Research Society on Alcohol Post-graduate Course

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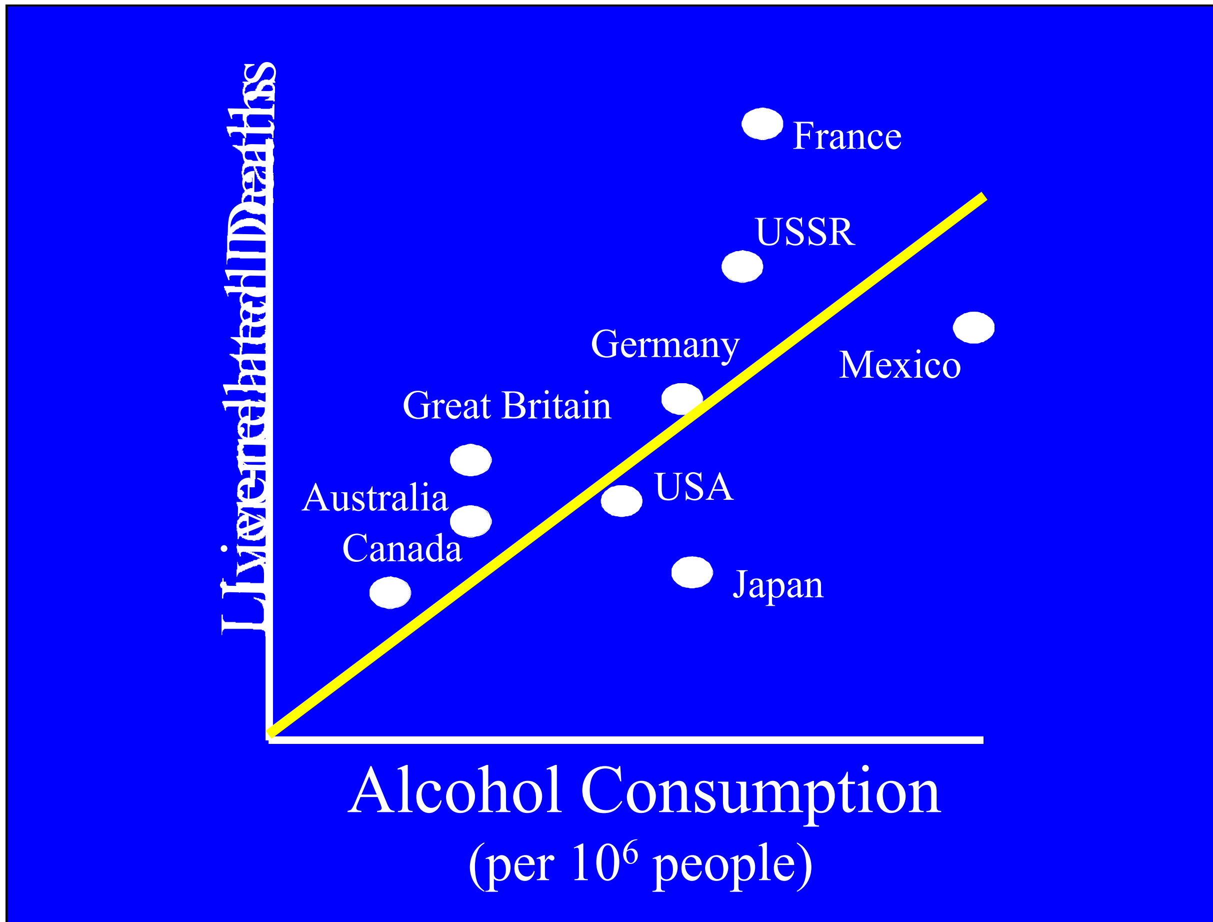
Slide 1.



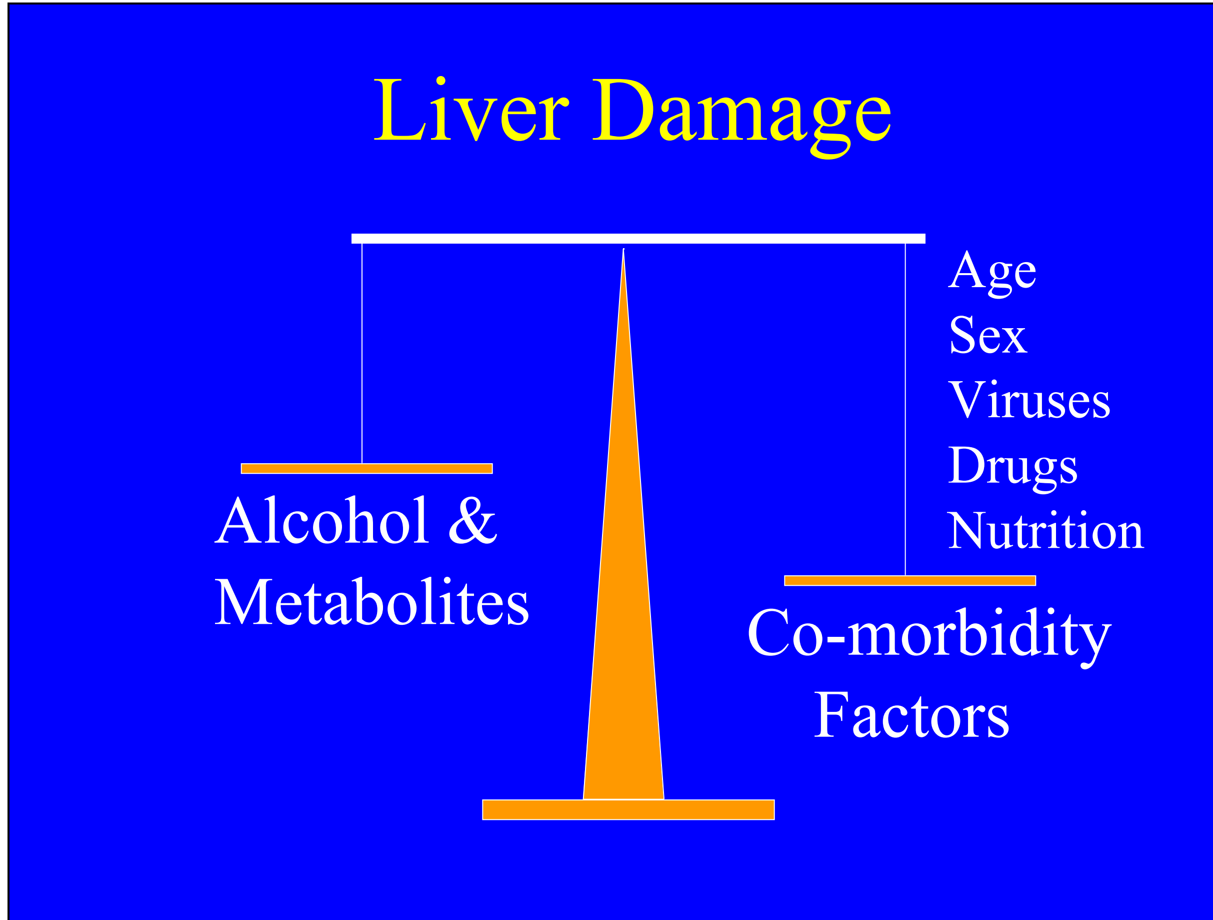
Epidemiology of Alcoholic Liver Disease (slides 1- 3)

Alcohol is one of the best known hepatotoxins. In many different societies, death rates from liver disease correlate well with the per capita consumption of alcoholic beverages.

