Grand Rounds April 1969

ALCOHOL AND THE LIVER - ACUTE EFFECTS

OUTLINE

1. Significance of Problem

2. Effects of Alcohol on Liver

    a. None
    b. Pharmacologic
    c. Hepatic Damage

        1. Histology
        2. Etiology
        3. Clinical Features
            Fever in Alcoholic Hepatitis;
            Obstructive Syndrome

3. Prognostic Features in Alcoholic Hepatitis

4. Therapy of Alcoholic Hepatitis

1. Significance of Problem (4, 5, 110)

   a. Cirrhosis is the 4th leading cause of death in the U.S. at ages 45-64. Cirrhosis death rate in U. S. has increased from 10.7/100,000 in 1956 to 12.8/100,000 in 1965. From 1930 (prohibition) to 1960 death rate from cirrhosis in 35-44 year age range doubled for males and females, white and black populations. Death rates from cirrhosis for Baltimore residents in 1957-1958 vs 1965-1966 increased markedly, especially for sudden non-traumatic death with large fatty liver on autopsy, and especially in Negro women. In general, the mortality from cirrhosis is higher in men than women and in black than white populations (110).

   b. 50% - 66% of patients with cirrhosis in U. S. are alcoholics. Some 6-10 million alcoholics in U. S.

   c. Cirrhosis is seven times as common in alcoholics as in non-alcoholics. However, only about 1 out of 12 alcoholics develops cirrhosis.

2. Alcohol and Its Effects on Liver

   a. No effect evident

   b. Pharmacologic Effect (Induction of Enzymes)

   c. Hepatic Damage:

      Fatty Liver: Total lipid > 5% of total liver weight (65)

      Alcoholic hepatitis: Necrosis - Mallory's Hyaline Inflammation (Fat, fibrosis-cirrhosis may be present but are not essential for the diagnosis)

      Cirrhosis: Disruption of architecture by fibrous tissue

No Evident Effect of Alcohol on Liver:

Only about 1/12 alcoholics develop overt cirrhosis (5). Incidence of

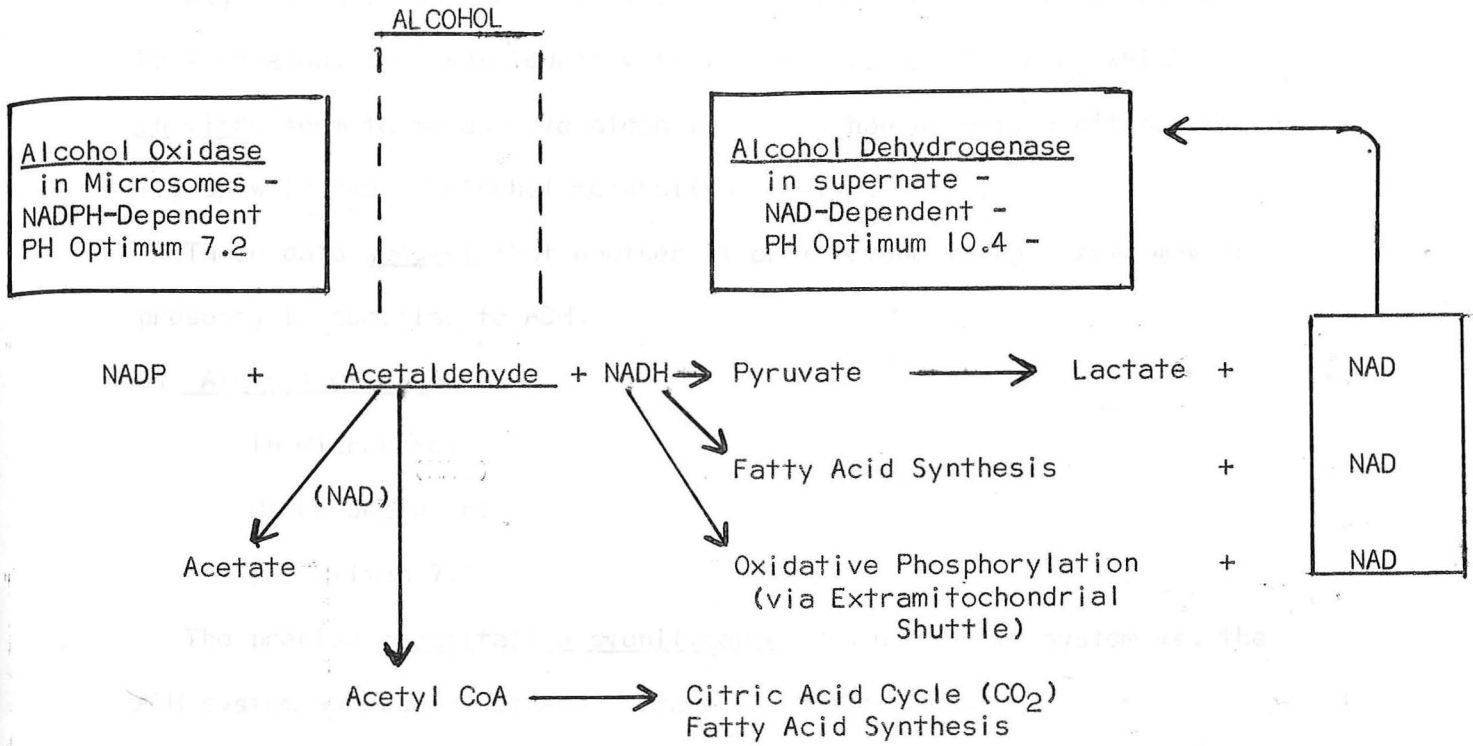
milder liver damage is uncertain but probably higher; in one series about 30%. Reason for development of liver damage in only some alcoholics is unknown (4, 5, 109). Possible explanations are:

1. Many alcoholics may actually have liver damage too subtle to be detected by liver function tests or perhaps even light microscopy;
2. Good nutrition may prevent or decrease liver damage from alcohol;
3. Genetic differences may result either in faster metabolism of alcohol or inherent greater resistance of liver to "toxic" effect of alcohol.

PHARMACOLOGIC EFFECTS OF ALCOHOL ON LIVER (1, 2, 3, 4, 6-15, 109)

Fig. 1

Metabolism of Alcohol in the Liver (90%+ of Total)



1) Alcohol is rapidly absorbed from the stomach and small intestine and 90-98% is metabolized in the liver. 2-10% of the absorbed dose is eliminated by the kidneys and lungs. The brain possesses the enzyme (ADH) necessary for metabolism of alcohol but in fact probably does not convert much alcohol to its metabolites, i.e., acetaldehyde, CO_2, etc., *in situ* (114)

2) Two enzyme systems in liver for metabolism of alcohol:

a) Alcohol Dehydrogenase (ADH)

In supernate, NAD-dependent, pH optimum 10.4, considered until recently the only key alcohol metabolizing enzyme system in liver.

Via its operation believed to be responsible for generation of excess NADH in liver and through this believed (at least, in part) responsible for alcohol-induced fatty liver, rise in serum lactate, depression of hepatic gluconeogenesis.

However, pH optimum for the enzyme activity in vitro much higher than intracellular pH, there is reasonable evidence that alcohol may induce (i.e., increase) its own metabolism but hepatic ADH activity may not be increased, and individuals with isozymes of hepatic ADH, which in vitro seem to metabolize alcohol faster than normal, don't necessarily show increased alcohol metabolism in vivo.

These data suggest that another alcohol metabolizing enzyme may be present, in addition to ADH.

b) Alcohol Oxidase -

In Microsomes

NADPH-dependent

pH-optimum 7.2

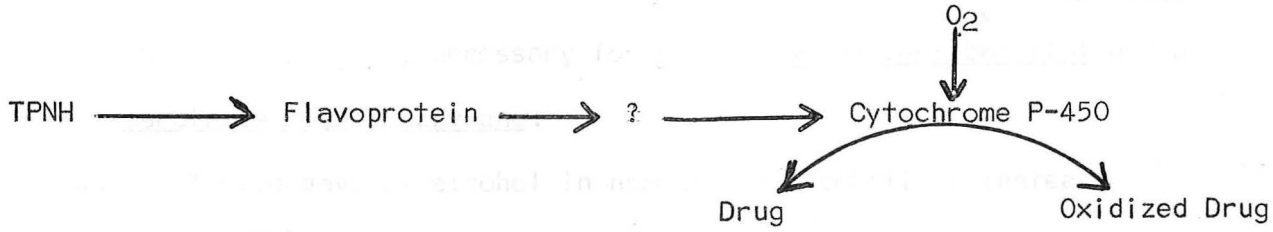
The precise quantitative significance of this enzyme system vs. the ADH system as regards ethanol metabolism is unknown.

Many other aspects of the alcohol oxidase enzyme system are unknown, but it is both inducible by alcohol and apparently non-specific so that alcohol may alter the metabolism of other drugs metabolized via this system.

This system, therefore, may be responsible both for the development of some of the tolerance to alcohol seen in chronic alcoholics (the remainder of tolerance is at the CNS tissue level) and may effect the disposition of other drugs, used by or given to alcoholics, which are metabolized via the microsomal system.

Fig. 2

Microsomal Oxidizing System in Liver



Drugs Believed Effected by Long-term Use of Alcohol

a) Table I (10, 11)

Drug	Half-Life in Hours Control	Drinkers*
Warfarin (40 mg p.o.)	41.0	26.5
Dilantin (100 mg t.i.d. x 3)	23.5	16.3
Tolbutamide (1 Gr I.V.)	5.8	2.8

*20 oz. 86 proof alcohol/day (or 5 Martinis) for 3 weeks or more. No liver function test abnormalities. In some histology of liver normal.

This study is only suggestive since same patients not studied before and after alcohol and nutrition not carefully controlled. (However, in other studies (8) a deficient diet potentiated the inducing ability of alcohol).

b) Carefully controlled studies (7, 8, 9) in animals and man have shown cross-induction of hepatic microsomal enzymes with alcohol and a variety of drugs.

