol reduces both glucose and immunoreactive insulin concentration, Figure 4. Thus, the present

evidence lends no support to the thesis that elevated insulin levels are of etiological significance in the development of alcohol induced hypoglycemia. Why this fall in insulin level occurs is not known but it may be an important counter-regulatory mechanism to protect against more severe hypoglycemia.

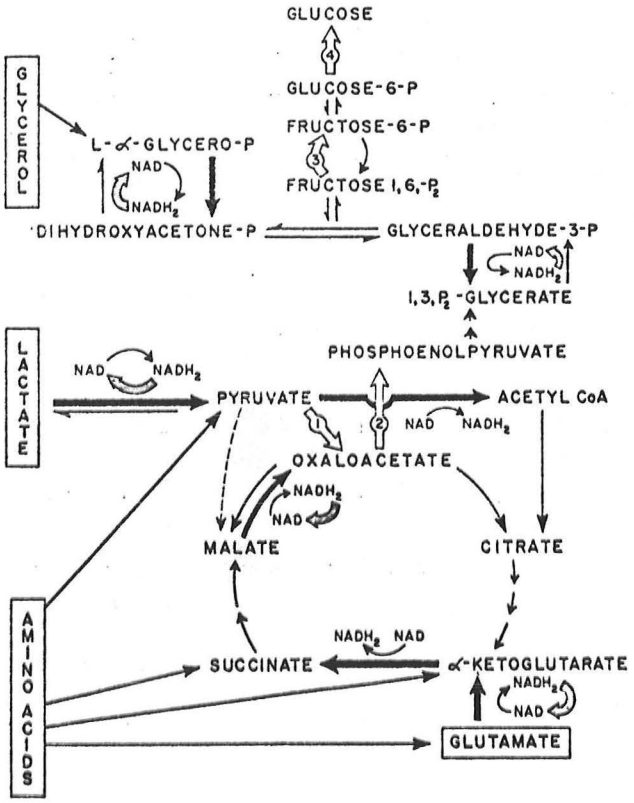

FIGURE 3. Pathways of hepatic gluconeogenesis during starvation. The specific enzymes upon which gluconeogenesis is dependent are numbered within the large arrow. The NAD-dependent points in the pathway of gluconeogenesis are shown by the bold solid arrows. The direction of reactions in the presence of an elevated $NADH_2$/NAD ratio is depicted by the stippled curved arrows. (From Madison, et al. Diabetes, 1967)

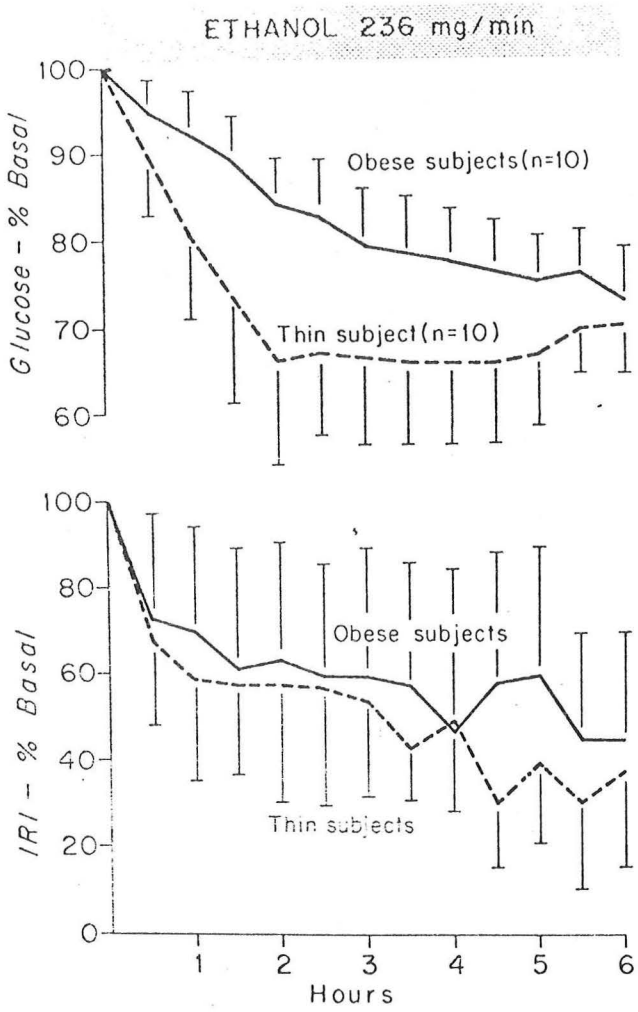

FIGURE 4. Mean (± 1 S.E.) changes in plasma glucose and serum immunoreactive insulin (IRI) levels expressed as percentages of preinfusion basal level during six-hour alcohol infusions in ten obese and ten thin subjects. (From Bagdade, et al. Diabetes, 1972)

Acid-base Balance. The acid base status of an alcoholic may be quite complex with varying contributing factors. Most meaningfully acid-base balance should be considered as the effect of alcohol in normal volunteers, the acid-base status of alcoholics and acid-base disturbances in the withdrawal period.

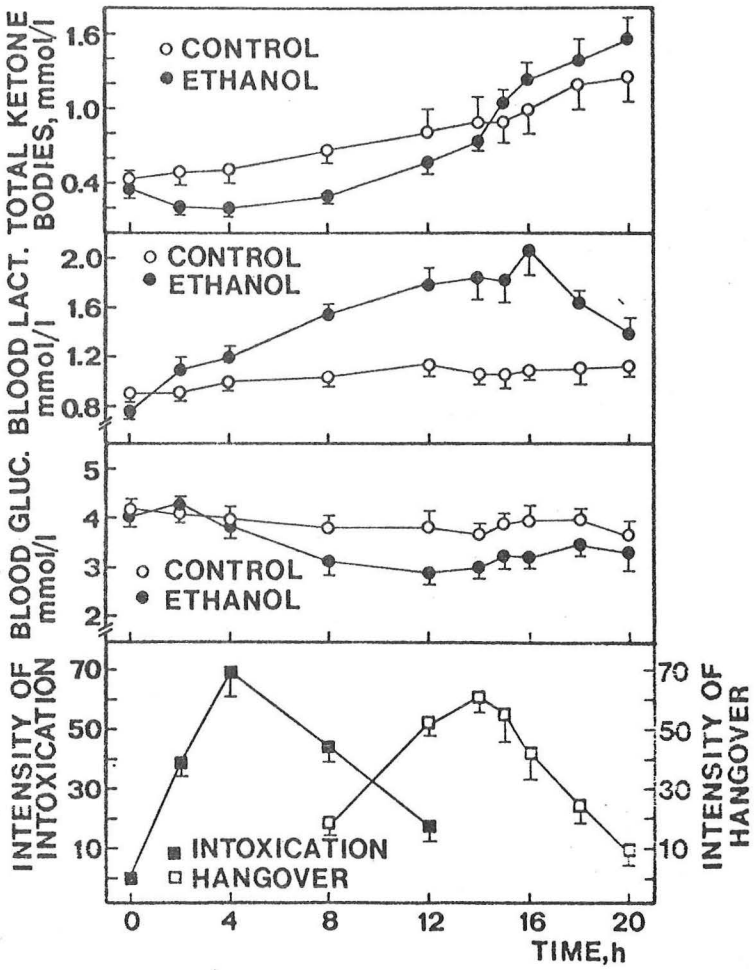

FIGURE 5. Intensities of alcohol intoxication and hangover, and changes in the concentrations of blood glucose, lactate and total ketone bodies during experimental drinking session. (From Ylikahri and Huttunen in Alcohol Intoxication and Withdrawal--IIIb, 1976)