Slide 2.

Although alcohol ingestion is fairly ubiquitous, most people who consume alcohol, even in large amounts, do not develop serious alcohol-related liver injury.

Slide 3.



This finding indicates that environmental or host factors influence an individual's susceptibility to alcoholic liver disease. Efforts to define these "co-morbidity factors" are becoming a major focus for alcohol researchers and should help to clarify the mechanisms by which alcohol injures liver cells.

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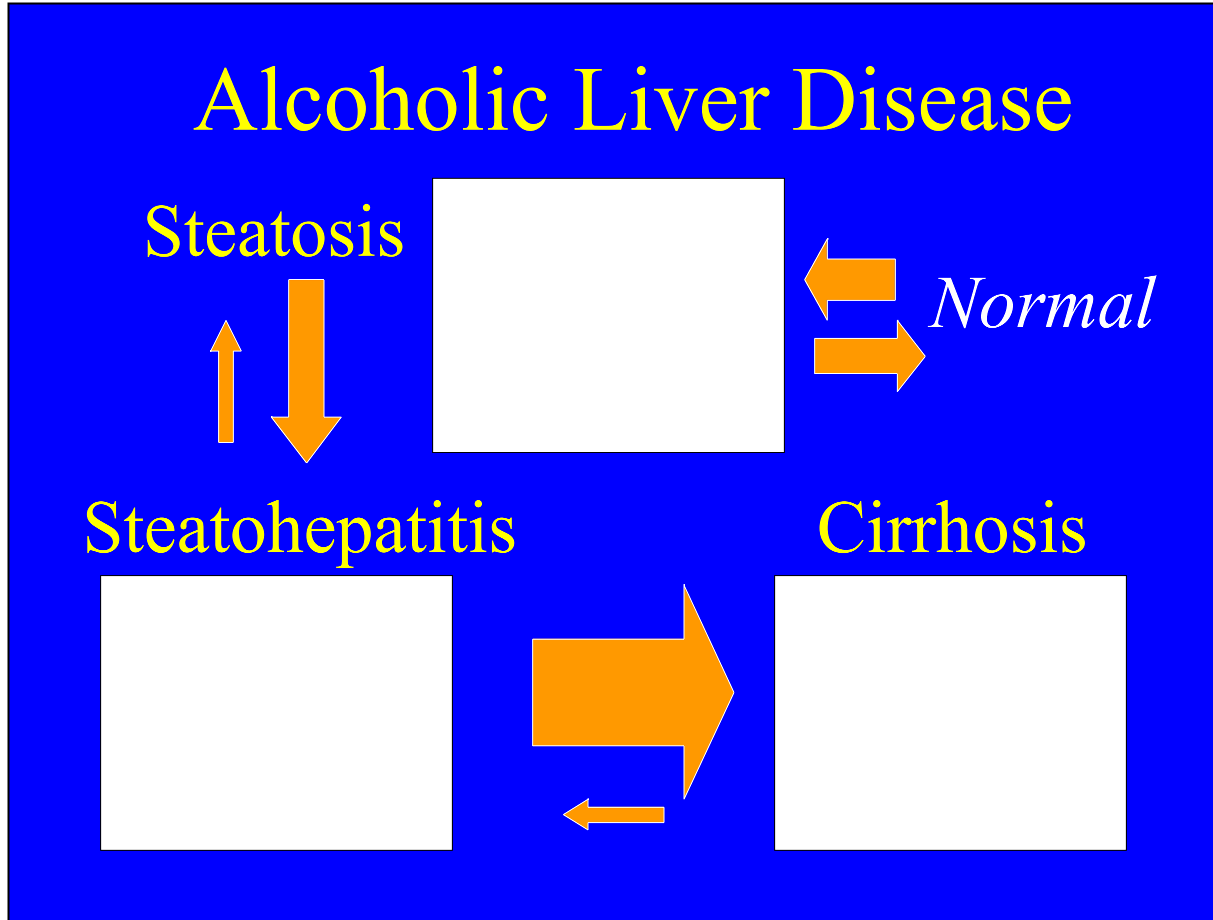
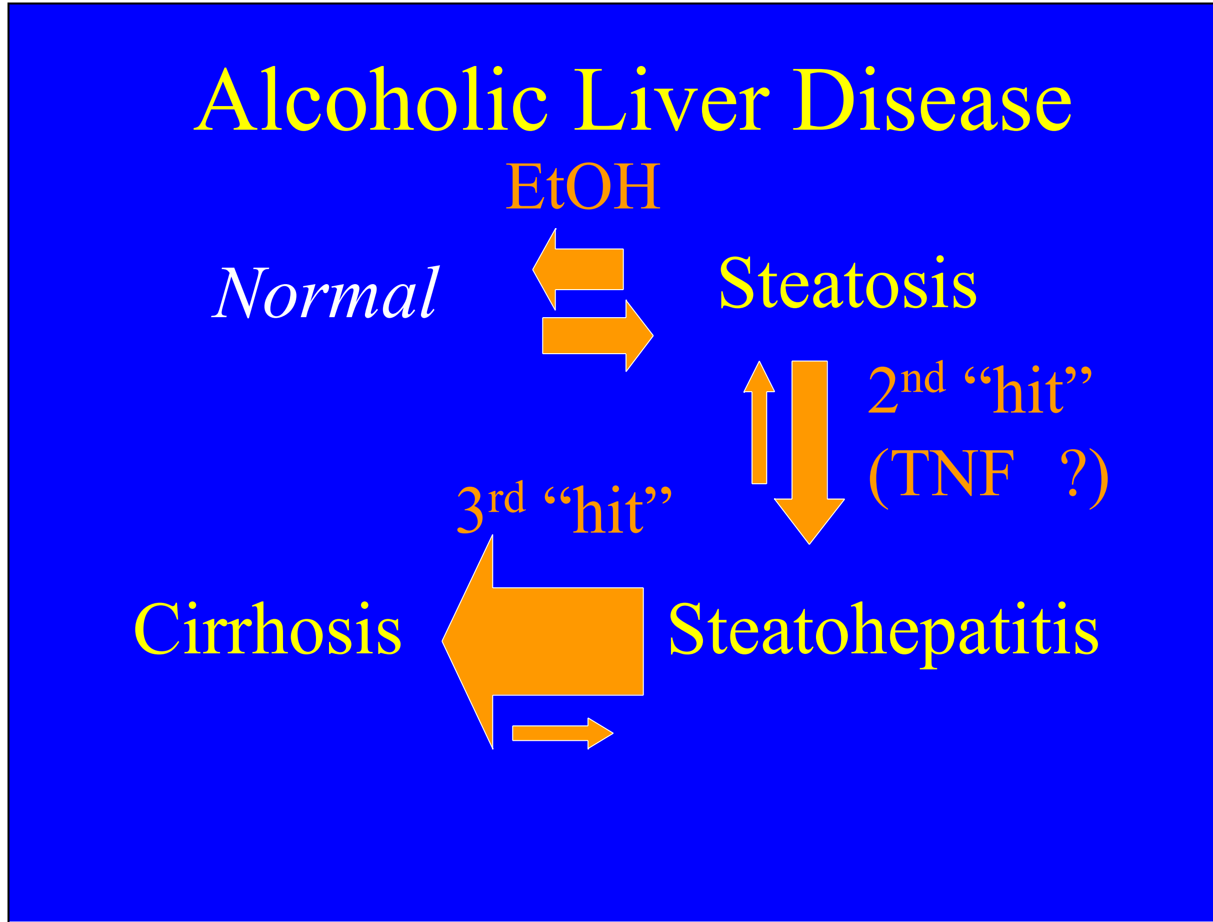