1. Alcohol causes a proliferation of smooth endoplastic reticulum, the ultrastructural site of these microsomal enzymes in both rat and man, and increases microsomal cytochrome P-450 and total microsomal protein.

2. Isocaloric substitution of alcohol for carbohydrate for 2 weeks in rats results in a striking increase in activity of two hepatic

microsomal enzymes - aniline hydroxylase, an oxidative enzyme, and nitroreductose, a reducing enzyme.

3. A similar study in rats showed that alcohol causes an increase in enzyme activity necessary for metabolism of pentobarbitol and a carcinogen 3,4 benzpyrene.

4. Twelve days of alcohol in normal non-alcoholic volunteers caused a doubling in activity of pentobarbitol hydroxylase. Alcohol given was 36-42% of calories, giving blood alcohol levels of about 80 mg%. Optimal diet was given. This may explain tolerance of alcoholics, while not intoxicated, to various sedatives.

It should be noted, however, that high concentrations of alcohol in liver may depress the microsomal enzymatic activity for various drugs. Thus an acutely intoxicated person may metabolize these agents more slowly and this, in addition to the synergistic CNS effect, may explain the sensitivity of inebriated persons to CNS-depressive drugs.

5. Various drugs metabolized via microsomal system (i.e., chlorpromazine, pentobarbital, psychic energizers, etc.) enhance metabolism of alcohol.

Table 2 (12)

EFFECT OF OVERNIGHT PRETREATMENT WITH VARIOUS DRUGS ON ETHANOL SLEEPING TIME IN MICE

Pretreatment	Ethanol Sleeping Time, min.	
Drug*	Treated	Control
Chlorpromazine (2 mg/Kg)	18.7 ± 3.2	43.5 ± 6.1
Pentobarbital (50 mg/Kg)	22.4 ± 4.7	43.5 ± 6.1

* Given as single dose i.p. 21 hours prior to alcohol. No overt CNS effect from these drugs when alcohol given.

Conclusions:

1. It appears that alcohol over a prolonged period of time may alter the metabolism of other drugs detoxified by hepatic microsomal system.

   Conversely other agents may alter hepatic alcohol metabolism.

2. The development of actual liver disease will modify these effects, perhaps by decreasing a stimulatory effect of chronic alcohol. At least this seems to be true for the effect of alcohol on alcohol metabolism.

3. Details about quantity of alcohol, duration of exposure and the pharmacologic events taking place are not available.

HEPATIC DAMAGE (16-24)

MORPHOLOGY

a. Light Microscopy: Spectrum of findings:

   Fatty liver - Alcoholic hepatitis - Cirrhosis

   1. Fatty Liver: greater than 5% of fat by weight. Most of the fat is triglyceride. Also slight increase in phospholipids and probably cholesterol. Causes of fat in liver other than alcohol: Obesity, diabetes mellitus, heart disease with congestive failure, ulcerative colitis, children with kwashiorkor, toxins such as carbon tetrachloride and chloroform, excess tetracycline and its analogues, fulminant viral hepatitis, Faye's Syndrome, fatty metamorphosis of pregnancy.

   2. Alcoholic Hepatitis: Hepatocellular necrosis with Mallory's hyaline and inflammation. Fat and fibrosis or cirrhosis may be present but are not essential to diagnosis. Synonyms: Steatonecrosis, florid hepatitis, sclerosing hyaline necrosis of alcoholic, etc.

      Cellular necrosis presumably evokes inflammatory response and often leads to alcoholic Mallory's hyaline.

      Mallory's hyaline: Degenerative change in liver cytoplasm - eosinophilic slightly refractile material, virtually pathognomonic for "alcohol"-induced liver damage. Insoluble basic protein complex, containing arginine, tyrosine and lysine and not reacting with stains for lipid, hemoglobin, bilirubin, DNA, RNA and probably not for phospholipid. Consists of filamentous meshwork - width of fibrils - 165 Angstroms. Not definitely correlated with damage of any organelle such as mitochondria, endoplasmic reticulum or lysozomes. Mallory's hyaline not

induced experimentally so far in either animals or man.

3. Cirrhosis - Usually portal, may be post-necrotic. Defined as disruption of hepatic parenchyma and its circulation by fibrous tissue. Often associated with fatty liver and/or alcoholic hepatitis.

b. Ultrastructure: (Non-specific for alcohol)

1. Giant Mitochondria with inclusion bodies which may represent excessive phospholipid hydration within the damaged mitochondria.

2. Increase and dilatation (vessiculation) of smooth endoplasmic reticulum. Rough endoplasmic reticulum decreased and distorted. These changes reproduced experimentally in rats and man with alcohol and also noted in alcoholics with liver damage. Temporal sequence in man not established. In rats, mitochondrial changes occur late. Changes in mitochondria and rough endoplastic reticulum may be toxic, while those in smooth endoplasmic reticulum may be adaptive.

PATHOGENESIS

a. Increased Hepatic Fat (25-46, 106, 109, 111)

Table 3

Possible Mechanisms of Increased Hepatic Fat

1. Increased Delivery of Peripheral Depot Fat to Liver
2. Decreased Output of Fat from Liver via:
   a. Decreased triglyceride secretion out of liver
   b. Decreased hepatic oxidation of fat
3. Increased Hepatic Synthesis of Fat.