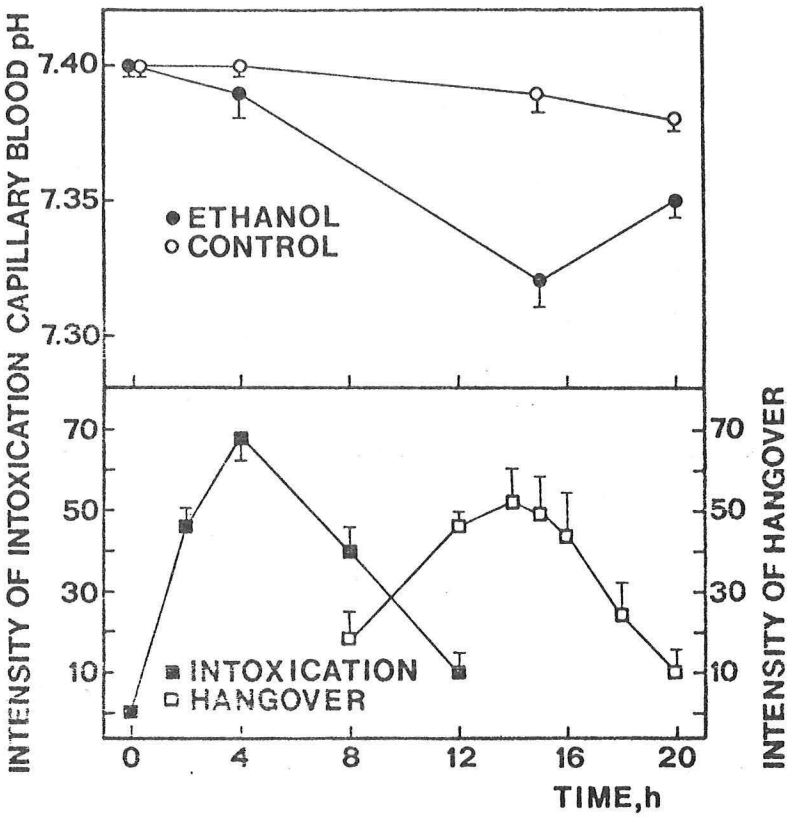

FIGURE 6. Intensities of alcohol intoxication and hangover and capillary blood pH during the experimental drinking session. (From Ylikahri and Huttunen in Alcohol Intoxiccation and Withdrawal--IIIb, 1976)

The effect of alcohol on normal subjects is to cause mixed metabolic and respiratory acidosis. Part of the metabolic acidosis has been shown to be enhanced hepatic ketogenesis (both due to the increased delivery of free fatty acids to the liver and increased de novo synthesis of ketone bodies) and part of the acidosis may be the result of enhanced formation of lactate and β-OH-butyrate, Figure 5 & 6. If normal volunteers are exercised after alcohol they have an exaggerated degree of lactic acidemia. Also a number of cases of severe lactic acidosis have been reported in patients with premature labor treated with ethanol. The respiratory component of acidosis is the results of alcohol being a depressant of the respiratory center's sensitivity to pCO_2. In chronic stable alcoholics the metabolic component of acidosis seems to be a consistent feature with increased concentrations of lactate and ketone bodies. Also, tissue hypoxia may contribute to lactic acidosis of an alcoholic. Occasionally this acidosis can be life threatening with pH <7.0. Of significant interest in pathogenesis of the withdrawal symptoms has been the observation that arterial pH may rapidly rise during imposed abstinence from alcohol. These patients have the underlying metabolic acidosis with overriding component of primary respiratory alkalosis. The exact mechanism by which the respiratory center becomes hyperresponsive to pCO_2 is not known, but evidence does suggest that the rapid changes in pCO_2 may be responsible to symptoms of withdrawal syndrome by either primary or secondary mechanisms (such as rapid decrease in ionized Ca and Mg).

Hyperuricemia. It has been well established that acute alcoholism may precipitate gout. Most acutely intoxicated subjects have significantly elevated serum uric acids on admission which drop to normal after several days of alcohol abstinance. The rise in serum uric acid is due predominently to a decreased urinary output of uric acid.

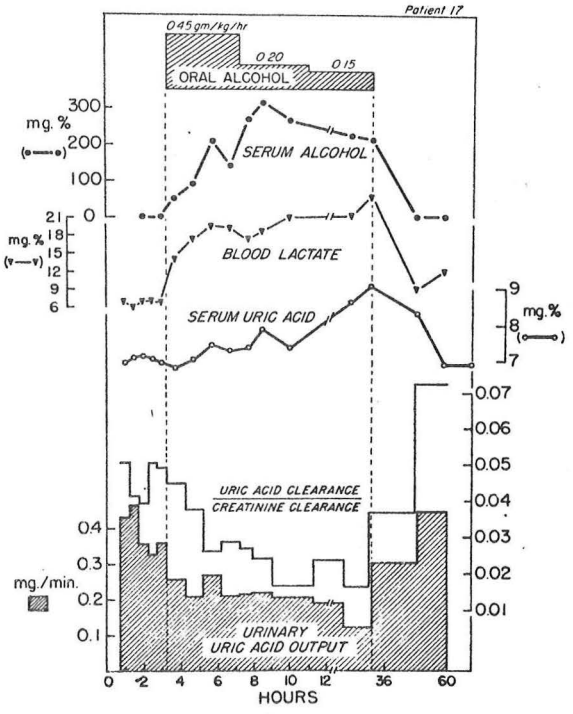

FIGURE 7 Blood and urine studies with oral ethanol. (From Lieber, et al. J. Clin. Invest., 1962)

The decrease in urinary uric acid in turn is most likely due to elevated plasma lactate values which compete for secretion of uric acid. Alcoholic hyperuricemia can be distinguished from primary hyperuricemia by its reversibility upon discontinuence of alcohol use, Figure 8.

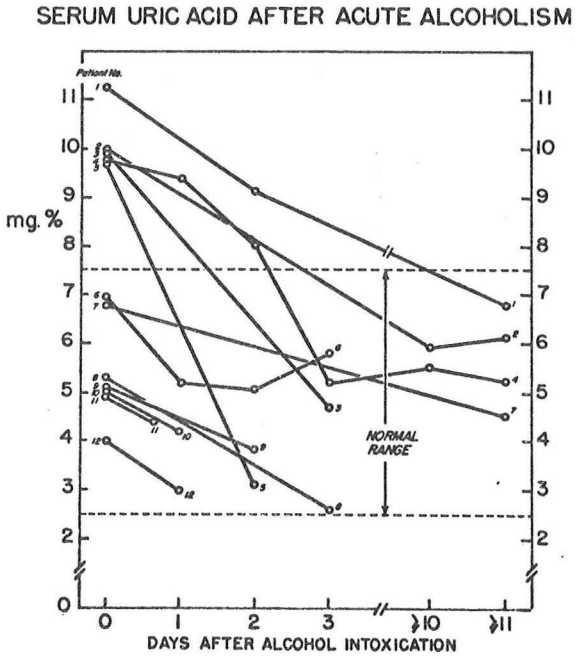

FIGURE 8 Serum uric acid concentrations in 12 subjects when acutely intoxicated and at various intervals thereafter, with the normal range (mean ± 2 SD). (From Lieber, et al. J. Clin. Invest., 1962)

Hypertriglyceridemia. It is well established that chronic and acute alcoholism induces hypertriglyceridemia. The mechanism of this induction is not well understood. In vitro and in vivo animal studies as well as those conducted in humans suggest that multiple factors contribute to hypertriglyceridemia. In vitro liver perfusion studies have shown that addition of ethanol to the perfusate increases the release of triglycerides and pre-β-lipoproteins. This release is significantly greater if the livers have been harvested from ethanol-pretreated rats. Though decreased peripheral utilization of triglycerides from plasma has also been suggested as a cause of hypertriglyceridemia, not all investigators have found supportive data. Unfortunately consensus does not exist with respect to the pathogenesis of hypertriglyceridemia of alcoholism. Part of this lack of consensus is due to the extreme technical complexity and animal variation inherent in these experiments and part may be due to the different factors which may be operative at different pathophysiological settings.

The incidence of hypertriglyceridemia after alcohol is quite common. Its magnitude is dependent on the duration of alcoholisms, previous history of fatty food intake and basal serum triglyceride level. It is interesting that normal individuals (without baseline hyperlipedemia) will routinely elevate their serum triglyceride levels in the evening after several "social" cocktails. Some 25% of these patients maintain abnormally elevated values through the morning hours. Patients with endogenous hypertriglyceridemia and history of heavy fatty food intake have exaggerated hyperlipemic responses. Though often the level of triglyceride elevation is moderate, there are occasions when very large increases have been noted. These rises in serum triglyceride levels may contribute to the development of pancreatitis, fatty liver and promote atherogenesis.