Histologic Spectrum of Alcoholic Fatty Liver Disease (slides 4 - 5)

Habitual consumption of alcohol produces a spectrum of hepatic pathology, ranging from simple steatosis (fatty liver) on one extreme, to cirrhosis on the opposite end of the spectrum. Steatohepatitis, a liver disease characterized by hepatic steatosis, inflammation, and increased hepatocyte death, is usually an intermediate stage between simple fatty liver and cirrhosis (slide 4). Steatosis is a very common result of chronic alcohol ingestion, occuring in many, if not most, human beings and experimental animals that consume alcohol daily. In contrast, cirrhosis is a relatively rare outcome of chronic alcohol ingestion. It has been difficult to produce cirrhosis in animal models of chronic alcohol consumption and this lesion has been demonstrated in only about 20% of human alcohol abusers. As will be discussed subsequently, the inconsistent occurrence of cirrhosis in chronic alcohol users is thought to reflect inter-individual differences in the tendency to develop alcohol-related steatohepatitis.

Slide 5.



Because different degrees of liver damage result from exposure to similar "doses" of alcohol, some have speculated that the progression from mild to severe forms of alcohol-related liver damage requires the cumulative effects of several, distinct insults (i.e., "multiple hits"). Because of time constraints, this lecture will discuss how alcohol injures hepatocytes, the predominant type of cell in the liver. However, it is important to acknowledge that other cells, particularly Kupffer cells, resident hepatic macrophages, and stellate cells, which make the scar tissue that accumulates in cirrhotic livers, are also altered by alcohol exposure.

Slide 6.

Steatosis

(Fatty Liver)

- Common
- Reversible
- Few symptoms
- Hepatomegaly
- Slightly ↑ liver enzymes

Clinical Features (slides 6-8)

Steatosis is rapidly reversible, and, even when chronic, it is typically associated with few clinical problems. Most patients with hepatic steatosis feel relatively well, although they may have liver enlargement and/or mildly increased serum levels of liver-associated enzymes.

Slide 7.

Steatohepatitis

(Fat + inflammation & injury)

- Less common
- Precursor of cirrhosis *
- Generally few symptoms
- Can → multi-organ failure, death

* Can also occur in patients with cirrhosis

In contrast, steatohepatitis seldom (i.e., in < 10% cases) reverts to normal hepatic histology, even when the precipitating condition is removed. Rather, patients with steatohepatitis often develop increased hepatic fibrosis and, with time, cirrhosis occurs in a substantial fraction (i.e. in almost 50%) of these individuals. Liver-related morbidity and mortality occur in patients with steatohepatitis. Unless liver biopsy is performed, it is difficult to distinguish most patients with steatohepatitis from those with simple steatosis. However, some patients with steatohepatitis become acutely ill with a syndrome that resembles overwhelming infection or multiple organ failure, and require hospitalization. Patients typically have fever, anorexia, muscle wasting, tender hepatomegaly (enlarged liver), and jaundice. Their one month mortality can be as high as 50%.

Slide 8.

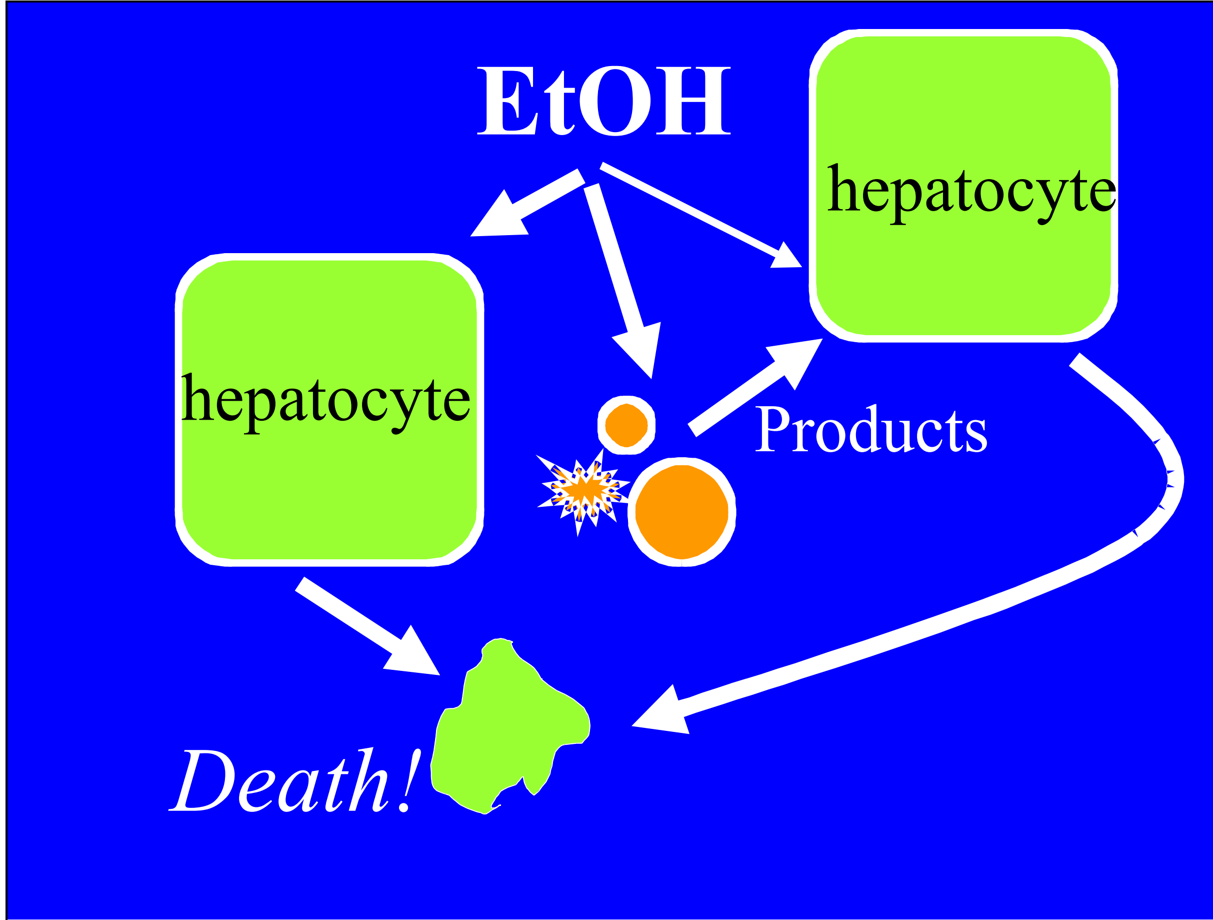
Cirrhosis

Scar, nodules

- Eventually develops in 20%
- Morbidity common
  (jaundice, ascites, bleeding, cachexia, infections, encephalopathy)
- Liver cancer, death in most within 10 years

The probability of liver failure and death from steatohepatitis increase significantly in patients with associated hepatic fibrosis or cirrhosis. Thus, the transition from simple steatosis to steatohepatitis appears to represent a rate-limiting step in the progression to cirrhosis and clinical liver disease in patients with alcoholic fatty liver disease.

