GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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THE EFFECT OF ALCOHOL ON THE NERVOUS SYSTEM

Outline

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Alcoholism

1. Definition: Compulsive (uncontrolled), excessive, frequent alcohol consumption resulting in interference with smooth social, economic and psychological function and in deterioration of physical health (1).

2. Prevalence and Significance (2,3,):

a) About 80 million Americans drink. They consume about 300 million gallons/year - an increase of 45% over 10 years with population rise of only 18%. The cost of this, in most instances, moderate consumption is about $10 billion/year.

b) Six and one-half million of these are alcoholics, by above definition - up 1.5 million since 1958. Of these only 3-5% are "skid row" derelicts.

c) Business and industry lose about $2 billion and employees $430 million per year as a result of alcoholism.

d) About one-third of all violent deaths in U.S. occur in intoxicated individuals (3) and such individuals are involved in auto accidents 33 times more often than sober people.

e) Parkland Admissions

	Medical Admissions	Acute Intoxication	DT's
1964	3091	15	36 *
1965	3311	26	65 †

* One death

† Seven deaths

TABLE I

CLASSIFICATION OF NEUROLOGIC SYNDROMES

	Syndrome	Etiology	% Incidence for Inpatients*	
	Acute inebriation	Alcohol excess	21†	
1. a)	Intoxication (excitement)			
b)	Stupor or coma			
2. a)	Acute alcoholic tremulousness	Alcohol withdrawal	34.6	65.
b)	Tremor and transient hallucinations		11.3	
c)	Acute auditory hallucinosis		2.3	
d)	"Rum fits"		12.0	
e)	Delirium Tremens		5.3	
3. a)	Wernicke's Neuropathy	Nutritional (thiamine mainly)		3.
b)	Korsakoff's			
c)	Peripheral Neuropathy			
4. a)	Cerebellar degeneration	Probably nutritional		Rar
b)	Amblyopia			
c)	Marchiafava-Bignami (degeneration of corpus collosum)			
d)	Central Pontine Myelinolysis			

* Based on 266 consecutive patients admitted with obvious alcoholic complications to Boston City Hospital over 60 days (4).

† It is estimated that for each acutely inebriated individual at least 10 are turned away as not requiring admission.

Acute Alcohol Intoxication

I. Metabolism of Alcohol (C_2H_5OH)

a) Absorption:

Alcohol is a small (M.W. 46), neutral, water-soluble molecule which requires no digestion and is absorbed by passive diffusion (5) via stomach and small intestine (6).

Rate of absorption: From stomach initially rapid, then slow. From small intestine faster probably due to greater surface area. Absorption complete in 2-6 hours. Peak blood levels usually within 2 hours and often within 1 hour, if taken on empty stomach. Ingestion of food, especially milk, delays gastric emptying and decreases both rate of absorption and height of blood alcohol (7). Beer acts like food - alcohol from it gives lower blood levels - partly because alcohol is more dilute (6,7). In practical terms this means that 44 g of alcohol taken as whisky (4 oz) or Martini cocktail (5.5 oz) on an empty stomach gives maximum alcohol values of 90 mg% and after a mixed meal one-half that much. Ingestion of same amount of alcohol as beer (1.25 qt) on an empty stomach gives a maximum concentration of about 45 mg% and after a mixed meal one-half that much. Signs of intoxication generally begin at about 50 mg% though there is much variation noted.

b) Distribution:

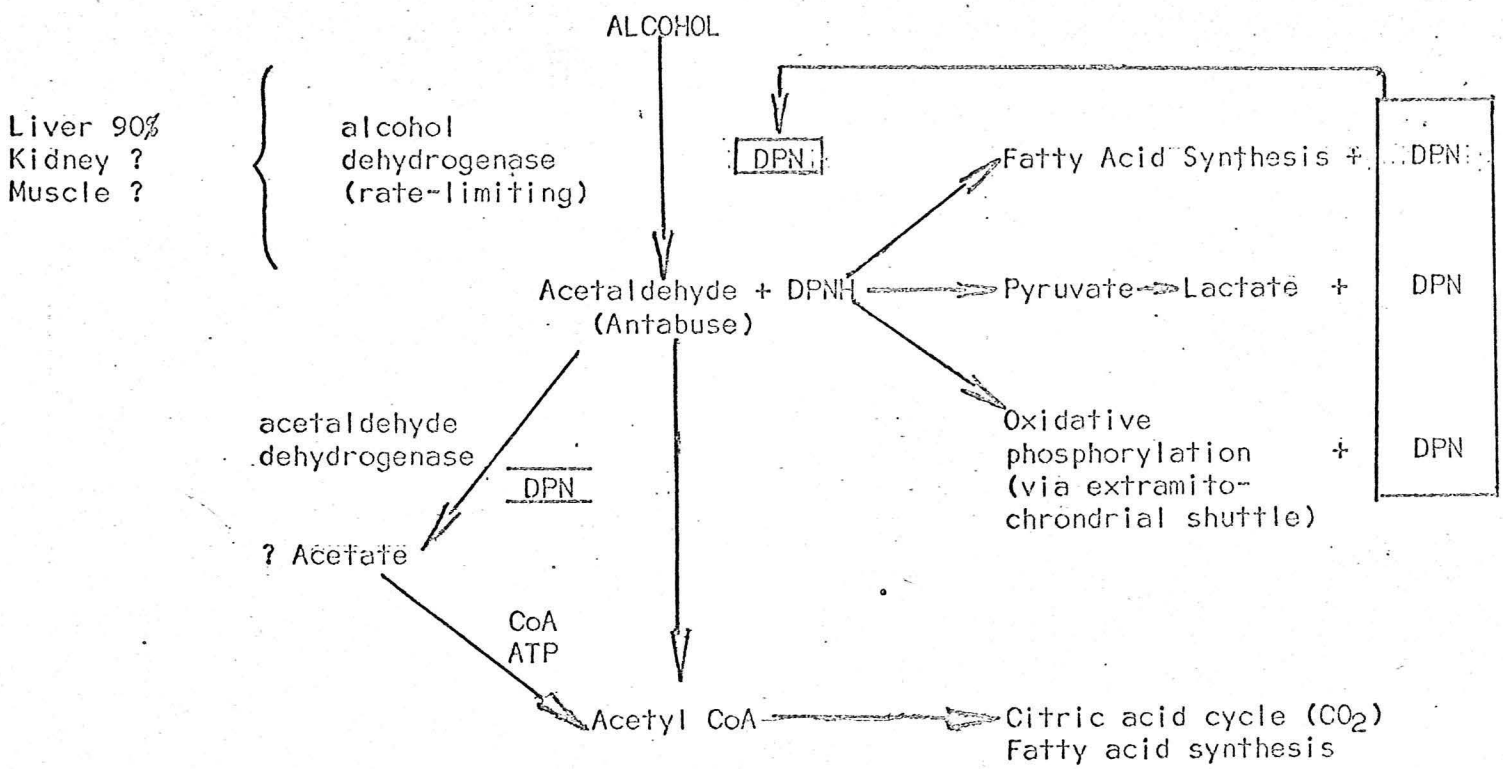
Alcohol is distributed throughout body in proportion to water content of various tissues. CNS alcohol level quickly approaches that of blood and thereafter parallels it closely.