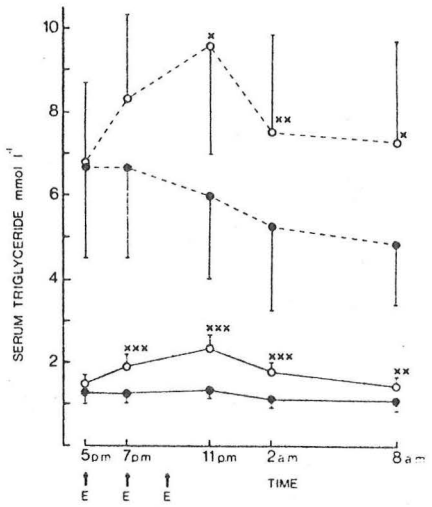

FIGURE 9 Mean serum triglyceride values during the night after either a sober evening (●) or intake of ethanol, 1.5 g/kg (○) at times shown by arrows. —= normolipidemic subjects, ---= hypertriglyceridemic patients. The bars indicate S.E.M. x = $p<0.05$, xx = $p<0.01$, xxx = $p<0.001$ for the difference ethanol/control. (From Taskinen and Nikkilä Acta Med. Scand., 1977.

Phosphate Depletion. Many of the hospitalized alcoholics are phosphate depleted. In a recent study from our VA Hospital (Anderson, et al. Mineral & Electrlyte Metabolism 4:106-112, 1980) determined the total muscle phosphorus levels to be low in 10 of 12 patients who were admitted with alcoholic myopathy. However, on admission the serum phosphate level may be in the normal range only to drop precipitously with therapy if phosphate is not repleted. Dr. Knochel's Grand Rounds of 1975 is the best published source for causes of phosphate deficiency in alcoholics. There it is pointed out that phosphate deficiency in alcoholics is multifactorial. First, many alcoholics have a dietary deficiency of phosphate. While malnutrition per se does not lead to a decrease in phosphate-to-

nitrogen ratio of cells (definition of phosphate depletion) it nevertheless does decrease the total phosphate content of the body and sets the stage for severe hypophosphatemia when phosphate sequestration is stimulated by refeeding. In addition, there is increased efflux of intracellular phosphate with chronic metabolic acidosis which is not uncommon in alcoholics. With correction of acidosis there is movement of both potassium and phosphate into cells. With decreased intake of phosphate and increased shift of intracellular to extracellular phosphate there also occurs an increased renal excretion of phosphate during alcoholism. Part of the increase in phosphate excretion may be the result of increased diuresis with increased fluid intake, increased phosphaturea due to increased parathyroid hormone levels (the result of hypomagnesemia and hypocalcemia), and due to chronic ketonurea. All of the above factors contribute to the development of total body phosphate deficiency.

However on admission the serum phosphorus may be quite normal. With IV glucose administration or with refeeding the plasma phosphate concentration will rapidly fall, Fig. 10. The rate of fall is a function of degree of existing phosphate deficiency and rapidity of glucose administration. The rapid intracellular shift of phosphate is in part the result of increased phosphate uptake with glucose and increased utilization of phosphate for synthesis of phosphate containing organic molecules. Though hyperglycemia causes increased urinary excretion of phosphate this increased excretion plays no significant part in hypophosphatemia seen in alcoholism following hospitalization.

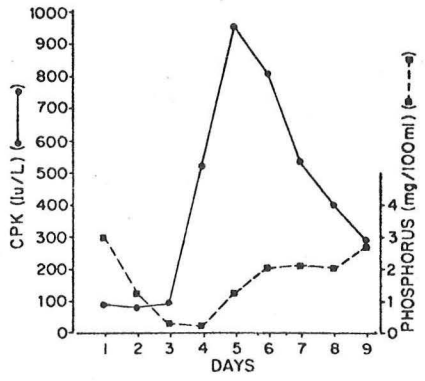

FIGURE 10 Comparison of serial values for serum creatine phosphokinase activity and serum inorganic phosphorus concentration in a chronic alcoholic. (From Knochel, et al. Ann. N.Y. Acad. Sci., 1975)

Magnesium Depletion. Alcoholism is the most common cause of hypomagnesemia in the United States. Though most alcoholics with good nutritional states are not magnesium deficient, magnesium deficiency may be quite severe in some patients, especially patients presenting with DT's, Fig. 11.

Magnesium deficiency is the result of various additive factors, and can be reproduced in a hospital setting, Fig. 12. Many alcoholics ingest a diet which is deficient in magnesium. In addition, urinary magnesium excretion is increased in alcoholics by unknown mechanisms. Blood alcohol may increase magnesium excretion directly, or alcohol associated aldosteronism, or lactic acidosis may secondarily increase magnesium excretion. In addition to increased excretion of magnesium, alcoholics may have decreased intestinal absorption of alcohol. Furthermore, chronic alcoholics may have magnesium deficiency as a result of tissue wasting. Muscle magnesium concentration is currently the most sensitive index of magnesium deficiency, though it is not without uncertainty also. In the recent study from our VA Hospital (Anderson, et al, Mineral & Electrolyte Metabolism 4:106-112, 1980) it was shown that 13 of 13 patients with alcoholic myopathy had decreased magnesium content in their skeletal muscles. Ideally, the combination of serum magnesium concentration, urinary excretion of magnesium, and muscle magnesium will give the most accurate estimation of total body magnesium stores. This subject is nicely reviewed in depth by Dr. Cronin in his Medical Grand Rounds of 1979.

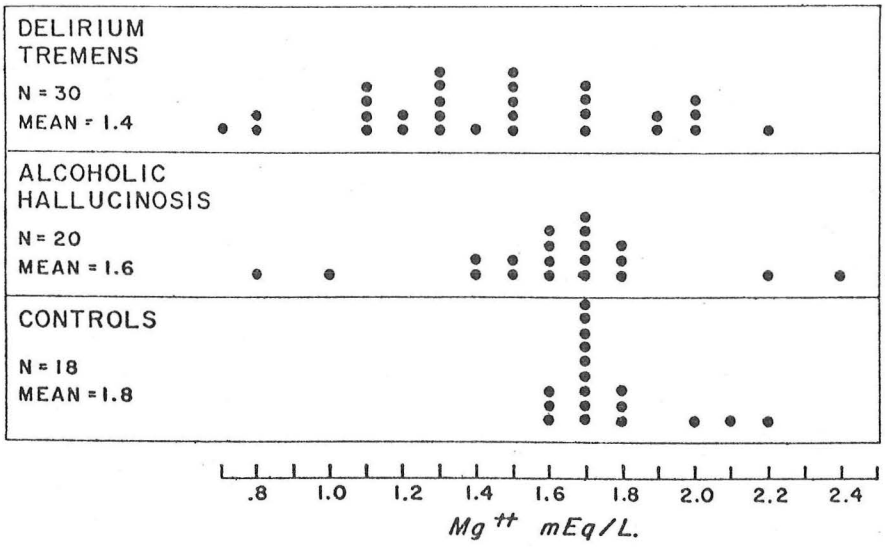

FIGURE 11 The distribution of serum magnesium levels observed in patients with delirium tremens, alcoholic hallucinosis, and in control subjects. (From Mendelson, et al. J. Nerv. Ment. Dis., 1959)

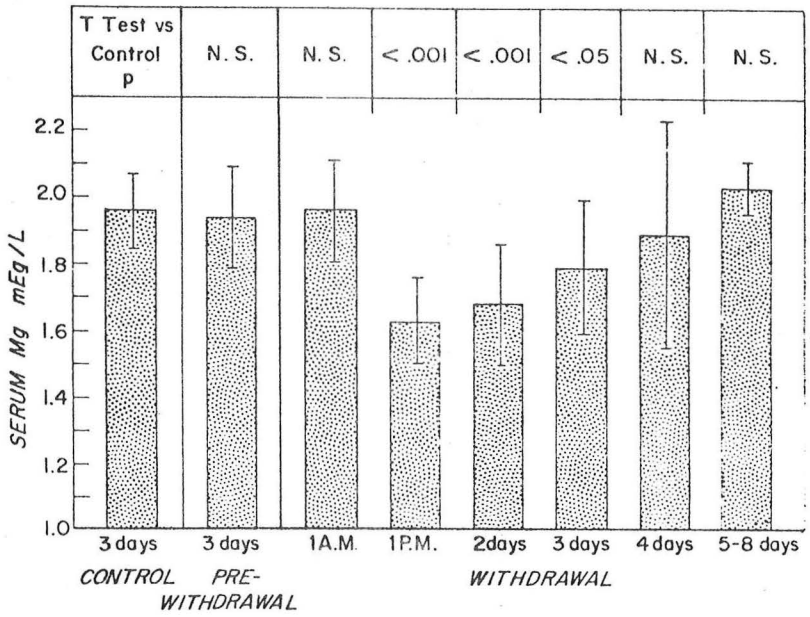

FIGURE 12 Mean serum magnesium levels (and standard deviations) of seven alcoholic subjects during control, prewithdrawal, and withdrawal days. These subjects ingested approximately 30 oz of beverage alcohol per day for 21 consecutive days under experimental ward conditions. (From Mendelson, et al. Ann. N.Y. Acad. Sci., 1975)