Conclusions:

1. Issue not agreed upon due to a) extrapolation of data from rats to men; b) varying results for apparently comparable experiments; c) Varying interpretations of some data. However:
2. Increased fat delivery from periphery to liver, if a factor, seems to be of significance only with very large single dose of alcohol. With more chronic drinking and reasonable fat intake, dietary fat accumulated in liver. With low fat diet, fat is synthesized within liver primarily. Thus evidence for physiologically significant peripheral mobilization of fat due to alcohol is scanty.

3. Evidence for decreased fat secretion very fragmentary and much data vs it. Perhaps with liver damage, it might become a factor.

4. Increased endogenous fat synthesis within liver may be of import, presumably due to increased NADH/NAD ration, but subject is controversial.

5. Probably best current evidence: decreased oxidation of fat in liver. The postulated mechanisms of this are: a) alcohol-induced depression of tricarboxylic cycle in liver and/or b) toxic effects of lipid-peroxidation products. Neither mechanism is proven as yet.

b. Alcoholic Hyaline: Cytoplasmic Necrosis. (16, 18, 23, 24, 20) Precise ultrastructural origin unknown. Not induced in experimental animals by alcohol or poor diet or both. Mechanism is uncertain, probably direct effect of alcohol since it occurs only in alcoholics, and not with malnutrition alone.

c. Inflammation: Non specific. Probably a secondary response to necrosis.

ETIOLOGY OF LIVER DAMAGE IN ALCOHOLICS (47-61, 104, 112, 113)

1. Poor Nutrition

   a. Choline deficiency

2. Direct Toxic Effects of Alcohol

3. Combined Effects of Alcohol and Malnutrition

POOR NUTRITION

Evidence in Favor

1. Choline deficiency (and a decrease in other lipotropic factors) in rats causes a fatty liver and this may progress to cirrhosis. Alcohol may increase the requirements for choline in rats, especially growing ones.

2. Malnutrition is a common finding in alcoholics with cirrhosis.

3. Malnutrition in children may cause a fatty liver.

Evidence Against

1. In starved adults (tropics, patients studied after war time dietary deprivation and in those with prolonged anorexia nervosa) fatty change in liver is rare.

2. Likewise in man dietary deprivation alone for prolonged periods of time probably only rarely leads to cirrhosis although a slight fibrosis may be seen.

3. Even in rats choline supplements are either not at all or only partly protective against alcohol-induced fatty liver.

4. Choline requirements for rats and mice are much greater than for man. This seems to correlate directly with level of liver choline oxidase which metabolizes the choline. This is shown in Table 4.

Table 4

Liver Choline Oxidase Activity in Nine Species

Species	Choline Oxidase Activity (µliters O_2 /hr/g wet weight	Time for Inducation of fatty liver
Rat	2408	Few days
Chick	1311	
Mouse	895	Few days
Dog	485	
Hamster	361	
Rabbit	202	
Monkey	144	Months
Guinea Pig	136	4-6 weeks-slight
Man	40	?

5. Fatty liver can be induced in man by alcohol over a few days despite massive choline supplementation and protein X 2 recommended amount.

Conclusion:

These data do not support, but do not fully rule out, poor nutrition or choline deficiency alone as a cause of liver disease in alcoholics.

Direct Toxic Effect of Alcohol

EVIDENCE IN FAVOR:

1. Ethanol given to rats and men, 36% of total calories for 8-18 days, induced a 3-10 fold increase in liver triglyceride despite diet adequate in protein and choline (and even with significant supplements of these).

This effect of alcohol was reproduced both in alcoholics without significant liver disease and in normal volunteers. Alcohol intake was about 18-24 oz. of 86 proof alcoholic beverage/day (or the equivalent of 5-6 Martinis). Blood alcohol levels were only 20-80 mg% and subjects were not intoxicated. In one subject only 10 oz./day for 8 days induced increased fat in liver. Change was reversible after alcohol discontinued.

2. Ultrastructural changes in liver of these subjects - megamitochondria, vessicular endoplasmic reticulum, cytoplasmic degradation - similar to those seen in alcoholics were observed. Some biochemical mitochondrial abnormalities in rats given alcohol have also been ovserved.

3. Liver function remained normal except for a slight rise in SGOT. This is also seen in some alcoholics given alcohol under controlled conditions.

4. Recent studies in Germany of a large group of alcoholics suggest that development of liver disease correlates with both quantity and duration of alcohol consumption rather than diet.

5. Alcohol is believed to damage directly skeletal muscle, bone marrow, previously damaged heart and probably the pancreas.

EVIDENCE AGAINST:

1. Fat in liver has not been proven in man to lead to cirrhosis. (a) For example obese patients with fat in liver fail to develop cirrhosis. (b) Rats with prolonged fatty liver from orotic acid administration do not show progressive liver disease. (c) Regenerative activity in human liver biopsies, measured with labeling of mesenchymal and ductular cells in connective tissue by H^3-thymidine, correlated with necrosis and inflammation and not fat. (d) Fever of alcoholics correlates better with necrosis than presence of fat.