c) Metabolism:

Ninety to ninety-eight percent of absorbed alcohol is oxidized - most to CO_2. Two to ten per cent is eliminated via kidney and lung. Alcohol levels in blood and urine are similar at equilibrium while alveolar air contains about 0.05% as much alcohol as blood (i.e., 2. liters of air = 1 ml blood) (6). Very small amounts excreted in bile, sweat, tears, saliva and gastric juice.

FIGURE 1

METABOLISM OF ALCOHOL IN THE LIVER (90% + of total) (6,8,9)



Rate of Alcohol Oxidation:

In man - at blood levels below 10 mg% exponential disappearance since rate-limiting alcohol dehydrogenase is not saturated. Above this level - linear decay. Maximum metabolism in normal man about 200 mg alcohol/kg body weight/hour. This equals 840 ml of alcohol per day or one-fifth of 100 proof whisky/day70 kg man. A more conservative estimate is 720 ml/day or 1 ounce of whisky/hour (6,10). There is some evidence (not conclusive) that liver disease (11,12) and starvation (13) may impair alcohol metabolism - possibly through decrease in hepatic alcohol dehydrogenase.

Clinical Syndrome (14,15,16)

1. "Excitement" Stage

a) Mental. Exhilaration; loss of restraint; decrease in finer discrimination; impairment of memory, concentration and insight. Confidence abounts, affect exaggerated with loquaciousness, loudness, mood swings and uncontrolled emotional outbursts.

b) Physical. Spinal reflexes increased, motor performance decreased. Pulse rises, face flushed, pupils dilated. Speech slurred, gait abnormal.

2. Stupor and Coma Stage

Gross decrease in consciousness, hypo and then areflexia, pallor, normal or constricted or terminally dilated and fixed pupils, respiratory depression, hypotension, hypothermia. No localized neurologic signs.

Medical Significance:

a) More than 1000 deaths reported each year in U.S. from acute alcohol intoxication. Massachusetts alone reported 4,500 deaths from acute effects of ethyl alcohol and 118 from other alcohol intoxications in 10 years (1928-1937).

b) Incidence of coma among alcoholics difficult to determine. However, in 1000 consecutive patients with acute alcoholism (confirmed by blood alcohol level) only 15 were comatose (15). On the other hand, of 37,438 admissions to a large municipal hospital in one year, 3% (1167 patients) entered in coma. Alcohol was the most common etiologic diagnosis accounting for 59.1% of these but the mortality in this group was only 2% (17).

TABLE II

INCIDENCE OF OVERT INTOXICATION* AT VARIOUS BLOOD ALCOHOL LEVELS (15)

% Intoxicated (1000 patients)	Blood Alcohol Level	Alcohol Ingestion
10.5	50 mg%	2 oz whisky
18.4	100 mg%	
47.0	150 mg%	6 oz whisky
83.6	200 mg%	
90.0	250 mg%	
95.1	300 mg%	12 oz whisky
96.0	350 mg%	→ Coma
100	450 mg%	

* Intoxication defined as presence of abnormal gait, plus presence of any 2 of the following: abnormal speech, alcohol on breath, dilated pupils, flushed face.

Decreased toxicity with:

a) Concomittant ingestion of food (especially fat)
b) Slow ingestion of alcohol
c) Ingestion of very dilute (< 10%) or very concentrated (> 50%) alcohol
d) Tolerance (chronic alcoholism)

Increased toxicity:

a) During rising blood alcohol
b) In fat individuals (alcohol does not diffuse well into adipose tissue)

Differential Diagnosis

Excitement stage: Other drugs

Coma: Trauma, hypoglycemia, other drugs, CNS vascular disease, hepatic coma, etc.

Mechanism of Acute Alcoholic Intoxication

Pertinent Background Information:

1. CNS pathology is normal and syndrome usually fully reversible.

   Conclusion; Metabolic defect.

2. Effect of alcohol on CNS blood flow and metabolism (18,19,20):

   In man, mild-moderate state of intoxication (blood alcohol levels 68-200 mg%) - no effect. In severe intoxication (mean alcohol level 320 mg%) - ↑ CBF (67 ml/100 g/min) and decrease in cerebral oxygen consumption (2.2 ml/100 g/min). Energy-forming processes not affected *in vivo* in experimental animals by ethanol (23).

   Conclusion: No evidence that decreased *total* CNS oxidative metabolism is the *cause* of intoxication. No data, however, on regional brain metabolism. Observed late ↓ in O_2 consumption likely is nonspecific *result* of CNS depression, as with other such agents.

3. No evidence that brain has capacity to metabolize alcohol.

   Conclusion: Effects are those of alcohol *per se* (21).

4. No good evidence that accumulated acetaldehyde (produced in liver) is responsible for cerebral effects of alcohol, though this may be true after Antabuse (22,23).

   Conclusion: Acetaldehyde not critical factor.

5. Congeners in alcoholic beverages vary considerably (Appendix I) (24) and do experimentall increase alcohol toxicity (LD_{50}) as well as apparently decrease rate of alcohol metabolis (25) but intoxication present in their absence (i.e., with vodka).

   Conclusion: Congeners not critical factor.

Current Hypothesis:

1. Alcohol is a cerebral depressant which *initially* depresses the ascending reticular formation. This releases the cortex from normal regulatory impulses emanating from reticular area. As a result cortical functions are chaotically "stimulated" resulting in the behavior characteristic of early intoxication. Subsequently, depressing effect spreads to cortex and becomes generally more severe, resulting in stupor.

   Evidence for this is good:

   a) Regional microelectrode studies of effect of alcohol strongly suggest this (26,27).

   b) Explains in a unified manner the initial "stimulation" and subsequent depression characteristic of alcoholism.

   c) Agrees with the effect of other anesthetic agents which exhibit a similar pattern of response and are believed to act on similar brain areas (38).