Slide 9.

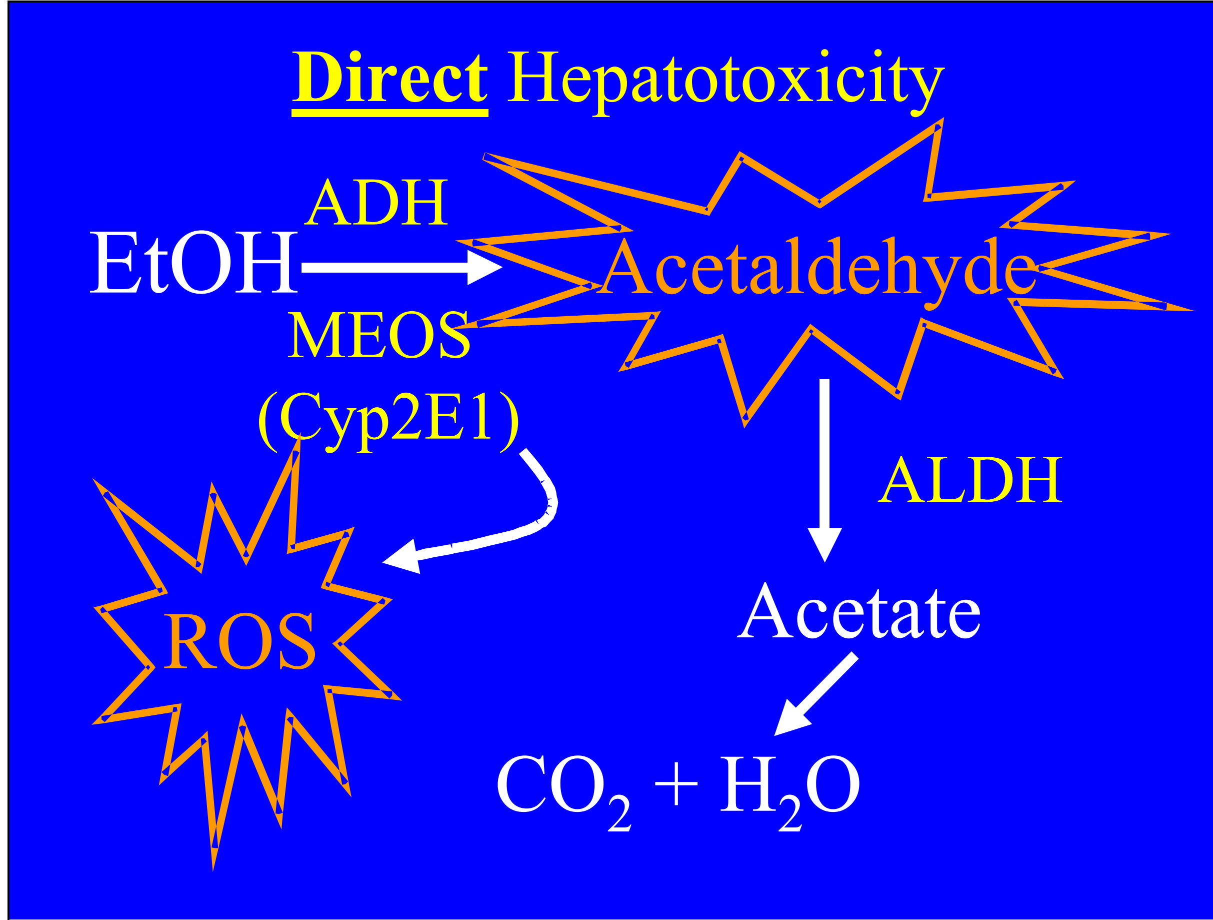


Pathogenesis (slides 9 - 21)

Hepatocytes as direct cellular targets of ethanol toxicity (slides 9 - 11)

Although the pathogenesis of alcohol-induced liver damage has been investigated for more than three decades, the cellular and molecular mechanisms involved remain poorly understood. Liver damage might be the result of direct toxic actions of ethanol or its metabolites within hepatocytes.

Slide 10



According to this theory, ethanol is metabolized to acetaldehyde, a toxic intermediate, by hepatocyte enzymes (slide 10). Under conditions of infrequent ethanol exposure, ethanol is oxidized to acetaldehyde predominately by cytosolic alcohol dehydrogenase (ADH) and the resultant acetaldehyde is quickly detoxified to acetate by mitochondrial-associated aldehyde dehydrogenase (ALDH). Acetate, in turn, becomes a substrate for intermediary metabolism, generating CO_2 and H_2O. ADH/ALDH polymorphisms and drugs (Antabuse) that result in an overactivity of ADH relative to ALDH have been associated with increased liver damage in people, supporting the importance of acetaldehyde as an hepatotoxic substance.

Slide 11.

Direct Hepatotoxicity

Pro's

- ADH/ALDH polymorphisms
- Cyp2E1 induction liver injury (chronicity, zonality, other drugs, over-expressing cell lines)

Con's

- Dietary effects (CHO, PUFA)
- Kupffer cell depletion

However, it is not entirely clear how acetaldehyde injures hepatocytes. Some evidence suggests that acetaldehyde forms adducts with vital cellular molecules. This inhibits the normal biological activities of these molecules and also creates novel antigens that become targets for immunologic attack. According to this theory, activation of the immune system by acetaldehyde adducts also contributes to liver damage.

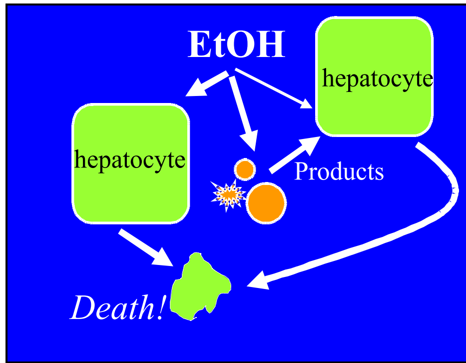
Chronic exposure to ethanol induces ethanol-metabolizing enzyme systems, particularly microsomal cytochrome P450 isoforms such as Cyp2E1, that generate large amounts of potentially toxic reactive oxygen species (ROS), as well as acetaldehyde, during ethanol oxidation (slide 10). The combination of increased acetaldehyde and ROS (such as the 1-hydroxyethyl radical, superoxide radical and H_2O_2) that result from Cyp2E1 induction are thought to explain why habitual alcohol ingestion is more likely to result in liver damage than sporadic alcohol consumption. Similarly, induction of Cyp2E1 by drugs (e.g., carbon tetrachloride, isoniazid, acetaminophen) or certain diets (high unsaturated fats, high iron, low carbohydrates) might explain why these factors potentiate alcoholic liver damage (slide 11). Other observations also support the importance of Cyp2E1 induction in the pathogenesis of ethanol hepatotoxicity.

In patients and baboons, the zonal distribution of Cyp2E1 expression matches the zonal distribution of alcohol-induced liver injury. Cyp2E1 expression and activity are also induced in

rat liver during continuous intragastric administration of ethanol and correlate with lipid peroxidation and liver damage in that model. Moreover, unlike normal cultured hepatocytes which have little endogenous Cyp2E1 activity and are relatively insensitive to ethanol-induced lethality, hepatocyte cell lines that have been engineered to over-express Cyp2E1 die when exposed to ethanol. On the other hand, other data suggest that the induction of Cyp2E1, per se, is not sufficient to cause alcoholic liver damage (slide 11). For example, in rats, high carbohydrate diets inhibit ethanol induction of Cyp2E1 but do not prevent alcohol-induced fatty liver. Moreover, treatment of rats that are receiving continuous intragastric infusions of ethanol with gadolinium chloride, an agent that inhibits Kupffer cells, prevents steatohepatitis despite ethanol-related Cyp2E1 induction.