Hypocalcemia. Though acute ingestion of alcohol does not have a significant effect on serum calcium levels, hypocalcemia is not an infrequent finding in a "skid-row" alcoholic. Again numerous factors can contribute to the hypocalcemia but the two postulates which have received the most recent attention are decreased release of PTH or decreased peripheral response to PTH in association with magnesium deficiency. While some studies have found low circulating concentrations of parathyroid hormone in magnesium deficient patients, most studies have found elevated values of PTH. The studies which have found lower than normal concentration of PTH have noted a prompt rise in serum PTH and calcium concentrations after magnesium repletion. On the other hand, studies which have found high PTH values with hypocalcemia have noted that serum calcium rises after magnesium administration. These two series of studies are consistent with the view that both a deficiency in release of PTH and end organ (bone and gut) unresponsiveness to PTH may exist to explain the frequent association of hypocalcemia and hypomagnesemia of chronic alcoholism. Why one or the other of these two mechanisms predominates in a given alcoholic has not been settled.

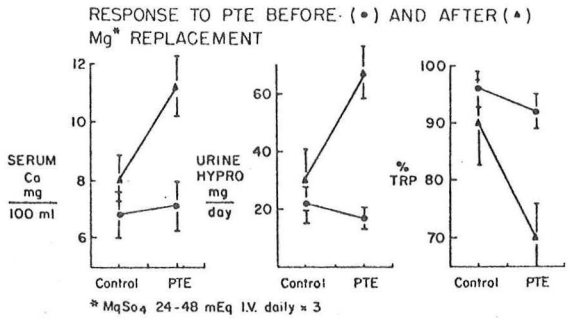

FIGURE 13 Mean and standard deviations of values are shown for the first (●) and second (▲) tests with PTE in the resistant group of patients. Serum magnesium averaged 0.8 mEq/L during the first test. One day after the last infusion of magnesium sulfate, when the second test was begun, mean serum magnesium was 2.4 mEq/L. (From Estep, et al. J. Clin. Endocr., 1969)

Potassium Depletion. Hypokalemia is a common occurrence in hospitalized alcoholic. In one study (Arch. Int. Med. 120:536, 1967) 9 of 50 consecutive patients admitted to the hospital for acute alcohol withdrawal symptoms had severe hypokalemia (1.5-2.5 mEq/L) while an additional 23 patients (46%) had moderately reduced serum potassium concentrations (2.6-3.4 mEq/L). There, however, was no correlation between the symptoms of DT's and the degree of hypokalemia. These potassium concentrations were on admission, and therefore, may underestimate the frequency of hypokalemia if acid-base balances were corrected first.

TABLE II

Pretreatment Serum Potassium Concentrations in 50 Patients Undergoing Alcohol Withdrawal (data put together from Vetter et al, Arch. Int. Med. 120, 1967)

Serum Potassium (mEq/L)	Number Of Patients	Percentage Of Patients
1.5 - 2.0	5	10%
2.1 - 2.5	4	8%
2.6 - 3.4	23	46%
3.5 - 4.4	18	36%
>4.5	0	0%

Perhaps the muscle concentration of potassium would be a more accurate estimate of total body potassium deficiency. In a recent study by Anderson and coworkers from our VA Hospital (Mineral and Electrolyte Metabolism 4:106-112, 1980) it was noted that 5 of their 13 patients who were admitted with alcoholic myopathy had definite decrease in potassium content of muscle when expressed in terms of non-collagen nitrogen. Thus it is clear that hypokalemia and total body potassium depletion is not uncommon in alcoholics. A number of different mechanisms are operative in the genesis of potassium depletion of chronic alcoholism. Inappropriately high excretion rate does not seem to cause potassium deficiency in alcoholism since ethyl alcohol per se does not cause kaliuresis. However, there may be increased excretion of potassium due to shift of intracellular-to-extracellular potassium in association to chronic acidosis of alcoholism. In addition, patients with alcoholism tend to have nutritional deficiency of potassium in addition to frequent bouts of vomiting and diarrhea.

Diuresis

It has been repeatedly demonstrated that acute ingestion of alcohol causes diuresis. Following administration of alcohol to normal volunteers there is a rapid increase in free water clearance, decrease in urine osmolality while the glomerular filtration rate remains unchanged, Fig. 14, 16. Since alcohol per se has no effect on the collecting duct water permeability these observations are consistent with alcohol inhibiting the release of ADH. Also supportive of this view are those studies in which no diuresis was noted after alcohol ingestion if serum ADH values were raised prior to alcohol by infusions of hypertonic sodium chloride solutions, Fig. 15. The most direct studies to demonstrate that alcohol inhibits ADH release are the studies of Helderman and co-workers where it was demonstrated by sensitive and specific radioimmunoassay that acute alcohol infusions decrease the plasma concentration of ADH, Fig. 17. However, diuresis does not persist during chronic ingestion of alcohol. Perhaps initially the antidiuresis of chronic alcohol ingestion is due to stimulation of ADH by the increase in serume osmolality which is the result of prior diuresis, however, in addition, other factors no doubt are operative later to explain an increase in total body water, increase in intracellular water and sodium, and a tendency towards hyponatremia which is more common in animals and humans with chronic alcoholism.