2. Alcohol exerts its depressant effect on nerve cell membranes responsible for propagation of electrical impulses. This effect seems to be either on the depolarization phase of nerve conduction (the generation of an action current) or more likely on the re-polarization phase wherein according to current concepts* an ATPase-dependent active Na-K shift maintains the polarity of the membrane (allowing continued impulse conduction).

Evidence for this is fair:

a) Ethanol at low concentrations interferes with transport of cations in cerebral cortex slices and depresses activity of Na^+-K^+-activated ATPase (28).

b) Ethanol inhibits the rapid fall of creatine phosphate, turnover of ATP^{32}, and excess respiration during electrical stimulation of brain tissue (29).

c) Ethanol depressed ionic conduction in squid axon membranes (30).

d) In vivo experiments with an electric eel indicated that ethanol (100-700 mg%) significantly diminished the frequency of spontaneous low voltage electrogenesis (28).

Tolerance to Alcohol

Definition:

When after repeated administrations, a given dose of a drug (alcohol) produces a decreasing effect or, conversely when increasingly larger doses must be administered to obtain the effects of the original dose (34).

Tolerance to alcohol definitely develops (31-33) and is lost after several months of abstinence.

Evidence for this is excellent:

a) Incidence of intoxication at same blood alcohol levels is less in alcoholics than in abstainers (16).

(See Table III on page 10)

* Some experiments (88) suggest an alternate mechanism of impulse conduction, but the weight of evidence supports the above concepts for in vivo events.

TABLE III

Concentration of Blood Alcohol mg%	Alcoholics, % Intoxicated	Abstainers % Intoxicated
75-125	18	50
125-175	47	57
175-225	83	100

b) Chronic alcoholics may be fed very large amounts of alcohol without developing severe intoxication (14,34).

c) Individuals intoxicated previously will be sober at the same alcohol level 5 hours later (32).

d) At the same high blood alcohol level, dogs habituated to alcohol exhibit a significantly lesser degree of intoxication (33).

Mechanism of Tolerance:

1. Metabolic - faster alcohol disposition. No evidence of difference in alcohol absorption or transfer into brain. Most older studies do not indicate a difference in rate of alcohol metabolism (33). However, some recent investigations have shown:

   a) Very low blood alcohol levels in chronic alcoholics given large doses of ethanol (8,14).

   b) In a group of 6 individuals given moderate quantities of alcohol for 3-14 days, 5 showed a significant increase in metabolism of C^{14} ethanol after the prior drinking phase (35).

   c) There is at least one report of increase in hepatic alcohol dehydrogenase in man (36) and one in rats (37) after chronic alcohol administration.

   Conclusion: There may be some enhancement of alcohol metabolism in chronic alcoholics, probably by induction of hepatic alcohol dehydrogenase.

2. Tissue-cellular tolerance - adaptation of brain to alcohol. Definitely a major factor (32,33) as shown by lack or decrease in intoxication in habituated man or dogs at blood alcohol levels which are intoxicating for the abstainer. Mechanism of adaptation is unknown. A form of desensitization to alcohol has been postulated (51,61), but it probably does not explain the very rapid (5 hours) onset of tolerance.

Treatment of Acute Alcoholic Intoxication

A. Excitement

1. Acute mild-moderate intoxication (excitement) usually requires no specific Rx. The usual measures: coffee, walking the patient, hot and cold showers, etc. do not increase rate of alcohol metabolism. They appear to stimulate a drowsy individual through direct cerebral effect but do not exert a beneficial affect in one acutely excited.

2. In some excited individuals, sedation may be necessary. Sedative drugs such as promazine, Librium appear logically best but there are no good controlled studies to validate this.

Caution: Sedative, if used, must be in low doses and patient observed frequently as sedative and alcohol effect may summate in an excited patient and induce coma (40).

B. Stupor-Coma

1. Usual measures as in all comatose states - i.e., attention to respiration and circulation. Obviously other causes of coma must be ruled out.

2. No value to gastric lavage since alcohol absorbed very rapidly - unless perhaps seen very early (< 90 minutes).

3. No good evidence in man that analeptics increase survival (41) though in experimental animals they may decrease duration of coma (40).

4. No specific indication for use of steroids (circulating steroid levels are normal or high (42).

5. Very difficult to enhance alcohol metabolism in body. With exception of probable, small beneficial effect of glucose/insulin (41) - none available.

6. Alcohol can be removed to some extent by increasing urine flow - since a quart of urine may contain as much as 5 g of alcohol. A much more efficient system is dialysis, a point clearly established by Schreiner in experimental animals and in patients (43).

Alcoholic Withdrawal Syndrome

Clinical Syndrome (4,39,41):

Major manifestations are tremulousness, hallucinations and delirium; each may occur in pure form but usually in combination.

1. Tremulousness - ("jitters, shakes"). Most common cause of hospital admissions in alcoholics. Patient usually alert (though on careful questioning may reveal a mild disorientation in time), aware of surroundings and illness, jumpy, startles easily. Preoccupied with his misery, inattentive (often rude), craves rest. Anorexia universal, nausea and vomiting common. Face flushed, conjunctivae injected and usually mild tachycardia.

Tremor: Coarse, generalized, fluctuates greatly - almost absent at rest, increased by purposeful movements and under stress.

Onset: During falling of alcohol level (in the morning) - often relieved by alcohol. Peak symptoms usually within 24 hours of cessation of drinking. Typically occurs in spree drinker. Usually disappears within a few days to a week. An inner "shaky" feeling may persist for 2 weeks.

2. Hallucinosis ("horrors") -

a) Present in 1/4 of tremulous individuals. Patient experiences "nightmares", misinterprets surrounding sounds and shadows, hears nonexistent voices or music, conjures up nonexistent forms. Especially common at night or on closure of eyes. Hallucinations may be visual, auditory, a mixture of the two or very rarely olfactory. Visual are most common, 80% or > of total.

Onset: Most often within 24-48 hours of cessation of drinking. Duration is usually 3 days or less.

b) Auditory - purely auditory hallucinosis without confusion or psychomotor overactivity of delirium tremens. Voices are vivid, usually threatening and patient responds appropriately to them. Suicide is a real risk.

Onset: Usually shortly after alcohol withdrawal. Duration few days-two weeks (usually < 6 days). Full recovery is characterized by the realization that voices were imaginary and there is full recall for the episode. About 20% of these patients develop chronic quiet auditory hallucinosis which gradually develops into a paranoid-schizophrenic-like state.