These observations demonstrate that super-induction of Cyp2E1 is not sufficient to cause alcoholic liver disease, even when large amounts of alcohol are present, and suggest that other factors must also be involved. Potentially pertinent in this regard is growing evidence that the ingestion of polyunsaturated fatty acids (PUFAs) potentiates alcohol-related liver damage in several experimental model systems. Peroxisomes are known to play an important role in PUFA metabolism and ethanol is also a substrate for peroxisomal catalase, which can generate potentially toxic molecules. Diets enriched with unsaturated fatty acids, such as linoleic or oleic acid, or situations (e.g., obesity, type 2 diabetes mellitus) that increase circulating levels of free fatty acids also increase the DNA binding activity of the peroxisome proliferator alpha receptor (PPARa) in the livers of rats and mice. Increases in PPARa activity, in turn, induce hepatic expression of the PPARa-regulated microsomal enzymes, Cyp4A1 and Cyp4A2. Thus, it is conceivable that increases in these other P450 isoenzymes might "substitute" for Cyp2E1 induction and produce equally noxious outcomes as those that have been attributed to Cyp2E1 activation.

Indeed, increased Cyp4A-mediated omega-oxidation of long chain fatty acids to toxic dicarboxcylic acids is one of the mechanisms that has been proposed to explain the association of steatohepatitis with increased PPARa activity in fatty acyl CoA oxidase (AOX)-null mice.

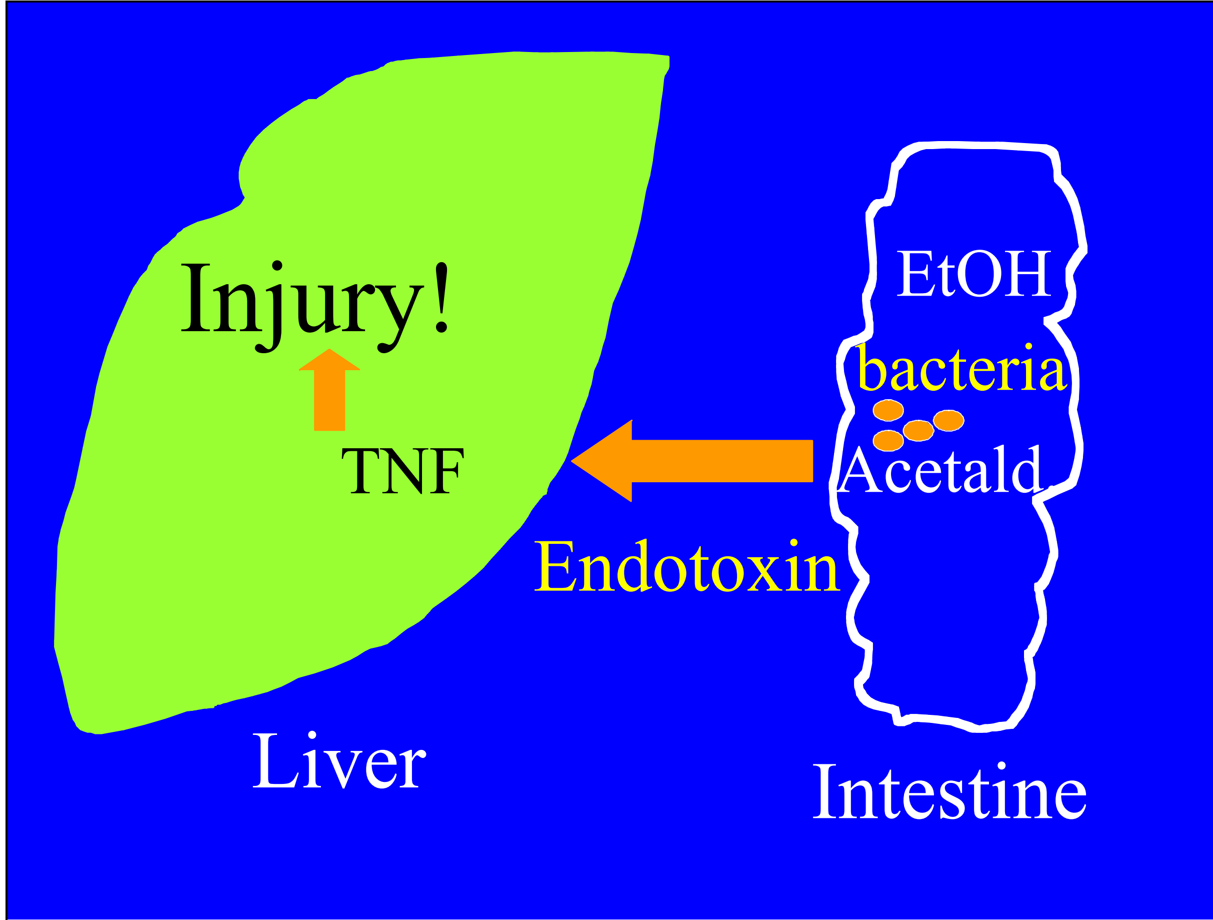


[Slide 9.]

Hepatocyte injury as an indirect result of ethanol's primary effects on other cells (slides 9, 12 - 21)

Hepatocytes injury might not require the direct interaction of ethanol (or its metabolites) with hepatocytes. Indeed, anecdotal clinical observations and a growing body of evidence in experimental animals supports the possibility that alcohol-related hepatotoxicity occurs indirectly, i.e., as a result of products that are released when other tissues are effected by alcohol

Slide 12.



For example, studies in small animal models of alcoholic liver disease indicate that intestinally-derived products, such as bacterial endotoxins, are critical for liver injury because various treatments that decontaminate the intestine inhibit alcohol from damaging the liver. At least in these animal models, endotoxin-inducible cytokines, such as tumor necrosis factor (TNF) a, are probably the direct mediators of alcohol hepatotoxicity, because alcohol feeding does not cause as much liver damage when TNFa is neutralized by antibodies or when the genes that encode type 1 TNF receptors have been disrupted.

However, while these discoveries are quite exciting and suggest novel therapeutic targets, many questions remain unanswered. For example, first, given that all of us have bacterial endotoxins in our intestines, exactly how does chronic alcohol ingestion lead to increased concentrations of endotoxin in portal or systemic blood? Second, what is the evidence that endotoxin or endotoxin-induced cytokines injure hepatocytes and how does this occur? Third, how might chronic alcohol ingestion increase hepatocyte vulnerability to endotoxin lethality? The next part of the lecture will consider these issues briefly.

Slide 13.