2. Alcoholics with alcoholic hepatitis given a good diet in hospital and modest amounts of alcohol recuperate well. However with greater amounts of alcohol - damage seems to persist longer.

CONCLUSIONS:

1. Evidence is good that alcohol alone may induce a fatty liver and ultrastructural changes.

2. It is not certain if these changes are sufficient, if persistant over long term or repeatedly, to cause overt alcoholic hepatitis or lead to cirrhosis. The burden of proof rests with those who think that they do not.

3. Fat may be a final expression of varying types of liver alteration - some relatively bening, as in obesity, some perhaps adverse.

MALNUTRITION AND ALCOHOL

Evidence in Favor

1. In experimental animals malnutrition potentiates the hepatic abnormalities (fat, ultrastructural changes) induced by alcohol.

2. Patients with alcoholic hepatitis removed from alcohol do not improve as a rule unless adequate protein intake is provided.

3. The known physiologic effects of protein depletion, i. e., secretion of hepatic triglyceride, regeneration, etc., would reasonably tend to potentiate any deleterious effect of alcohol.

Conclusion:

Malnutrition, especially of protein, probably potentiates the adverse effect of alcohol on liver.

OVERALL CONCLUSIONS AS TO ETIOLOGY:

1. Malnutrition *per se* probably does not cause the liver damage seen in alcoholics.

2. Alcohol probably is a direct hepatotoxin.

3. Malnutrition most likely potentiates and interacts with the damaging effect of alcohol on liver.

4. The final word on the above is not yet in.

CLINICAL PATTERN (62-75, 108)

FATTY LIVER (65, 66, 67)

TABLE 5

PRESENTING CLINICAL FEATURES (FREQUENCY)

	Series I (270 pts.)	Series 2 (83 pts.)
Hepatomegaly	75 %	86%
Hepatic Tenderness	18 %	50%
Observed Jaundice	15%	40%
Abdominal pain	--	35%
Nausea and Vomiting	--	35%
Spider angiomata	8%	8%
Splenomegaly	4%	0
Ascites and Edema	12%	10%
Peripheral Neuropathy	21%	18%
Other vitamin deficiency	59%	---

With accompanying cirrhosis (67) (but not alcoholic hepatitis) there was increased incidence of signs and symptoms of portal hypertension (viz ascites, GI bleeding, splenomegaly) as well as coma and degree of jaundice.

Note however that rapidly reversible portal hypertension may be seen with just fatty liver done. The hypertension may be a mixture of presinusoidal and sinusoidal.

ALCOHOLIC HEPATITIS: (63, 68)

TABLE 6

PRESENTING CLINICAL FEATURES (FREQUENCY)

	Biopsy		Autopsy (100 pts.)
Symptoms	Series I (75 pts.)	Series 2 (50 pts.)	
Weight loss, weakness, anorexia	28%	~ 72%	10%
Jaundice	13%	38%	19%
Ascites	9%	40%	26%
Abdominal pain or discomfort	12%	44%	5%
Hepatic Coma	1%	--	11%
Nausea and Vomiting	11%	42%	4%
Signs			
Hepatomegaly	99%	96%	90%
Observed Jaundice	53%	38%	81%
Ascites	32%	58%	72%
Spider Nevi	23%	50%	40%
Splenomegaly	23%	40%	24%
Coma	9%	22%	57%

LABORATORY DATA:

TABLE 7

FATTY LIVER (66) vs ALCOHOLIC HEPATITIS (64)

Laboratory Data

TEST	% ABNORMAL FATTY LIVER (83)		ALCOHOLIC HEPATITIS (175)	
BSP ↑	76	(32%)†	99	(67%)†
Bilirubin ↑	35	(2.6 mg%)*	93	(43 mg%)
Alkaline Phosphatase ↑	48	(11 BU)	83	(30 BU)
SGOT ↑	39	(210)	92	(350)
Flocculations ↑	7		66	
Albumin ↓	23		67	
Globulins ↑	26		53	
Prothrombin Time ↑	--		75	

† Highest value shown in brackets.

* In a few accompanied by hemolysis - higher values - Overt Zieve's Syndrome (hyperlipemia + hemolysis) very rare - 1% of 270 pts. (65).

CONCLUSIONS:

1. Much overlap in symptoms in patients with fatty liver alone vs those with alcoholic hepatitis. Patients with well-established cirrhosis seem to present more often with symptoms of portal hypertension.

2. Much overlap in signs in patients with fatty liver alone vs those with alcoholic hepatitis. Patients with alcoholic hepatitis seem to have on average more jaundice, spider angiomata, splenomegaly ascites, and coma.

3. Patients with alcoholic hepatitis vs. fatty liver alone have on average a substantially higher incidence of abnormal liver function tests and these are more elevated (i.e., more abnormal) in the former.

4. Fewer laboratory abnormalities are seen in patients with histologically mild fatty liver (1+) and with mild alcoholic hepatitis (i.e., few Mallory bodies, little inflammation), but beyond this no apparent correlation between severity of morphologic findings and degree of abnormality in liver function tests.