3. "Rum Fits" - Seizures in a non-epileptic individual (normal EEG in seizure-free interval) brought on by alcohol withdrawal.

Characteristics: Bursts of 2-6 seizures most common but sometimes only one or very rarely status epilepticus develops. Seizures are grand mal and in about 30% followed by overt delirium tremens (see below). Almost never see rum fits after onset of DT's. Focal seizures almost never seen in alcohol withdrawal alone.

Onset: Usually 12-48 hours after cessation of drinking.

Note: Epilepsy is also worsened by drinking, especially during sobering-up period (44).

4. Delirium Tremens - Term coined by Thomas Sutton in 1813 (56). State characterized by profound confusion, delusions, vivid hallucinations, tremor, agitation as well as increased autonomic activity i.e., tachycardia, dilated pupils, profuse perspiration and fever (73). Defined in this way, incidence is fairly low - about 5% of alcoholics admitted to general hospital (4). No specific or focal neurologic signs are seen in DT's (57). No characteristic laboratory findings are available.

Characteristics: Onset usually 25-96 hours after last drink. (See Table 4, page 13)

TABLE 4 (4)

Relation of DT's to Cessation of Drinking (44 cases)

Hours after last drink	No. of cases	
24 or <	2	
25-48	11	80%
49-72	7	
73-96	17	
74	7	

Duration usually less than ≥ 96 hours, termination abrupt, episode nonrecurrent.

TABLE 5 (4)

Course and Termination of DT's (101 cases)

1. Single episode - abrupt ending - 49 cases
   - gradual ending - 27 cases
2. Recurrent episodes (3-31 days) - 10 cases
3. Duration of single episodes of DT's (69 cases)

24 hours or <	14.5%	82.6%
25-48 hours	24.6%	
49-72 hours	43.5%	
73-96 hours	8.7%	
> 4 days	8.7%	

Mechanism of Alcoholic Tremulous-Hallucinatory-Delirious Syndrome

1. Well-established that this is due to a relative decrease in blood, and presumably brain, alcohol level after prolonged exposure to the alcohol.

Evidence:

a) Careful history shows that it occurs after decrease or cessation of alcohol intake (4).

b) The symptoms are different from those of acute alcoholic intoxication and are helped not augmented by therapy with alcohol (39).

c) Careful history establishes that it is unrelated to poor nutrition and it resolves despite poor nutrition (39).

d) The syndrome has been reproduced fully in volunteers given alcohol for 3-13 weeks (and otherwise normal diet) and then deprived of alcohol (14,31).

2. The Role of Mg^{++} depletion in Alcoholic Withdrawal States.

Evidence in favor:

a) Low serum Mg^{++} levels, decreased exchangeable Mg^{++} and decreased urinary Mg^{++} excretion after Mg^{++} loading may be seen in some of these patients (45,46,47).

b) Syndromes of withdrawal and low Mg^{++} states similar.

c) Patients with withdrawal appear to respond to magnesium therapy.

Evidence against:

a) Some patients with withdrawal do not have low Mg^{++} levels (48).

b) Withdrawal may be induced in volunteers while their Mg^{++} is maintained at normal levels (49).

c) Most cases of alcoholic withdrawal improve quickly without Mg therapy.

Conclusion: Magnesium deficiency is not the cause but only an associated (and possibly complicating) factor.

3. Mechanism of Withdrawal Syndrome.

Precise biochemical explanation of withdrawal at the cellular level is not available. No consistent pathologic changes in CNS (56).. Best hypothesis (50,51) stipulates the following sequence:

a) When a substance (alcohol) depresses neural activity in a given structure of CNS, elements therein become more sensitive to all neurohumoral agents to which they could previously respond.

b) When the depression is removed quickly, this increased sensitivity results in overactivity of the functional system and withdrawal reactions. When the depression is dissipated slowly, the sensitivity of the structures decays gradually and withdrawal is less marked. The biochemistry of this is not known (50).

Evidence in favor:

a) Consistent with principle of "denervation hypersensitivity" observed both in peripheral and CNS structures (50,51).

b) Consistent with observations that after a depressive effect alcohol induces rebound hyperexcitability. Thus, mice given a single large dose of alcohol first have a higher and then lower seizure threshold (52). This may represent the counterpart of "rum fits" in man.* In man, some hours after alcohol intoxication there is a nystagmus opposite in direction to that seen initially (53). This phenomenon is seen with many drugs that cause withdrawal.

c) This may explain the protective effect of other CNS depressants, barbiturates, etc., which suppress alcoholic withdrawal.

Note: It is likely that a hangover after brief ethanol intake is a mild case of withdrawal since withdrawal states in experimental animals can be very rapidly induced with relatively small doses of various drugs (morphine).

Addiction: Compulsive use of alcohol. Depends on complex psychologic factors and possibly physiologic factors which have not been sorted out. Likely physical dependence (withdrawal symptoms after stopping use of alcohol) serves as another motivating factor to continued drinking (54).

Mortality Associated with Delirium Tremens (57)

Analysis of all DT's (as defined strictly above) in PGH - 1950-1958. Three hundred twenty patients, 39 fatalities; of these DT's were a major cause of death in 36 cases and apparent sole cause of death in 18 cases. (It is of interest that 92% of these individuals developed DT's about 48 hours after entering hospital.) Overall mortality for period in 320 patients with DT's = 11.8%. There had been a threefold drop in mortality in last 4 years. In 1908 the mortality had been 37%. Other general hospital series (4) = 15%.

* The possibility of pyridoxine deficiency as contributing to convulsive disorder in some alcoholics also has been suggested (55) but is unconfirmed.

TABLE 6

Frequent Clinical Findings in Total Group (39 fatal) cases)

Pulmonary symptoms and signs	21 (15%)*
Tp of 104° or ≥ (rectal)	20†(8%)†
Liver enlargement	19 (18%)
Hypotension (terminal)	19
Traumatic lesions	13 (5%)
Malnutrition-dehydration	13
Convulsions‡	12 (13%)
G.I. problems (N, V, diarrhea)	11

* Incidence in nonfatal DT's group of 291 cases

† No obvious cause, other than DT's in 11

‡ Convulsions usually generalized, associated with high fever

TABLE 7

Major Pathologic Findings in Fatal Group (27 cases)

1.	Liver	Normal	0
		Fatty	18 (striking in 9)
		Cirrhosis	17
		Congestion	8
2.	Lungs	Normal	9
		Congestion (some with bronchopneumonia)	18
		TBC	3
3.	Brain	Normal	0
		Congestion	18*
4.	Heart†	Normal	4
		Dilation	12
		Mild nonspecific changes	9

* Felt to be terminal or nonspecific changes

† Changes interpreted as mild. No clinical congestive failure in any of 39 patients.