Indirect Hepatotoxicity

Pro's

- Risk factors for bacterial translocation in liver disease
- ⬆ endotoxin, TNF , cytokines in patients with steatohepatitis
- Experimental animal data

Con's

- Co-location of EtOH/bacteria
- Usual TNF effects on hepatocytes

Alcohol and Intestinal Endotoxin

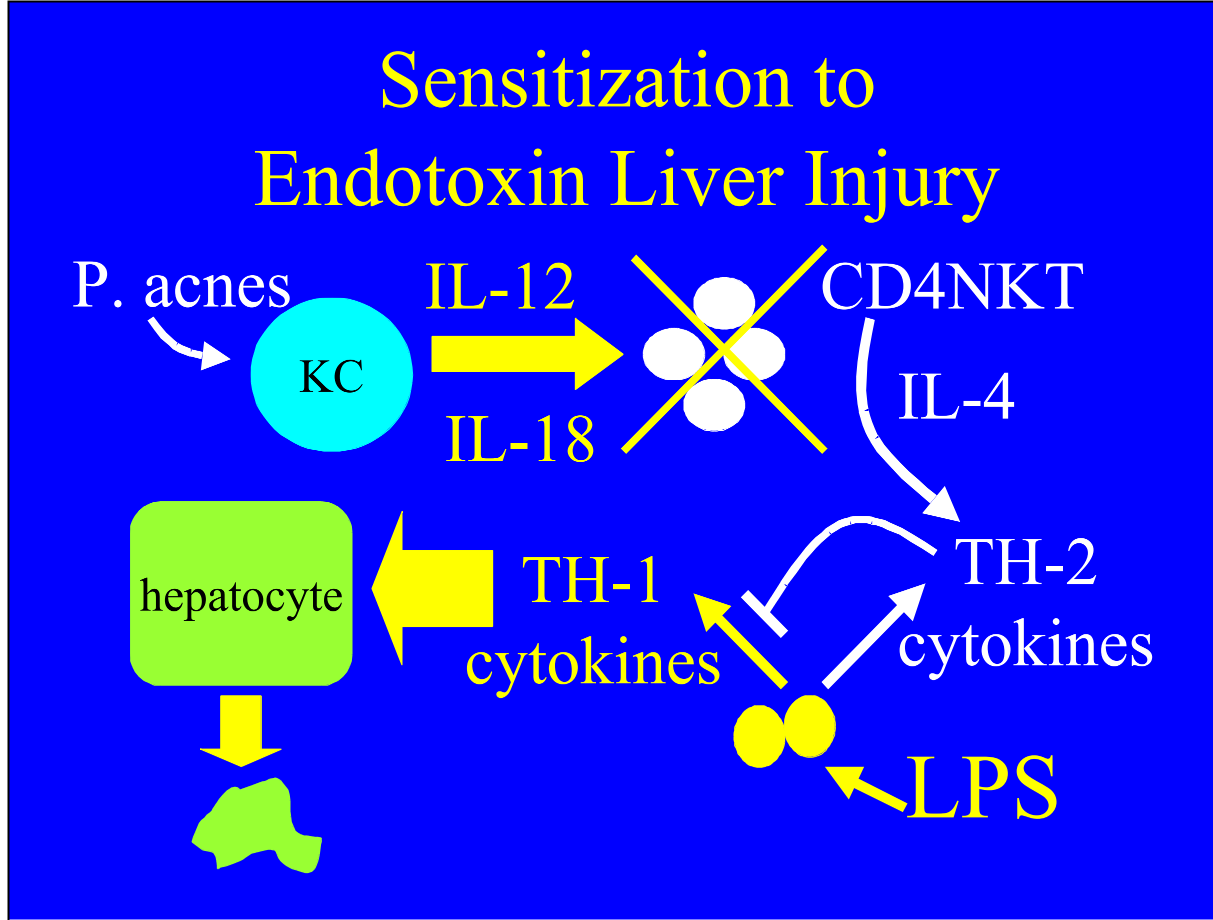
Several observations in patients with clinically severe alcoholic steatohepatitis support the possibility that increased exposure to gut-derived bacterial products increases the severity of alcohol-related liver damage. For example, florid features of decompensated alcoholic liver disease often become manifest in clinical settings that are known to promote intestinal bacterial translocation, such as malnutrition, pancreatitis, or hypotension related to gastrointestinal hemorrhage or cardiac dysfunction. Moreover, increased concentrations of endotoxin and the endotoxin-inducible cytokines, TNFa) and IL-1, and other TNF-inducible cytokines, including IL-6 and IL-8, have been reported in patients with alcoholic steatohepatitis.

Indeed, several groups have noted an inverse correlation between the degree of cytokine elevation and the severity of alcoholic liver disease. The most direct evidence that gut-derived bacterial products are responsible for the induction of the proinflammatory cytokines that cause liver injury comes from experimental animals. When rats are treated with antibiotics or lactobacillus to decontaminate the intestine while receiving alcohol-containing diets, steatohepatitis does not develop. Moreover, in these animal models, the expected increase in TNFa) and IL-6 does not occur in hepatic macrophages.

Treatment with gadolinium chloride, an agent that inhibits Kupffer cells, also inhibits alcoholic liver damage in rats, as does treatment with neutralizing anti-TNF antibodies. Finally, mice that are genetically deficient in type 1 TNF receptors are completely protected from alcoholic liver disease. Taken together, all of these results suggest that chronic ingestion of alcohol promotes the escape of endotoxin from the intestinal lumen; in turn, extra-intestinal endotoxin induces cytokine production by liver nonparenchymal cells, and at least one of these cytokines (i.e., TNFa) injures hepatocytes.

However, there are several conceptual difficulties with this model of alcoholic liver disease. First, the bacteria that are the major sources of endotoxin typically reside in the colon, yet most alcohol is absorbed from the proximal small intestine and metabolized in the liver, and thus, should not reach the colon. Thus, it is difficult to understand how, in the absence of overt malnutrition or hypotension, chronic alcohol ingestion enhances the absorption of endotoxin from the colon. One possibility is that high blood ethanol concentrations cause increased colonic permeability. Alternatively, perhaps chronic ingestion of ethanol (or some ethanol-related change in dietary composition) alters intestinal motility, promoting stasis in the upper intestinal tract, which favors intestinal colonization and over-growth with colonic bacterial strains. In addition, given that certain strains of colonic bacteria can actually produce ethanol during the fermentation of dietary carbohydrates, as well as metabolize ethanol to acetaldehyde, ethanol-related changes in the bacterial flora might promote the accumulation of high concentrations of acetaldehyde near the intestinal epithelial surface. The toxic effects of acetaldehyde on the intestinal mucosa might increase intestinal permeability, permitting the escape of enteric bacteria. To my knowledge, this concept has not been fully evaluated in either experimental animals or humans, but hopefully, this discussion will stimulate investigation of this issue.

Slide 14.



Alcohol and Sensitization to Endotoxin Liver Injury

Another conceptual problem is an overwhelming amount of experimental evidence which indicates that hepatocytes are not usually killed either by endotoxin or the endotoxin-induced cytokine, TNFa. In fact, TNFa acts as a co-mitogen for normal hepatocytes, promoting hepatocyte proliferation, rather than cell death, both *in vivo* and *in vitro*. On the other hand, it is clear that in certain situations, including chronic alcohol exposure, hepatocytes become very vulnerable to TNF-induced lethality. In order to understand why this occurs, it is important to consider the role of factors that are produced outside of hepatocytes, as well as factors that are produced within hepatocytes. First we will review, briefly, the knowledge about how extra-hepatocyte factors regulate hepatic sensitivity to endotoxin-induced damage.