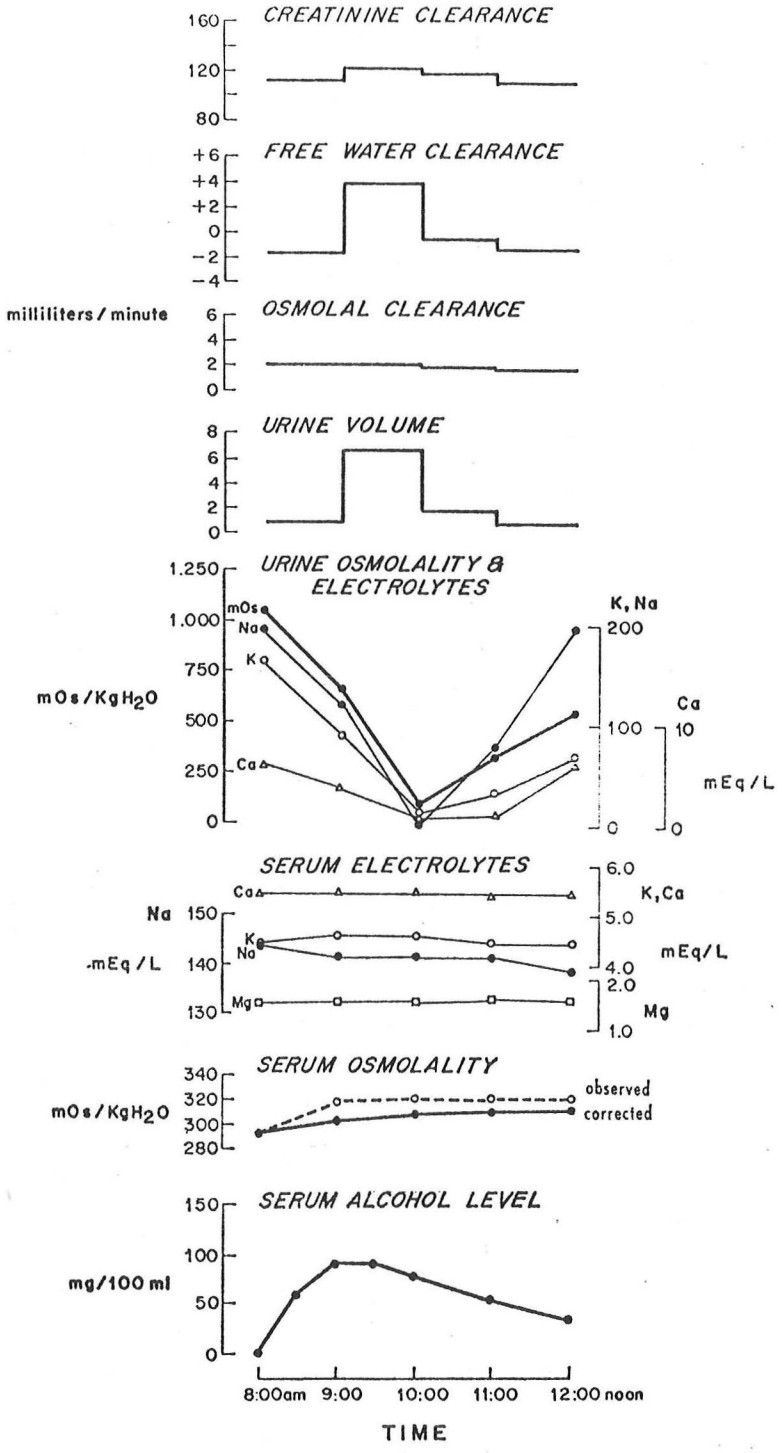

FIGURE 14 Nonalcoholic Subject 1 (acute test). Urine and serum indexes following acute administration of ethanol. (From Ogata, et al. Psychosomatic Medicine, 1968)

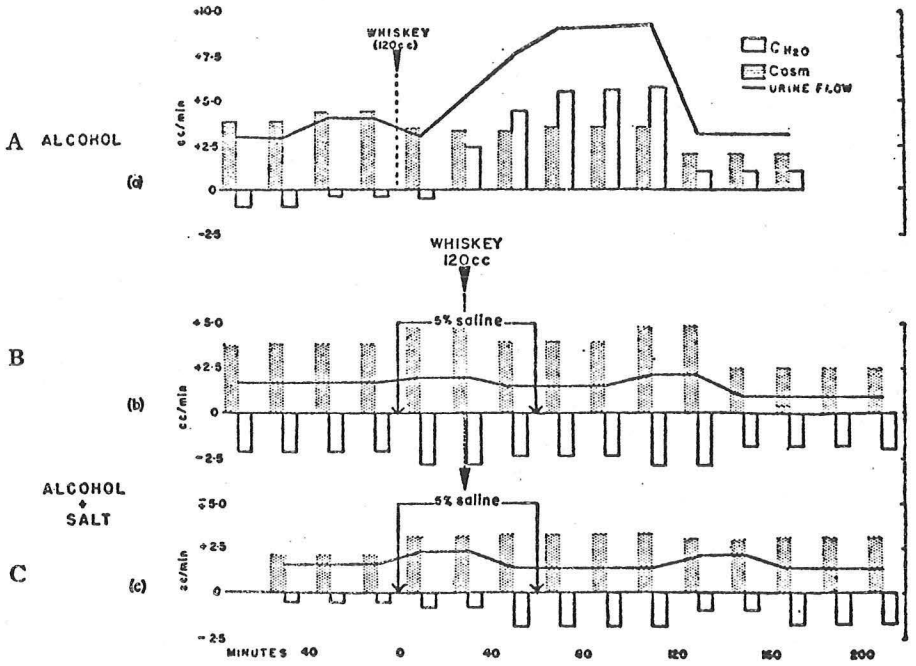

FIGURE 15 Prior administration of hypertonic saline (15B and 15C) blocked the characteristic diuresis following alcohol (15A). (From Kleeman, et al. J. Clin. Invest., 1955)

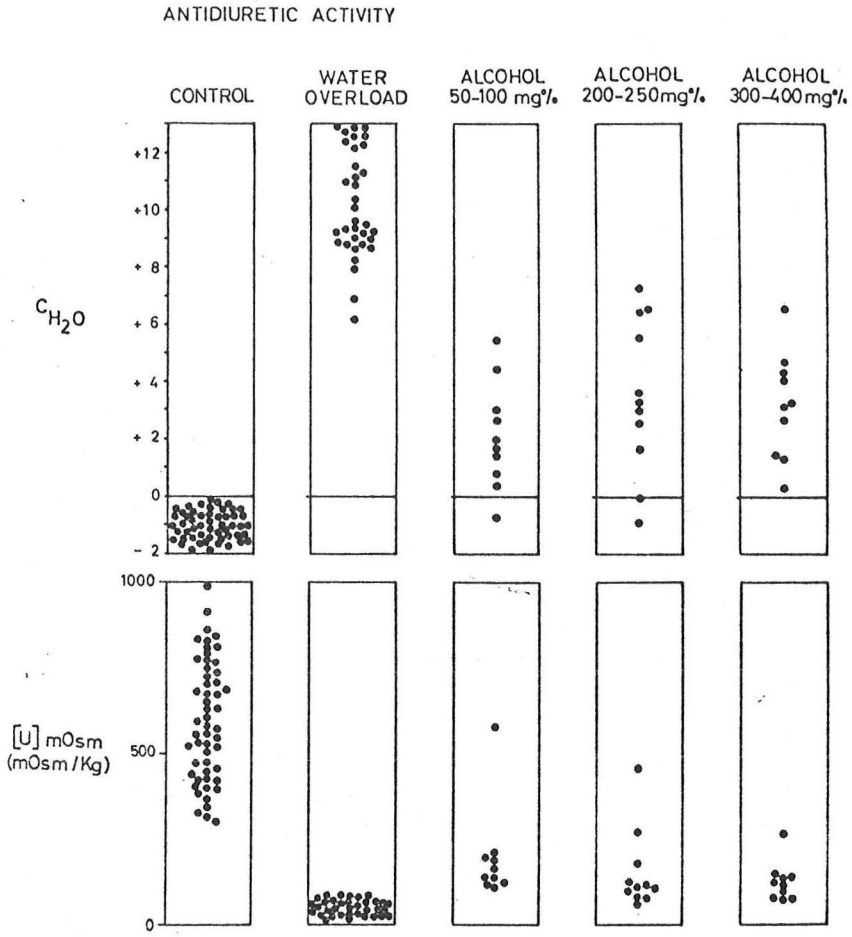

FIGURE 16 Absolute values of free water clearance and urinary osmolality, obtained in the five groups studied. Antidiuretic activity was clearly depressed with water overload and in a minor degree with different doses of ethanol. (From Cobo and Quintero J. Obstet. Gynocol., 1969)

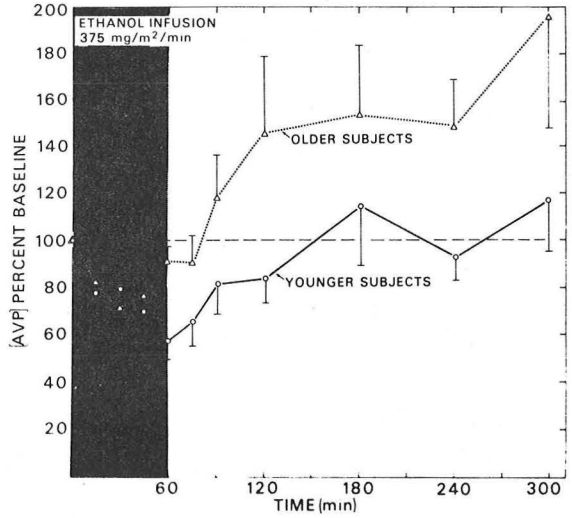

FIGURE 17 Plasma arginine vasopressin response to a 1-hour intravenous ethanol infusion in young and old subjects. (From Helderman, et al. J. Geront, 1978)

WITHDRAWAL

Withdrawal symptoms occur commonly after abstinence from alcohol. These symptoms may vary from the common hangover to delirium tremens depending on prior history of nutritional and alcohol intake.