DIFFERENTIAL DIAGNOSIS:

1. Usually presents as hepatocellular disease.
Classical differential is viral hepatitis and toxins. Features which point to diagnosis of alcoholic liver damage: a) Positive history for alcohol and poor diet. b) Negative history for contact with viral hepatitis, blood transfusions, flu-like onset of illness. c) Negative history for other toxins. d) Physical findings of chronic liver damage (spider angiomata, splenomegaly, etc.)

e) SGOT less than 500 and usually less than 300. (This test most helpful if SGOT is higher than 500 and especially ≥ 1000 units when it very strongly points away from alcoholic liver injury alone. In late viral hepatitis the SGOT may be in non-diagnostic range (< 300). f) Liver biopsy.

2. Chronicity best confirmed by history, evidence of long standing parenchymal damage - spider angiomata, ascites, etc., low serum albumin, evidence of cirrhosis on biopsy.

3. On occasion acute alcoholic liver injury presents as obstructive picture difficult to differentiate from extrahepatic (surgical) jaundice (62, 69). These patients present with:
   a) Alcoholic history
   b) Abdominal pain, nausea, vomiting, anorexia
   c) Jaundice, large tender liver
   d) Fever and leukocytosis
   e) Obstructive liver profile (Bilirubin ↑, Alkaline phosphatase ↑, flocculations normal, SGOT ~ 200, cholesterol ↑, often no urinary urobilinogen).
   f) Liver biopsy + ↑ fat, often with or without inflammation + necrosis (hyaline).
   g) Liver Scan may give false + picture of tumor deposits or abscesses.

Mechanism(s) of Jaundice - uncertain? Compression of liver cells and canaliculi by fatty cysts. Probably not correct.

IMPORTANT TO DIFFERENTIATE FROM EXTRAHEPATIC OBSTRUCTION

Some Clues:
1. Shaking chills rare in alcoholic damage.
2. Patient sometimes not as "toxic" as one would expect with fever of this degree due to cholangitis.
3. Liver usually diffusely tender in alcoholic hepatitis vs point tenderness with gall bladder disease.
4. Liver biopsy helpful if shows evidence of alcoholic liver damage. If no alcoholic hepatitis on biopsy - speaks against obstructive-febrile syndrome of intrahepatic etiology.
5. Wise to obtain gall bladder Xrays in non-icteric alcoholics with mild liver damage for future diagnostic reference.
6. Serum alcohol dehydrogenase (72) reported to be elevated in patients with fatty liver and destructive profile (i.e., intrahepatic cholestasis with liver damage) but very rarely (3/40) in extrahepatic obstruction. More data on this are needed to establish reliability and usefulness in routine clinical practice.
7. Important to remember that pancreatitis is common in alcoholics and could be the reason for obstructive jaundice. This may occur even without elevation of serum amylase, especially if test run singly and late in course of illness. (69)

Difficult diagnostic problems remain. In absence of intraabdominal emergency (empyema of gall bladder, peritonitis) - frequently wise to treat with antibiotics, temporize with conservative treatment.

Evidence that surgery bad in such patients is scanty. Mortality for surgery in acute viral hepatitis is about 10% (71), morbidity higher (additional 12%). Data for alcoholic hepatitis suggest surgery equally unfavorable; with just fatty liver surgery probably less detrimental.

8. Other causes of intrahepatic Obstructive Jaundice are given in Appendix I.

PROGNOSIS

MORTALITY RATE (63, 64, 65, 77)

Mortality varies widely in different patient series depending on patient selection.

In patients diagnosed as having acute alcoholic hepatitis only by biopsy (i.e., those sufficiently well to undergo a liver biopsy) mortality was 4-8%. In those with fatty liver alone and no alcoholic hepatitis, the mortality is even less.

With analysis of selected populations - the mortality rises to 33-50-70% level (in various series) but this is probably a meaningless selected figure.

CAUSES OF DEATH

TABLE 8

CAUSES OF DEATH IN ALCOHOLIC HEPATITIS (Range in Various Patient Series)

CAUSE	%
Coma	33 - 57
Gastrointestinal Hemorrhage	14 - 20
Renal Failure	0 - 20
Sepsis	0 - 12
Other (Sudden death)	9 - 20

ADVERSE PROGNOSTIC FEATURES IN ACUTE LIVER DISEASE

1. As expected, the group that come to autopsy had higher (X 2) incidence of ascites, edema and jaundice and 3-fold rate of coma and variceal hemorrhage.