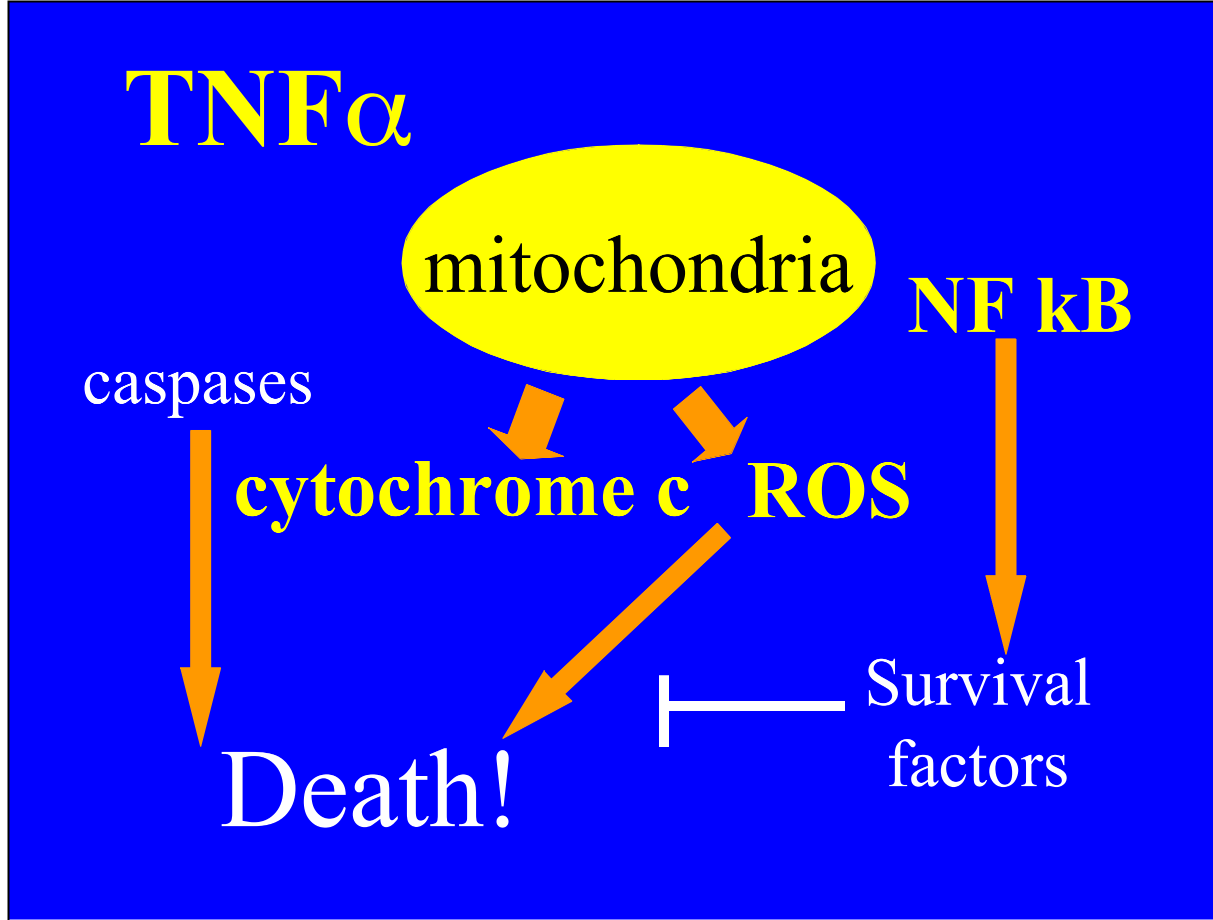
Most of this information has been obtained by studying a model of endotoxin-sensitization that is produced by infecting healthy rats with *Propionibacterium acnes*. *P. acnes* itself does not damage the liver. However, it activates hepatic macrophages (Kupffer cells) to produce interleukin (IL)-12 and IL-18. These cytokines cooperate to selectively deplete a certain sub-population of liver lymphocytes, the CD4+NK T cells. These cells are the principal source of hepatic IL-4, which modulates the balance between TH-1 (pro-inflammatory) and TH-2 (anti-inflammatory) cytokine production in the liver. When IL-4 is deficient, inflammatory signals, such as endotoxin, result in an unconstrained pro-inflammatory response because the production

of anti-inflammatory cytokines is inhibited. Thus, pro-inflammatory cytokines, such as interferon g, accumulate because hepatic production of anti-inflammatory cytokines, such as IL-10, is deficient.

The possibility that a similar process might be occurring during alcohol-induced liver injury has not been examined, but merits consideration, particularly since recent work has identified many similarities between the *P. acnes* model and obesity-related nonalcoholic steatohepatitis. Indeed, ethanol-related changes in immune cells and TNF-regulatory cytokines might explain previous observations that the Kupffer cell depleting agent, gadolinium chloride, prevents alcohol-induced liver damage in rats, despite other evidence that gadolinium increases hepatic TNFa expression.

Even in the absence of gadolinium chloride pre-treatment, there is now solid evidence in experimental animals that chronic alcohol ingestion increases the expression of TNFa and TNF receptors in the liver. Assuming that future work will demonstrate that chronic alcohol consumption also leads to other alterations in the cytokine microenvironment, it remains unclear how these changes in the local cytokine milieu might enhance hepatocyte vulnerability to TNF-induced lethality. In order to understand this, we must consider the cellular and molecular responses that determine the viability of cells that have been exposed to TNFa.

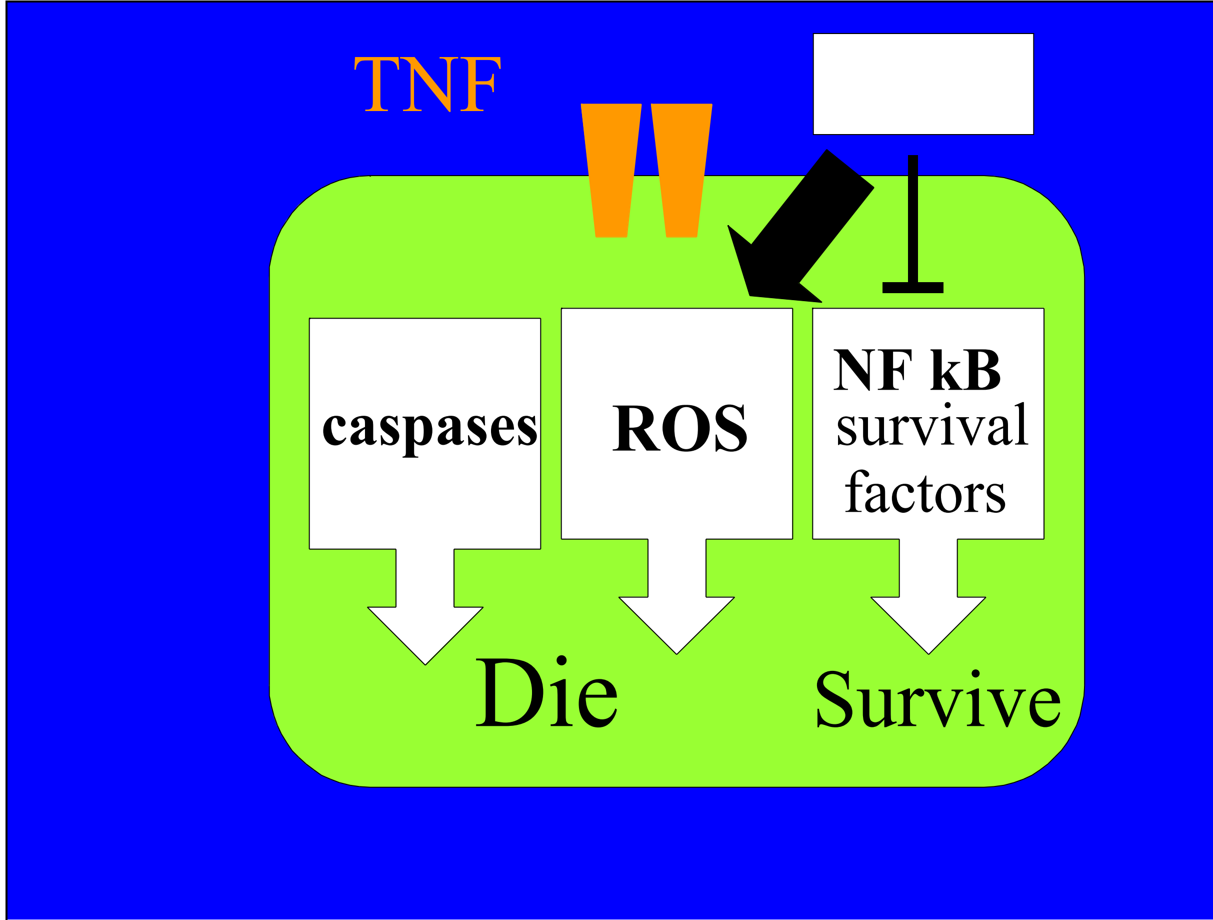
Slide 15.