Hangover. Numerous studies have tried to implicate metabolic and endocrine factors in the pathogenesis of hangover. The most consistent findings have been noted in the acid-base status of patients with a hangover. As noted earlier, alcohol causes both metabolic and respiratory acidosis (Fig. 5 and 6). In fact, it has been commonly presumed that more severe the hangover, the more severe the metabolic acidosis. Thus the concept has arisen that elevated levels of acetaldehyde, lactate and ketone bodies contribute to the hangover syndrome. However, recent well controlled studies in normal volunteers have failed to substantiate this view. In these studies normal volunteers were asked to drink 1.5 g/kg body wt of ethanol and then they were followed for twenty hours with sampling of blood and evaluation of hangover symptoms at two hour intervals. While the acetaldehyde concentrations were somewhat elevated, there was no correlation with the intensity of hangover when each patient was analyzed as his own control, Fig. 18. Also the concentrations of lactate and ketone bodies were elevated but these too did not correlate with the degree of hangover. Furthermore the degree of secondary respiratory alkalosis did not correlate with hangover intensity. Thus these studies do not support the view that hangover is the result of acid-base disturbances. Also it is not uncommon to see lower than normal blood sugars during hangover period. However, it is to be recognized that non-alcoholic induced hypoglycemia is not associated with hangover symptoms and the administration of fructose has been shown to prevent the ehtanol-induced decrease in blood sugar, but unfortunately, no consistent improvement has been noted in hangover symptoms. While thirst is a definite symptom of a hangover from acute alcoholism (presumably the result of acute diuresis) there has been no consistent correlation between electrolyte changes and hangover intensity. Perhaps secondary (result of hyperventilation) decrease of ionized magnesium and calcium will contribute to a hangover, but controlled studies have failed to show appropriate correlations. It can be argued, however, that unmeasurably small changes in all of these metabolic findings can contribute, but no single metabolic factor is of primary importance. Perhaps some toxic factor in alcohol is of importance in pathogenesis of a hangover. The most likely group of compounds are the congeners of alcohol. It is well appreciated that alcohols rich in congeners (such as congnac and wines) in general give more severe hangovers. Unfortunately, very little is known about the metabolic fate of congeners in humans but acetaldehyde and methanol concentrations are higher in individuals who drink bourbon as contrasted to grain alcohol. While the toxicity of higher alcohols is well established, I was unable to find studies correlating these concentrations to severity of hangover state. Of the potential endocrine factors which have been examined in hangover states, there have been no changes noted in growth hormone, thyroid stimulating hormone or luteinizing hormone.

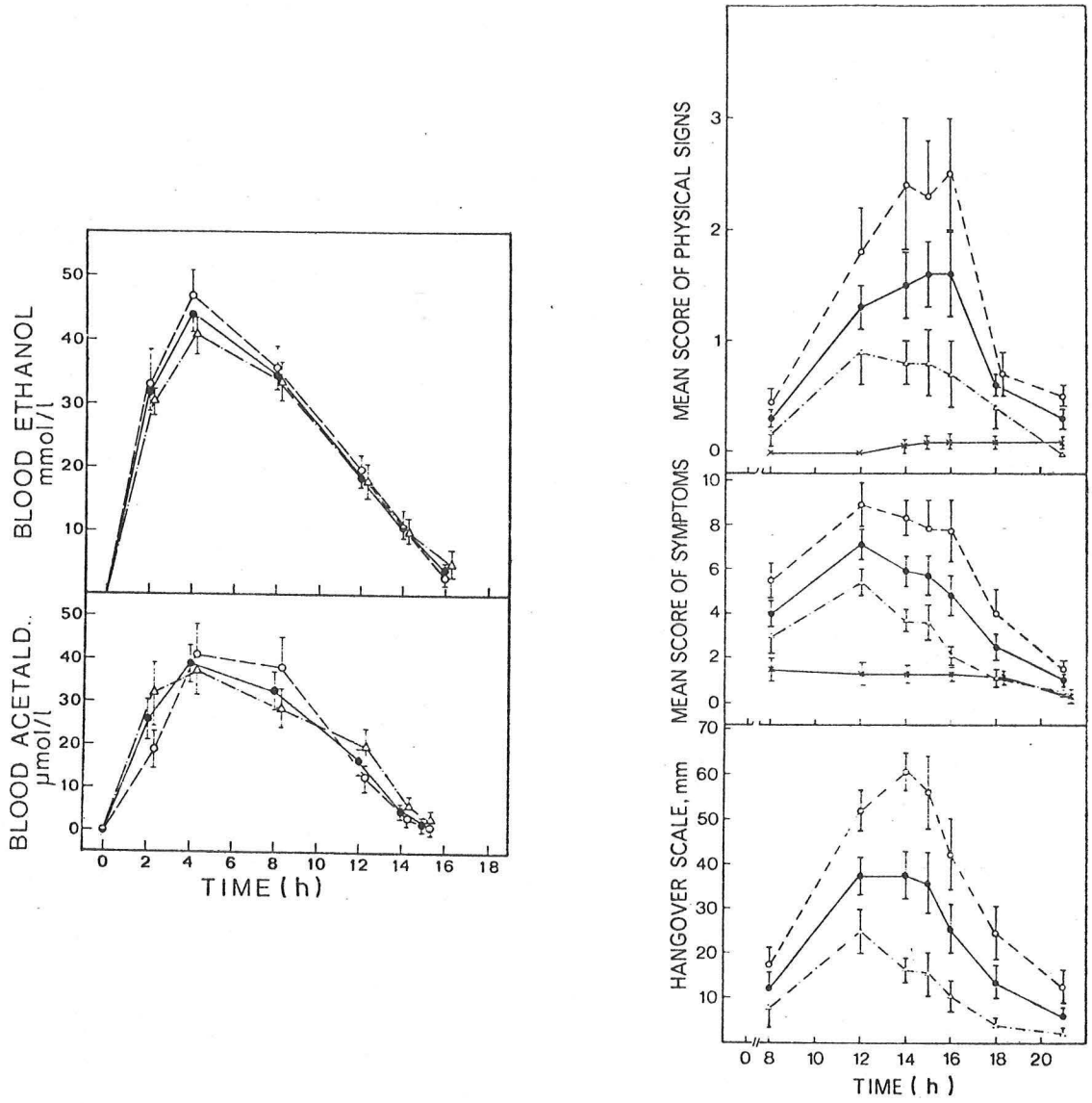

FIGURE 18 Blood ethanol and acetaldehyde concentrations during alcohol intoxication and hangover. All subjects fasted 10 hours after which they drank 1.5 g/kg body wt of ethanol during 3 hours (0 to 3 hours) as 20% water solution. There were 23 volunteers. Symbols: All subjects with ethanol: ●——●. Group I (severe hangover): o-----o, Group II (mild hangover):Δ—■—Δ (From Ylikahri, et al. J. European Clin. Invest., 1974)

However, it is interesting that during severe hangovers there is a decrease in serum testosterone values, Fig. 19, and diminished response of prolactin to thyroid releasing hormone. Whether these hormones have a direct role in

hangover is not known or whether they are indices of some neuroendocrine etiology to hangover remains to be established. Serum ADH and cortisol values are up during hangover but these may well be a secondary response to dehydration and stress of a hangover, and it is doubtful they have any role in pathogenesis of a hangover intensity.

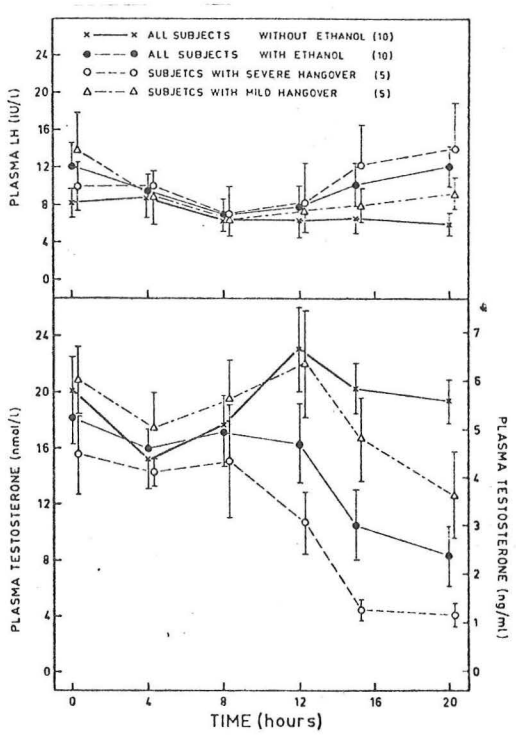

FIGURE 19 Plasma concentrations of testosterone and luteinizing hormone (LH) during alcohol intoxication and hangover. (From Ylikahri and Huttunen J. Steroid Biochem., 1974)