2. The subtler prognostic features are listed in Table 9.

TABLE 9

ADVERSE PROGNOSTIC FEATURES (64, 68)

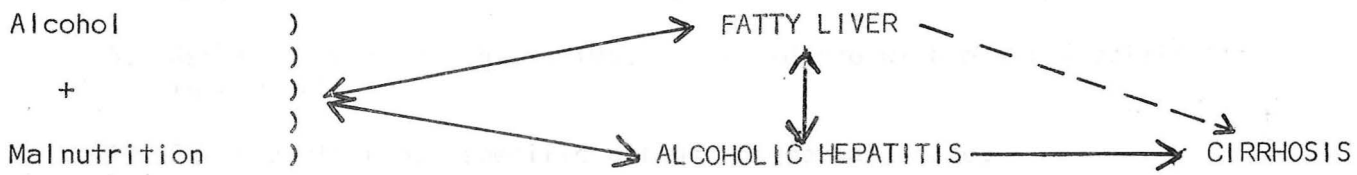
1. Asterixis
2. Azotemia
3. Bilirubin > 5 mg%, without fall at 6 days.
4. Prothrombin time prolongation > 4 sec. (Mortality rate ↑ 6-fold)
5. Leukocytosis (debatable)

3. Features not helpful in prognosis:

   a. SGOT level almost always below 300-500 units.
   b. Alkaline phosphatase level
   c. Serum albumin
   d. Hepatic histology in the individual patient with alcoholic hepatitis. Patients with fatty liver but no necrosis or inflammation have a better prognosis.

REVERSIBILITY OF LIVER INJURY

FIGURE 3



1. Fatty liver is known to be reversible.
2. Alcoholic hepatitis may be reversible.
3. Alcoholic hepatitis probably on occasion may develop without prior fatty liver but this is difficult to ascertain.
4. Fatty liver (without hepatitis) not believed by most to lead to cirrhosis BUT
   a) Leevy claims such progression although serial liver biopsies were not performed and thus alcoholic hepatitis at some stage was not excluded.
   b) Ultrastructural changes, which accompany fatty liver, have not been considered in most of these reports.
5. The precise factors which induce irreversibility at some stage of the disease are unknown.

FEVER DUE TO ALCOHOLIC HEPATITIS (70)

Definition: a) Fever in alcoholics with liver damage.
b) No specific cause of fever elicited (other than liver disease). This is then a diagnosis by exclusion of other causes of fever.

Incidence: About 25-50% in various series. (Fever due to specific cause noted in another 10-25% of these patients.)

Characteristics:

TABLE 10 (70)

CHARACTERISTICS OF FEVER IN 58 PATIENTS WITHOUT APPARENT INFECTION (38.6%)*

	Per Cent
1. Maximal height (°F. p.r.)	
< 101	26
101-103	67
> 103	7
2. Duration	
< 1 week	17
1-2 weeks	24
2-4 weeks	37
4-8 weeks	17
8 weeks	5
3. Chills (shaking)	3
4. Type	
Intermittent	53
Remittent	45
Hectic	2

* 14.7% had fever with infection. Total number of patients - 158

Note:

1. Prolonged duration of fever in many patients.
2. Rarity of fever in excess of 103° F p.r.
3. Rarity of shaking chills (vs. 25% incidence with overt specific infection).
4. Fever pattern not specific but hectic pattern rare.
5. No response to antibiotics.

FEATURES WHICH ACCOMPANY "HEPATIC" FEVER

TABLE II (70)

FEATURES IN PATIENTS WITH "HEPATIC" FEVER

1. ↑ incidence in females under 50 years.
2. Alcoholism greater, diet worse.
3. ↑ signs of liver disease (spiders, ascites, liver tenderness, liver > 4 f.b., splenomegaly, jaundice).
4. 2/3 had WBC > 10,000; 1/3 had WBC > 15,000. May rarely have peripheral WBC > 100,000.
5. Liver function tests worse - ↑ alkaline phosphatase, ↑ bilirubin and BSP.
6. Fever appeared to correlate with hepatic necrosis and inflammation. About 60% had slight or no fat. Afebrile patients showed much less necrosis and inflammation as a rule. Offset of fever seems to correlate with disappearance or decrease in these morphologic abnormalities.
7. Temperature of > 103° F (p.r.) and Rigor rare in hepatic fever.

ETIOLOGY (70, 103, 104, 105)

1. No known abnormality of sweating.
2. No specific infection found (unaffected by antibiotics).
3. Unconjugated etiocholonolone - ? pyrogenic material not adequately conjugated by diseased liver. Hypothesis not supported by studies which show no correlation between presence of the free etiocholonolone in blood and the presence of fever in patients with hepatic fever or in patients with cryptogenic fever (i.e., FMF, etc.). However, a delayed effect of the hormone or its accumulation in liver would be consistent with its postulated action as a pyrogenic mediator, i.e., releasing endogenous pyrogen from hepatic or other leucocytes. This concept not tested yet. (Etiocholonolone is a controversial subject).
4. Hepatic necrosis itself could stimulate an inflammatory response with release of endogenous pyrogen from WBC's and a subsequent effect of endogenous pyrogen on hypothalamus giving fever. This last seems the more reasonable theory.

THERAPY (76 - 93)

TABLE 12

THERAPY

1. Abstention from alcohol.
2. High Protein (1-2 gm/Kg) - Normal Fat Diet.
3. Multivitamins
4. Bed rest (?)
5. Specific treatment for effects of liver disease - viz, ascites, hemorrhage, etc.
6. Androgens - No definite evidence of benefit.
7. Corticosteroids - No evidence of benefit.