Bad Prognostic Features in DT's

a) Older age
b) Hyperthermia (104° or >) (45.5% mortality)
c) Convulsions (23.6% mortality)
d) Other severe illness (pneumonia, liver disease, etc.)

Cause of Death

1) Complicating illnesses: liver disease, bronchopneumonia, trauma, pancreatitis, fat embolism - ? Incidence (58,59)

2) Hyperthermia, shock, dehydration. Probably hypovolemic anoxic death.

3) Sudden death - no cause obvious at post mortem (60). (Some cases may be the result of fat embolism ÷ although incidence of clinically significant fat embolism in patients with fatty liver appears to be very small.)

Treatment of Alcohol Withdrawal State

1. Search for and treatment of associated illnesses (injury, infection, liver disease, pancreatitis, other drug ingestion, alcohol-induced hypoglycemia, vitamin deficiency syndromes).

2. General Supportive Treatment.

a) Fluid replacement. Retrospective analysis of records of 39 patients who died with DT's indicated that only 10 had received adequate amounts of fluid and that replacement may require often 6 liters/day.

b) Electrolytes, including Mg^{++} replacement. (Nature and quantity to depend on laboratory estimations). Magnesium replacement: 1-2 grams four times a day for 3-7 days (as 50% Mg SO_4) has been suggested if severe deficiency is suspected or Mg^{++} orally, if deficiency mild. Occasionally larger amounts over prolonged time needed. Caution: In presence of renal damage, Mg^{++} may accumulate and produce toxicity including narcosis and decrease in BP. Deep tendon reflex depression is good early clue to excess Mg^{++} accumulation (41,45,62).

c) Calories and vitamins, the latter in large amounts and parenterally to assure absorption. Nutritional "alcoholic " CNS disease i.e., Wernicke's and accentuation of peripheral neuropathy are often seen afteronset of DT's.

d) A well-lighted room, familiar people, decrease severity and duration of hallucinosis In people with auditory (and sometimes visual or mixed) hallucinosis, suicide precautions are in order.

3. Treatment of Severe Complications.

a) "Rum Fits." In most instances self-limited, one or only a few convulsions, and anticonvulsants unnecessary. If prolonged, Rx as for any convulsions with barbiturates. With concomittant presence of severe liver disease and/or hepatic encelphalopathy best to use phenobarbital (excreted partly (30%) via kidney), in smaller than normal doses and titrate patient's response clinically. Probably no value in subsequent anticonvulsant maintenance: if patient drinks, he will usually forget to take medications; if he does not drink, there is no need for medications.

b) Hyperthermia. Physiologic mechanism unknown, ? central hypothalamic effect. If not on infectious basis appears to be related to dehydration and increased somatic motor activity (especially convulsions) (57). Best, therefore, to prevent syndrome by adequate hydration and sedation. If hyperthermia ensues, nevertheless, temperature should be brought down toward normal by cold mattress, ice packs and alcohol sponging. It would make physiologic sense from findings noted in heat stroke patients to decrease body metabolic requirements at least by preventing chills (with phenothiazines (64)) and providing adequate oxygen.

c) Vascular collapse. Probably mainly on hypovolemic basis. Best treatment is preventive volume repletion. Pressor agents recommended but no physiologic data are available.

4. Drugs

Literature confused with few controlled studies. Worst problem is lack of assignment of patients to various experimental groups according to severity of illness.

General Conclusions:

a) In mild withdrawal states - phenothiazines (chlorpromazine, sparine) as well as chlordiazepoxide (Librium) were beneficial as compared with no therapy or placebo (65,66,72).

b) All the above drugs probably are of about equal value (65,67).

c) Most good studies suggest that in more severe DT's, paraldehyde is the best drug to use (68,69,70). This is especially well-established as compared with the phenothiazines. The data for Librium are inferential (65) and this is unsettled.

Suggested Recommendations:

a) If delirium tremens mild - i.e., pulse < 120 and no elevation in temperature (< 100° F) - and especially if severe liver disease is present - may use promazine, 100-200 mg p.o. q.4-6 hours prn (promazine may also be given I.M.). Most employ 200 mg as the initial dose. Alternately use Librium 50-100 mg p.o. initially, then an equivalent dose q. 8 hours prn. These doses are for adults. Dose must be titrated by individual response, standing orders are dangerous.

Note: Promazine may produce postural hypotension. Patients with liver disease appear to tolerate promazine quite well, though danger of cholestatic (hypersensitivity) jaundice does exist. Exact incidence of latter is not known. One theoretical advantage of Librium may be that it is an anticonvulsogenic drug.

b) If no response in DT's in 2 days or DT's severe from start - use paraldehyde 10 ml p.o. q. 4-6 hours prn. Object is to quiet patient, not suppress completely tremor and agitation as such a large dose may depress respiration. In presence of severe liver disease, follow-up doses may need to be reduced.

Note: Paraldehyde must be taken from a fresh, tightly-sealed brown bottle. Deteriorated paraldehyde may cause metabolic acidosis (71). Paraldehyde I.M. not advised - reported to cause necrosis and nerve damage.

5. Steroids

No evidence that they are of benefit (72). Some recommend their use in critically ill hyperthermic patients, pending further data (57).

Nutritional "Alcoholic" CNS Syndromes (4,39,74)

A. Clinical characteristics

1. Wernicke's. Definition:

   a) Abnormal eye signs consisting of nystagmus, paralysis of external recti muscles, paralysis of conjugated gaze. Occasionally ptosis and pupillary abnormalities.

   b) Ataxia of stance and gait.

   c) Mental disorder, apathy and disinterest (not drowsy).

2. Korsakoff's psychosis. Definition: Extension of Wernicke's characterized by:

   a) Memory defect - especially for recent events.

   b) Confabulations

   c) Impaired perception of time.

   d) Impaired concept formation, concentration, capacity to form visual or verbal abstractions.

3. Peripheral neuropathy. Definition:

   a) Generalized symmetrical affection of peripheral nerves which commences peripherally and spreads proximally. Legs affected early and cranial nerves very seldom. (7th then 3rd in order of frequency).

   b) Disorder both sensory and motor, characterized by muscular aching and tenderness progressive loss of sensation to "glove and stocking"type, decreased to absent DTR's, loss of power (especially in extensors), muscle wasting.