Tremulousness, hallucinations and rum fits. These symptoms are probably a spectrum of alcohol withdrawal syndrome with common etiological factors, but presenting in progressively severe manner. In each of these cases abrupt withdrawal of alcohol (either directly or via its secondary effects) has been shown to be responsible for development of the symptoms. Tremulousness is much more common than is hallucinosis which in turn is more common than rum fits. Each of these can occur any time after cessation of drinking up to a week but most commonly occur 24-48 hours after the last drink, Fig. 20. During tremulous state patients are alert, however, can have generalized tremor so severe as to prevent them from walking. Commonly they are irritable and have insomnia. Also common is diaphoreses and tachycardia. In addition to the factors discussed under hangover, increased catecholamines undoubtedly contribute to this state, Fig. 21. Hallucinosis is the next most severe withdrawal symptom. Initially hallucinations may be either visual or auditory. It is interesting that these epidoses of hallucinosis are intermittently associated with periods

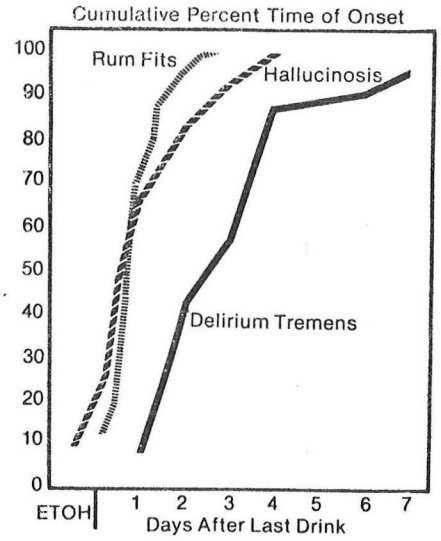

FIGURE 20 Estimated time of onset of hallucinosis rum fits, and delirium tremens following last drink as expressed as cumulative percentages. (From Thompson Arch. Int. Med., 1978)

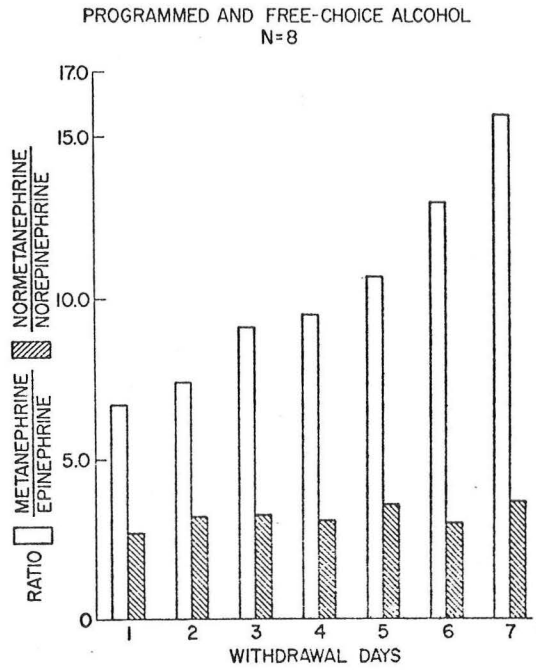

FIGURE 21 Ratios of metanephrine-epinephrine and normetanephrine-norepinephrine after alcohol withdrawal. During withdrawal there also was a marked increase in absolute excretion rates of epinephrine and norepinephrine though the relative increase in epinephrine excretion was greater than norepinephrine. (From Ogata, et al. Psychosomatic Med., 1971)

of perfect alertness if patients do not have true delirium tremens. The hallucinations occur most frequently at night and are often interpreted as nightmares. Auditory hallucinations are less likely to progress to true DT's as compared to visual hallucinations. "Rum fits" is a term which refers to grand mal seizures which occur after abstinence from alcohol. The seizure may be a single event or may occur on more multiple occasions. Often they are associated with postictal confused states which makes the differential from true delirium tremens difficult. The EEG while being abnormal during rum fits returns to normal within few days.

Delirium Tremens

Definition: Delirium tremens is a clinical syndrome occurring within 14 days after cessation of previously heavy intake of alcohol. It is a medical emergency with high mortality and morbidity. Its hallmark symptoms include disorientation and hallucinations. These major withdrawal symptoms most commonly occur two to three days after cessation of drinking being preceded by the minor symptoms (insomnia, irritability and tremor). The duration of the acute psychosis is often less than 72 hours but may be longer, Table III. Other clinical findings common in DT's include tachycardia, diaphoreses, hypertension (but terminally may die of vascular collapse and hypotension), fever, hyperactivity, and insomnia. I feel there is no advantage to classifying DT's into various stages as has been suggested in 1972 by the Criteria Committee, National Council of Alcoholism. There is too much overlap between these putative stages and no clearcut advantage can be seen therapeutically.

TABLE III
Duration of Delirium Tremens

Duration Days	≤1	>1 - 2	>2 - 3	>3 - 4	>4 - 5	>5 - 6	>6 - 7	>7 - 13	Total
n.	155	155	104	57	30	11	19	26	557[1]
p.c.	28	28	19	10	5	2	3	5	100

[1]Ten cases not included, in 9 of them the patients died during ongoing delirious state
(From I. Salum in Delirium Tremens and Certain Other Acute Sequels of Alcohol Abuse. Acta Psychiatrica Scandinavica, 1972)

Pathogenesis. The pathogenesis of DT's remains an enigma. Clearly it is related to withdrawal and not to underlying nutritional, neurologic or psychiatric abnormalities. The studies of Isbell et al (Quart. J. Study Alcohol 16:1, 1955) on former morphine addicts but otherwise healthy young individuals reproduced the symptoms of DT's after abrupt cessation of alcohol at a level of intoxication for a period of 6 to 13 weeks. These "volunteers" received normal nutrition with multiple vitamin supplements. They were carefully monitored throughout the study and received appropriate medical management during the withdrawal period. Six of the ten patients

had severe withdrawal symptoms with three having delirium tremens. Fortunately there was no evidence of residual neurologic impairment in any patient after three months of alcohol abstinence (characteristic finding of DT's). The general clinical impression is that the DT's will be more severe if the duration and quantity of alcohol consumption is greater. However, attempts to establish critical alcohol levels when DT's occur have been met with failure. DT's clearly can occur at any blood alcohol level but do occur at a time when alcohol concentration is rapidly dropping. The mechanism by which alcohol withdrawal produces DT's is not known. The component of respiratory alkalosis is more severe than in usual withdrawal syndromes. Whether this contributes to the DT's is not known but rapid decrease in pCO_2 can acutely affect concentrations of ionized calcium and magnesium.

While the above observations appear convincing that DT's are due to alcohol withdrawal, it is interesting to note that psychosis resembling alcoholic delirium tremens has been well documented with abrupt withdrawal of barbituates and other sedatives. Whether these observations reflect cross tolerance of alcohol with sedative receptors is conjectural or whether DT's can be caused by more than one mechanism is not known.

Time Course. Though it is commonly believed that DT's occur only after blood alcohol levels have decreased to undetectable levels this is not true. DT's can occur at any alcohol level but at a time when it has started to drop from its previous high level. Obviously it is very difficult to obtain an accurate history from an alcoholic but it appears that the most common time for DT's is 48 to 72 hours after the last drink. There, however, exists a bell shaped curve for incidence of DT's starting shortly after cessation of drinking lasting up until one week after the last drink. Most DT's are self limiting and are over within 72 hours. Rarely DT's may occur as repeating episodes lasting for weeks.

Patient Work-up. All patients with true DT's must be hospitalized. Even with optimal care some 15% of patients still die. If history is obtainable from a friend, meticulous care should be directed towards the possibility of toxin ingestion or history of trauma. In the physical examination careful attention should be given to localizing neurological findings since traumatic intracranial events may simulate DT's in a setting of alcoholism. Besides the routine laboratory values, blood should be obtained for evaluation of acid-base status and toxicology. Particular attention should be given to serum Na, K, Ca, Mg, glucose and phosphate values. Liver function studies should also be obtained. Urine should be examined for toxins and urine electrolytes obtained for index of volume contraction. Since CNS infections can simulate or trigger DT's all patients with DT's must have lumbar punctures. Any cells above normal is inconsistent with pure DT's. Similarly DT's require skull series and chest x-rays. In addition, patients with DT's must have EKG's due to the frequent occurrence of arrhythmias in these patients. Also patients with DT's especially ones with fever, require blood cultures. It is well established that alcoholics are more prone to infections than non-alcoholics.