1. Abstention from Alcohol

a) Data from at least five hospitals indicate that consumption of small to moderate amounts of alcohol (3-7 oz. 85%-95% alcohol/day for 1-18 months) when coupled with a nutritious diet did not interfere with gradual healing of alcoholic liver injury. In absence of nutritious intake, healing or improvement was not evident.

b) With larger amounts of alcohol and a nutritious diet, fat seems to persist in the liver for a longer time (92, 91, 65). (Data in three available studies are somewhat conflicting).

c) Main problem: To assume that an alcoholic will moderate his alcoholic intake and will eat adequately while drinking. This is usually impossible to achieve.

d) Effect of abstention from alcohol (plus good nutrition).

TABLE 13 (77)

PROGNOSIS IN 278 PATIENTS WITH LAENNEC'S CIRRHOSIS

		5 YEAR SURVIVAL IN %	
	Group	Stopped ETOH	Continued ETOH
1.	All patients*	63%	40.5%
2.	Patients after onset of ascites	52.4%	32.7%
3.	After onset of jaundice	57.5%	33.3%
4.	After onset of hematemesis	35.3%	20.7%
5.	Patients without ascites, jaundice, or hematemesis	88.9%	68.2%

* Survival in both sexes equal.

CONCLUSIONS:

1) Mild ethanol intake in face of nutritious diet probably not harmful to recovery from alcoholic liver disease. Data, however, are scanty.

2) Abstention from non-supervised excessive alcoholism vital for improving prognosis.

3) Most reasonable course until more data available: total abstention in these patients.

2. HIGH PROTEIN - NORMAL FAT DIET (80, 81, 85, 87, 82)

a) Data from several hospitals indicate that adequate (1-2 gm/Kg) protein intake important for recovery. Calories (1600) as glucose inadequate. Low protein intake (↓ 30 g/day) inadequate.

b) In presence of nutritious diet, lipotropic agents of no benefit. As substitute for nutritious diet, lipotropic factors of no consistent value.

c) In presence of nutritious diet - quantity of fat (high, moderate, low) no effect on recovery. However, a low fat diet given with alcohol to volunteers decreases accumulation of fat in liver.

Conclusions: High protein diet is optimal (assuming no encephalopathy). Lipotropic agents probably of no value with adequate nutrition.

3. MULTIVITAMINS (76, 65)

a) Incidence of vitamin deficiency very high - some only on measurement of the vitamins (i.e., subclinical). However, in two groups of 270 and 83 patients with fatty liver the incidence of overt peripheral neuropathy was 21 and 18%, respectively. Over 75% of such peripheral neuropathy is due to thiamine deficiency. Other deficiencies are: folate, pyridoxine, nicotinic acid and penthetenic acid. In all 59% of one group of 270 patients with fatty liver had some form of vitamin deficiency.

b) Vitamins should initially be given parenterally to assure adequate absorption. Main value is in treatment of non hepatic problems.

4. BED REST (65)

a) No definite proof that bed rest is essential for recovery if patient feels like ambulating. Although control studies are not available, Leevy cites 10 patients with "moderately fatty" liver who recovered nicely in hospital while ambulatory.

5. Treatment of complications beyond scope of this review.

6. ANDROGENS (78, 79, 65)

a) Two studies of patients with fatty liver (79, 65) suggest that anabolic steroids (Nilevar, Norethandrolone) may enhance the rate of mobilization of fat from liver by 3-5 fold. The dose of Nilevar was 40 mg/day. In one study testosterone propionate 100 mg/M achieved the same result whereas smaller doses in the second study were ineffective. Neither study was well controlled.

b) In the one well-controlled study (78) carried out in patients with alcoholic hepatitis no benefit from anabolic steroids was noted.

Conclusions:

1) Data regarding fatty liver inadequate. Since oral anabolic steroids may cause cholestasis, their use in this setting for routine therapy is not justified.

2) In severe alcoholic hepatitis - no evidence that these agents are of benefit.

7. CORTICOSTEROIDS (93)

a) One controlled study - double blind - still in progress.

Patients with alcoholic hepatitis - 15 received prednisone and 10 placebo-randomized. All other therapy standard. Prednisone 40 mg/day for one month.

Liver biopsy before therapy and at 5 and 17 weeks of study.

b) Results were: 1) Supportive care alone results in survival in most patients (mortality 17%).

2) Prednisone, in this dose, did not improve clinical or histologic healing in these patients with mild or moderate disease (Note: severely ill patients not studied).

3) Alcoholic hepatitis was shown to progress to cirrhosis.

4) Surprisingly, no prednisone side effects noted.

Conclusion: Tentatively, this dose of prednisone does not benefit patients with mild to moderate alcoholic hepatitis.

APPENDIX I

INTRAHEPATIC CAUSES OF OBSTRUCTIVE JAUNDICE

1. Inborn Errors of Metabolism - Dubin Johnson, Rotor
2. Viral Hepatitis (cholangiolitic)
3. Alcoholic "Fatty" Liver
4. Primary Biliary Cirrhosis
5. Drugs - chlorpromazine, C_{17}-alkylated anabolic steroids.
6. Recurrent Jaundice of Pregnancy
7. Recurrent Benign Cholestasis

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