B. Etiology

Wernicke's and Korsakoff's definitely proven to be on basis of thiamine deficiency - (4,39,75,76,77). Peripheral neuropathy usually due to thiamine deficiency but other B-complex vitamin deprivation, pyridoxine, nicotinic acid and panthatenic acid also may be important (74,78,79). Alcohol and liver disease may potentiate nutritional deficiency.

C. Pathology (76,77,80)

In Wernicke's-Korsakoff's: necrosis and vascular dilation in brain stem and mamillary bodies.

In peripheral neuropathy: demyelination of nerves, then degeneration of axons.

D. Pathogenesis

Basic lesion likely biochemical, at least for Wernicke's, since eye signs and ataxia respond within hours to days to thiamine, while brain lesions persist (39).

Biochemical lesion induced by thiamine deficiency not known but may relate to impairment of transketolase which is believed important in normal metabolism of myelinated nerve fibers (81,82).

E. Treatment

Thiamine and other vitamins. Rx: Early, large amounts, parenterally.

CNS Disease Associated with Alcoholism but Probably Mainly of Nutritional Origin

1. Cerebellar Cortical Degeneration (39,83)

Definition:

a) Ataxia of gait and of legs with little involvement of other areas.

b) Evolves rapidly, then usually stable.

c) Pathologically - degeneration of neurones of cerebellar cortex, especially Purkinje cells and strikingly localized to anterior and superior aspects of Vermis and hemispheres.

2. "Alcohol-Tobacco" Amblyopia (39,84,85,86)

Definition: Disorder of vision characterized by

a) Central or centrocecol scotomas (more prominent with colored test objects).

b) ? Degeneration of fibers of optic nerve, chiasma and optic tracts.

3. Marchiafava-Bignami Disease (39,87)

Definition:

a) Clinical manifestations are diverse and nonspecific: disorder of cognitive function and emotional control, delirium, convulsions, tremor, rigidity and paralysis and finally coma.

b) Pathology: symmetrical degeneration of myelin, and to lesser extent axis cylinders. Mostly in commissural fibers of corpus collasum.

4. Central Pontine Myelinolysis (87)

Definition:

a) Flaccid quadriplegia, weakness of tongue, inability to speak or swallow; course progressive and acute with death within 2-3 weeks of onset of illness.

b) Pathology: demyelination restricted to basal portion of pons, symmetrically disposed about the midline.

Etiology

Etiology of these probably mainly nutritional, since they occur in absence of alcohol ingestion in malnourished people and coexist with other evidences of vitamin deficiency (87). A toxic effect of alcohol has not been ruled out.

APPENDIX II

CONGENER CONTENT OF SIX TYPES OF DISTILLED SPIRITS*

	American Blended Whisky	Canadian Blended Whisky	Scotch Blended Whisky	Straight Bourbon Whisky	Bonded Bourbon Whisky	Cognac Brandy
Total Congeners wt/vol,%	0.116	0.085	0.160	0.292	0.309	0.239
	Grams/100 liters at 100 Proof					
Fusel Oil (other alcohols)	83	58	143	203	195	193
Total Acids	30	20	15	69	63	36
Esters	17	14	17	56	43	41
Aldehydes	2.7	2.9	4.5	6.8	5.4	7.6
Tanning (from barrels)	21	18	8	52	48	25

* Modified from Snell, C.A. - Congener Content of Alcoholic Beverages. Quart. J. of Studies on Alcohol 19:69, 1958.

APPENDIX II

APPROXIMATE NUTRIENT CONTENT OF BEER AND ALE (Per liter)*

Calories	Protein	Carbohydrate	Alcohol	Thiamine	Pyridoxine	Niacin	Riboflavin
440	3 gm	50 gm	38 gm	0.05 mg	0.6 mg	10 mg	0.5 mg

K	Na	Ca	Mg	Zn	Cu	Fe	Higher Alcohol
400 mg	70	40	200	Trace	Trace	Trace	60 mg

* American brews. Modified from Davidson, C.S., New Eng. J. Med. 264:185, 1961.

REFERENCES

1. Korman, M. and R.L. Stubblefield. Definition of alcoholism. J. Amer. Med. Assoc. 178:76, 1961.

2. National Council on Alcoholism, 1966.

3. Goodman, L.S. and A. Gilman. The Pharmacological Basis of Therapeutics. Third. Ed., MacMillan, New York, 1965, p. 150.

* 4. Victor M. and R.D. Adams. The effect of alcohol on the nervous system in Proceedings of Association for Research in Nervous and Mental Disease 27:526, 1953.

5. Wilson, T.H. Intestinal Absorption. W.B. Saunders, Philadelphia, 1962.

* 6. Westerfeld, W.W. and M.P. Schulman. Metabolism and caloric value of alcohol. J. Amer. Med. Assoc. 170:197, 1959.

7. Haggard, H.W. L.A. Greenberg, and G. Lolli. The absorption of alcohol with special reference to its influence on the concentration of alcohol appearing in blood. Quart. J. Studies on Alcohol, 1:684, 1940.

8. Isselbacher, K.H. and N.J. Greenberger. Metabolic effects of alcohol on the liver. New Eng. J. Med. 270:351, 1964.

* 9. Westerfeld, W.W. The intermediary metabolism of alcohol. Amer. J. Clin. Nutr. 9426, 1961.

10. Newman, H.W., R.H.L. Wilson and E.J. Newman. Direct determination of maximal daily metabolism of alcohol. Sci. 116:328, 1952.

11. Figueroa, P.B. and A.P. Klotz: Alterations of liver alcohol dehydrogenase activity and other hepatic enzymes in alcoholic cirrhosis. Gastroenterol. 43:10, 1962.

12. Donopoulos, E., K. Maratas and J. Logothetopoulos. Studies on alchol's metabolism in patients with atrophic liver cirrhosis. Acta Med. Scand. 148:485, 1954.

13. Kerner, E. and W.W. Westerfeld. Effect of diet on rate of alcohol oxidation by liver. Proc. Soc. 83:530, 1953.

14. Mendelson, J.H. and J. La Dou, Experimentally induced chronic intoxication and withdrawal in alcoholics. Quart. J. Studies on Alcohol. Suppl. 2, p. 14, May, 1964.