Cause Of Death. Significant percentage of patients with DT's still die regardless of apparent adequacy of therapy, Fig. 22. The primary cause of death appears to be cardiovascular collapse with hyperactivity and volume depletion. Hyperpyrexia itself may cause death for some reasons as in "heat stroke". Other common causes of death in DT's include infections (particularly of CNS), fat emboli, and arrhythmias (probably related to hypokalemia). Often the cause of death cannot be determined either before or after post mortem considerations. Respiratory arrest occurs for unknown reasons only too frequently.

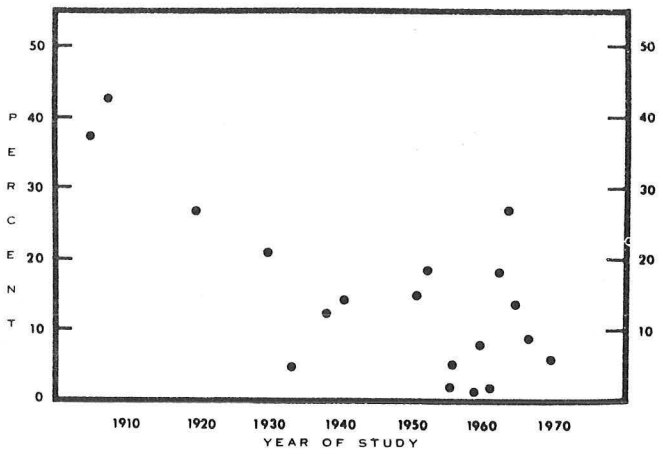

FIGURE 22 Mortality rate in patients with delirium tremens. (From Thompson Ann. Int. Med., 1975)

Treatment. True DT's is a medical emergency requiring prompt and correct therapy. Assuming intracranial (and systemic) infections and hematomas have been ruled out, the single most important initial approach is to calm the patient down. Patient should be placed in a well lit room without roommates who could agitate him further. If possible, an attendant should be in the room to give assurance to the patient and observe for sudden complications which otherwise might lead to death. IV should be started as soon as feasible for administration of sedatives and repletion of fluids. Sedatives should be given promptly at a dose to cause lethargy, but not over sedation. A physician should be present during the initial induction of a calm state. Though numerous sedatives have been tried, paraldehyde and diazepam (Valium®) have received most thorough and convincing evaluation. Both are excellent drugs when appropriately administered. Each has a problem in that it is difficult to guess the initial dose for adequate sedation. Diazepam, with a rapid onset of action and peak effects in less than 15 minutes, should be given IV at 5 minute intervals at doses of 5 mg until sedation and slight decrease in pulse rate and blood pressure is noted. Tremendous variability exists from patient to patient with

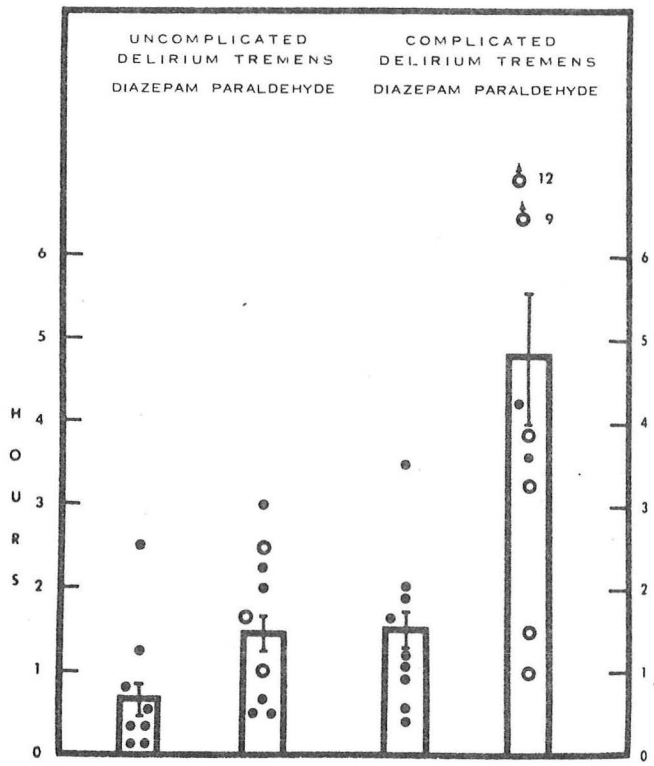

FIGURE 23 Hours between onset of therapy and achieving a calm but awake patient. Seventeen patients with delirium tremens alone are shown on the left; the points on the right represent seventeen patients with delirium tremens and pneumonia, pancreatitis, or hepatitis. Intervals in nine patients with adverse reactions are shown as open circles. Brackets show means ± SE. (From Thompson Ann. Int. Med., 1975)

higher doses being needed for those patients with associated illnesses (pneumonia, meningitis, hepatitis, pancreatitis), Fig. 23. The mean dose of diazepam was 46 mg IV in one recent study (Ann. Int. Med. 82:175, 1975) to achieve the initial calm state with some patients requiring over 500 mg. Oral absorption of paraldehyde is slower than IV diazepam with peak concentrations at 30 minutes while rectal absorption of paraldehyde is even slower with peak blood concentrations at 2.5 hours. Mean rectal paraldehyde (10 cc q 30 min) was 36 ml to obtain initial calm state in DT's. While patients with IV diazepam achieved a calmer state earlier than did rectall administered paraldehyde patients, this difference does not exist if paraldehyde is given IV. Paraldehyde (40 gms/L in D_5W) can be given IV with sedative effects appearing within minutes. When appropriate sedation is achieved, IV paraldehyde appears as a safe, short acting sedative with minimal interindividual variation (Clin. Res. 25:267A, 1977). The theoretical advantage of IV paraldehyde over IV diazepam is that the former has a shorter T 1/2 (about 5 hours) than does diazepam and its metabolites. Extreme care must be used to be sure that paraldehyde has completely dissolved before giving it IV. This may take several minutes of vigorous

shaking. If paraldehyde is not well dissolved it can cause pulmonary death by multiple small emboli. It also should be pointed out that no studies exist in refereed journals for the use of IV paraldehyde in DT's and if this approach is taken the physician should be well versed with all of the potential problems. During induction of a calm state patient should be restrained in such manner to prevent harm to the patient, attendant and to prevent aspiration pneumonia (retain in lateral decubitus or prone position). After induction of calm state patient should be placed on maintenance sedatives. In case of diazepam this usually is 5 to 10 mg IV every 1 to 4 hours and in case of paraldehyde it is 5 to 10 cc every 2 to 4 hours. Maintenance sedatives are needed usually for 3 to 5 days in mild DT's and up to two weeks in more severe DT's. After 48 hours of relative symptom-free state the drugs can be tapered slowly over several days to a week's period of time.

Initially many patients with DT's died of dehydration and cardiovascular collapse. However, with appreciation of the importance of volume repletion this mode of death is becoming more rare. In earlier days it was not at all unusual for patients to require over 10 liters of fluid a day but with calming of patient and decrease in diaphores the fluid losses are less and consequently total fluid replacements have become less. However, I personally prefer to keep the patient somewhat on the overhydrated state (providing he does not have CNS infection or trauma) to prevent the possibility of renal failure with myoglobinurea. Most patients, if adequately calmed, will do well with 4 to 6 liters of normal saline during the initial day. If hypotension should occur in spite of "adequate" hydration care should be directed to rule out a septic process. There are no controlled studies to indicate which drug should be given for hypotension and impending vascular collapse. Dopamine (Intropin®) would be my first choice in such an eventuality due to its inotropic and peripheral vasodilatory effects.

The three main potential electrolyte deficiencies (K, Mg and P) also need correction. Since a high percentage of patients with DT's have hypokalemia (which may get worse with IV administration of D_5W) should have K repletion with essentially the same guidelines as with the diabetic patient. Similarly phosphate should be given either IV as sodium or potassium salts or can be given orally. Magnesium should be given as magnesium sulfate, 2 gms at 6 hour intervals IV during the first 24 hours. Magnesium sulfate can be mixed in an IV bottle providing it does not contain bicarbonate. Also thiamine (100 mg) and multivitamins should be given IV on daily basis. Occasionally patients with DT's will present with extreme hypoglycemia and this should be treated with concentrated solutions of glucose.

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