15. Jetter, W.W. Studies in alcohol. I. The diagnosis of acute alcoholic intoxication by a correlation of clinical and chemical findings. Am. J. of the Med. Sci. 196:475, 1938.

16. Jetter, W.W. II. Experimental feeding of alcohol to non-alcoholic individuals. Am. J. of the Med. Sci. 196:487, 1938.

17. Solomon, P. and C.D. Aring. The causes of coma in patients entering a general hospital. Am. J. of the Med. Sci. 188:805, 1934.

*18. Battey, L., A. Heyman, and J.L. Patterson, Jr. Effects of ethyl alcohol on cerebral blood flow and metabolism. J. Amer. Med. Assoc. 152:6, 1953.

19. Fazekas, J.F., S.N. Albert and R.W. Alman. Influence of chlorpromazine and alcohol on cerebral hemodynamics and metabolism. Amer. J. of the Med. Sci. 230:128, 1955.

20. Sutherland, V.C., T.N. Burbridge, J.E. Adams and A. Simon. Cerebral metabolism in problem drinkers under the influence of alcohol and chlorpromazine. J. Appl. Physiol. 15:189, 1960.

21. Beer, C.T. and J.H. Quastel. The effect of aliphatic alcohols on the respiration of rat brain cortex slices and rat brain mitochondria. Canad. J. Biochem. 36:543, 1958.

22. Beer, C.T. and J.H. Quastel. The effects of aliphatic aldehydes on the respiration of rat brain cortex slices and rat brain mitochondria. Canad. J. Biochem. Phys. 36:531, 1958.

* 23. Wallgren, H. Effects of alcohol on biochemical processes in the central nervous system. Psychosomat. Med. Part. II. 28:431, 1966.

24. Snell, C.A. Congener content of alcoholic beverages. Quart. J. Studies on Alcohol. 19:69, 1958.

25. Haggard, H.W., L.A. Greenberg and L.H. Cohen. The influence of the congeners of distilled spirits upon the physiological action of alcohol. Quart. J. Studies on Alcohol 4:3, 1943.

* 26. Kalant, H. Some recent physiological and biochemical investigations on alcohol and alcoholism. Quart. J. Studies on Alcohol 23:53, 1962.

27. Olds, J. Self-stimulation of the brain. Sci. 127:315, 1958.

* 28. Israel-Jacard, Y. and H. Kalant. Effect of ethanol on electrolyte transport and electrogenesis in animal tissues. J. Cell Comp. Physiol. 65:127, 1965.

* 29. Wallgren, H. Rapid changes in creatine and adenosine phosphate of cerebral cortex slices on electrical stimulation with special reference to the effect of ethanol. J. Neurochem. 10:349, 1963.

30. Moore, J.W. Effects of ethanol on ionic conductance in the squid axon membrane. Psychosomatic Med. 28:450, 1966.

* 31. Isbell, H., H.F. Fraser, A. Wikler, R.E. Belleville and A.S. Eisenmann. An experimental study of the etiology of "Rum Fits" and delirium tremens. Quart. J. Studies Alcohol 16:1, 1955.

32. Mirsky, I.A., P. Piker, M. Rosenbaum, and H. Lederer. "Adaptation" of the central nervous system to varying concentrations of alcohol in the blood. Quart. J. Studies Alcohol. 2:35, 1941.

33. Newman, H. Acquired tolerance to ethyl alcohol. Quart. J. Studies Alcohol 2:453, 1941.

34. Fraser, H.F. Tolerance to and physical dependence on opiates, barbiturates and alcohols. Ann. Rev. Med. 8:427, 1957.

35. Mendelson, J.H., S. Stein and N.K. Mello. Effects of experimentally induced intoxication on metabolism of ethanol-1-C^{14} in alcoholic subjects. Metabol. 14:1255, 1965.

36. Unpublished data cited by C.M. Leevy at Third World Congress of Gastroenterology, Tokyo, 1966.

37. Dajani, R.M., J. Danielski and J.M. Orten. Utilization of ethanol. II. Alcohol-dehydrogenase systems in livers of alcohol treated rats. J. Nutrit. 80:196, 1963.

38. Arduini, A. and M.G. Arduini. Effect of drugs and metabolic alterations on brain stem arousal mechanism. J. Pharmacol. and Expt. Therap. 110:76, 1954.

* 39. Victor, M. and R.D. Adams. On the etiology of the alcoholic neurologic diseases. Am. J. Clin. Nutrit. 9:379, 1961.

40. Koppanyi, T. Treatment of acute alcoholic poisoning in alcoholism. Ed. Himwich, H.E. American Association for the Advancement of Science, 1957.

* 41. Victor, M. Treatment of alcoholic intoxication and the withdrawal syndrome. Psychosomatic Med. Part II. 28, 636, 1966.

42. Mendelson, J.H. and S. Stern. Serum cortisol levels in alcoholic and non-alcoholic subjects during experimentally induced ethanol intoxication. Psychosomatic Med. Part. II. 28:616, 1966.

43. Marc-Aurele, J. and G.E. Schriner. The dialysance of ethanol and methanol - a proposed method for the treatment of acute intoxication by ethyl or methyl alcohol. J. Clin. Invest. 39:802, 1960.

44. Lennox, W.G. Alcohol and epilepsy. Quart. J. Studies Alcohol. 2:1, 1941.

45. Flink, E.B., F.L. Stutzman, A.R. Anderson, T. Sontig and R. Frasier. Magnesium deficiency after prolonged fluid administration after chronic alcoholism complicated by delirium tremens. J. Lab. Clin. Med. 43:169, 1954.

46. McCallister, R.J., E.B. Flink and R.P. Dee. Magnesium balance studies in chronic alcoholism. J. Lab. Clin. Med. 55:98, 1960.

47. Mendelson, J.H., B. Barnes, C. Mayman and M. Victor. The determination of exchangeable magnesium in alcoholic patients. Metabol. 14:88, 1965.

48. Vallee, B.L., W.E. Wacker and D.D. Ulmer. The magnesium-deficiency tetany syndrome in man. New Eng. J. Med. 262:155, 1960.

49. Mendelson, J.H., J. La Dou, and C. Corbett. Serum magnesium and glucose. Experimentally induced chronic intoxication and withdrawal in alcoholics. Quart. J. Studies Alcohol Suppl. 2, p. 108, 1962.

50. Emmelin, N. Supersensitivity following "pharmacologic denervation. Pharm. Rev. 13: 17, 1961.

51. Sharpless, S.K. and L.M. Halpern. The electrical excitability of chronically isolated cortex studied by means of permanently implanted electrodes. Electroencephal. and Clin. Neurophysiol. 14:244, 1962.

52. McQuarrie, D.G. and E. Fingl. Effects of single doses and chronic administration of ethanol on experimental seizures in mice. J. Pharm. and Exp. Therap. 124: 264, 1958.

53. Goldberg, L. Alcohol, tranquilizers and hangover. Quart. J. Studies on Alcohol. Suppl. 1, p. 37, 1961.

54. Goodman, L.S. and A. Gilman. The Pharmacological Basis of Therapeutics. Third Ed. Macmillan, New York, 1966. Chapter 16.

55. Cherner, A.M. and E.S. Davidson. Association of pyridoxine deficiency and convulsions in alcoholics. Proc. Soc. Expt. Biol. and Med. 4:841, 1958.

56. Sutton, T. Tracts on delirium tremens, on peritonitis and on some other internal inflammatory affections and on gout. London, Thomas Underwood, 1813.

* 57. Tavel, M.E., W. Davidson and T.D. Batterton. A critical analysis of mortality associated with delirium tremens. Review of 39 fatalities in a 9 year period. Am. J. Med. Sci. 242:18, 1961.

58. Lynch, M.J., S.S. Raphael and T.P. Dixon. Fat embolism in chronic alcoholism. Arch. Pathol. 67:68, 1959.

59. Durlacher, S.H., J.R. Meier, R.S. Fisher and W.V. Lovitt. Sudden death due to pulmonary fat embolism in persons with alcoholic fatty liver. Am. J. Pathol. 30:633, 1954.

60. Clinicopathologic Conference. Chronic alcoholism, fatty liver and sudden death. Am. J. Med. 30:157, 1961.

61. Thesleff, S. Effects of motor innervation on the chemical sensitivity of skeletal muscle. Phys. Rev. 40:734, 1960.

62. Nahum, L.H. Magnesium deficiency and delirium tremens. Conn. Med. 29:196, 1965.

63. Hoagland, R.J. Treatment of delirium tremens. South. Med. J. 59:1041, 1966.

64. Hoagland, R.J. and R.H. Bishop, Jr. A physiologic treatment of heat stroke. Amer. J. Med. Sci. 241:415, 1961.

* 65. Sereny, G. and H. Kalant. Comparative clinical evaluation of chlordiazepoxide (Librium) and promazine in treatment of alcohol withdrawal syndrome. Brit. Med. J. 1:92, 1965.

66. Mitchell, E.H. Treatment of acute alcoholism with promazine (Sparine). J. Amer. Med. Assoc. 161:44, 1956.

67. Laties, V.G., L. Lasagna, G.M. Gross, I.L. Hitchman and J.A. Flores. A controlled study of chlorpromazine and promazine in the management of delirium tremens. Quart. J. Studies Alcohol. 19:238, 1958.

68. Thomas, D.W., and D.X. Freedman. Treatment of the alcohol withdrawal syndrome. J. Amer. Med. Assoc. 188:316, 1964.

* 69. Friedhoff, A.J. and A. Zitrin. A comparison of the effects of paraldehyde and chlorpromazine in delirium tremens. N.Y. J. Med. 59:1060, 1959.

70. Grunewald, F., T.E. Hanlon, S. Wachsler and A.A. Kurland. A comparative study of promazine and triflupromazine in the treatment of acute alcoholism. Dis. Nerv. Syst. 21:32, 1960.

71. Beier, L.S., W.H. Pitts, and H.C. Gonich. Metabolic acidosis occurring during paraldehyde intoxication. Ann. Int. Med. 58:155, 1963.

72. Figurelli, F.A. Delirium tremens. Reduction of mortality and morbidity with promazine. J. Amer. Med. Assoc. 166:747, 1958.

73. Roveché, B. The Neutral Spirit. Little, Brown and Co., 1960, p. 133-134.

* 74. Hornabrook, R.W. Alcoholic neuropathy. Am. J. Clin. Nutr. 9:388, 1961.

75. Phillips, G.B., M. Victor, R.D. Adams and C.S. Davidson. A study of the nutritional defect in Wernicke's syndrome. The effect of a purified diet, thiamine and other vitamins on the clinical manifestations. J. Clin. Invest. 31:859, 1952.

76. Joliffe, N., H. Watis and H.D. Fein. The Wernicke Syndrome. Arch. Neurol. and Psychiat. 46:569, 1941.

77. Sealock, R.R., A.H. Livermore and C.A. Evans. Thiamine inactivation by the fresh fish or Chastek-Paralysis Factor. J. Am. Chem. Soc. 65:935, 1943.

78. Strauss, M.B. Etiology of "alcoholic"polyneuritis. Am. J. Med. Sci. 189:378, 1935.

79. Fennelly, J., O. Frank, H. Baker and C.M. Leevy. Peripheral neuropathy of the alcoholic: I. Aetiological role of Aneurin and other B-complex vitamins. Brit. Med. J. 2:1290, 1964.

80. Prickett, C.O. The effect of a deficiency of vitamin B_1 upon the central and peripheral nervous system of the rat. J. Biol. Chem. 107:459, 1934.

* 81. Dreyfus, P. and G. Hauser. The effect of thiamine deficiency on the pyruvate decarboxylase system of CNS. Biochem. and Biophys. Acta 104:78, 1965.

82. Dreyfus, P. The regional distribution of transketalase in the normal and the thiamine deficient nervous system. J. Neuropathol. and Exp. Neurol. 24:119, 1965.

83. Victor, M., R.D. Adams and E.L. Mancall. A restricted form of cerebellar cortical degeneration occurring in alcoholic patients. Arch. Neurol. 1:579, 1959.

84. Victor, M., E.L. Mancall and P.M. Dreyfus. Deficiency amblyopia in the alcoholic patient. A clinical-pathological study. Arch. Ophthal. 64:1, 1960.

85. Carroll, F.D. The etiology and treatment of tobacco-alcohol amblyopia. I. Am. J. Ophthal. 27:713, 1944.

86. Carroll, F.D. The etiology and treatment of tobacco-alcohol amblyopia. II. Amer. J. Ophthal. 27:847, 1944.

* 87. Mancall, E.L. Some unusual neurologic diseases complicating chronic alcoholism. Am. J. Clin. Nutrit. 9:404, 1961.

88. Tasaki, I. and M. Shimamura. Further observations on resting and action potential of intracellular perfused squid axon. Proc. Nat. Acad. Sci. 48:1571, 1962.