TNFa-Modulation of Hepatocyte Viability (slides 16-22)

A detailed discussion of TNFa signal transduction can be found in several recent reviews and will not be repeated here. Briefly, mitochondria are now known to be critical targets for TNFa. In cells that are sensitive to TNF killing, the mitochondrial release of reactive oxygen species (ROS) and cytochrome c increase within minutes of TNFa exposure. This is quickly followed by the activation of effector caspases, including caspase 3, and completion of cellular apoptosis within an hour. TNFa also evokes cellular responses that inhibit apoptosis. The activation of the redox-sensitive transcription factor, NF kappa B, plays a central role in the TNF-survival response because various experimental strategies that abrogate NF kappa induction potentiate TNF lethality. Presumably, NF kappa B activation prevents apoptosis by increasing the transcription of survival genes, such as anti-apoptotic bcl-2 family members, inducible nitric oxide synthase (iNOS), and manganese superoxide dismutase (MnSOD), that limit mitochondrial permeability (Bcl-2), prevent caspase activation (NO), and detoxify superoxide anion (MnSOD). The necessity for cells to synthesis survival factors in order to remain viable after TNFa exposure probably explains why pharmacologic inhibitors of RNA and protein synthesis are used classically to sensitize hepatocytes to TNFa toxicity.

Slide 16.

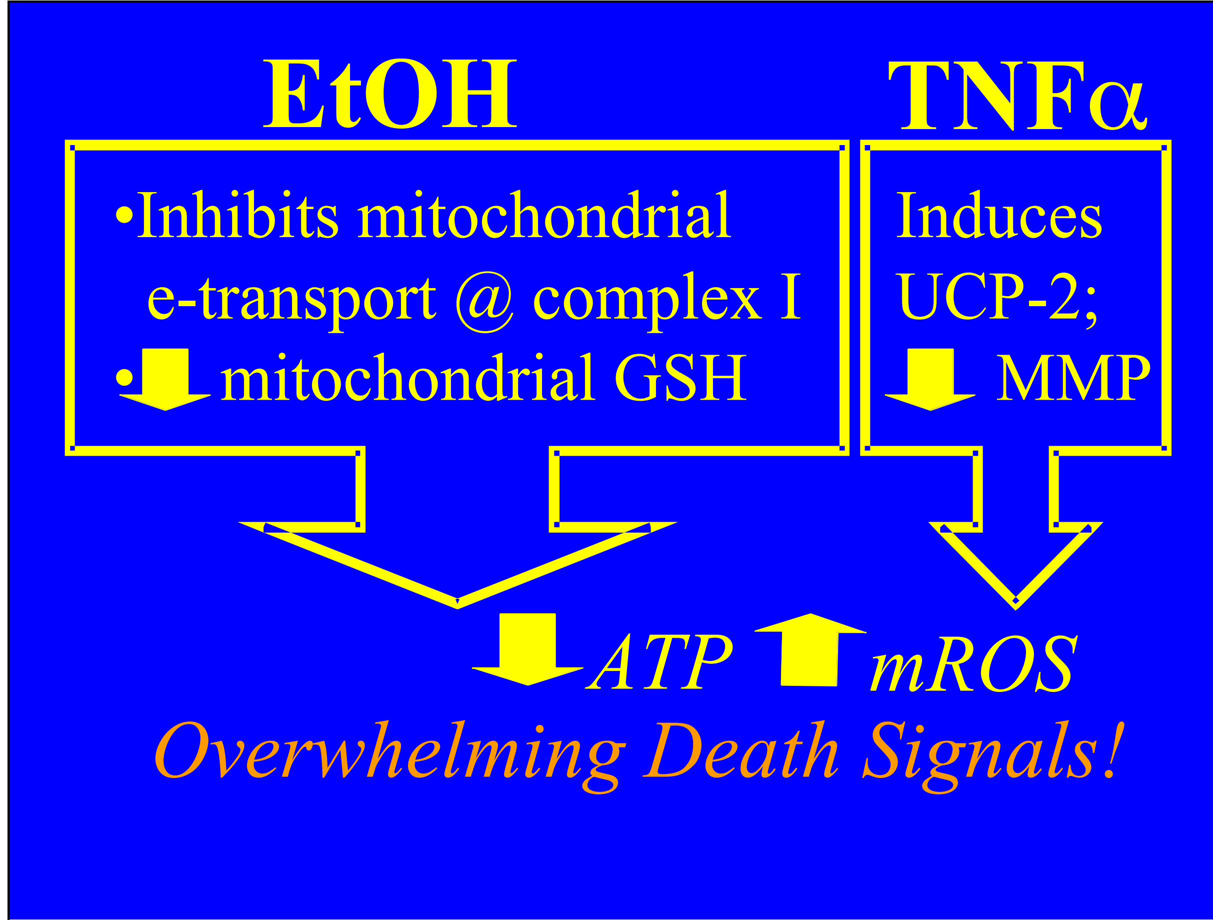


There is experimental evidence that chronic consumption of ethanol-containing diets impairs the TNF-related induction of NF kappa B and bcl-xL (an anti-apoptotic Bcl-2 family member) in hepatocytes. This might help to explain why increases in hepatocyte apoptosis have been reported in some models of chronic alcohol consumption.

However, other possibilities must also be considered because, while NF kappa B induction is necessary for cells to escape TNF-initiated apoptosis, it is not always sufficient to assure survival. Indeed, increases in NF kappa B-DNA binding activity precede apoptosis in some types of cells, including hepatocytes. The latter observation indicates that even when the NF kappa B-induced survival response occurs, protection from lethality is incomplete.

It is even conceivable that any transient survival advantage that accrues from adaptation to TNFa exposure might be off-set by an increased vulnerability to other insults. Stated another way, just as failure to adapt to TNFa might be fatal, adaptations to TNFa might also impair cellular viability.

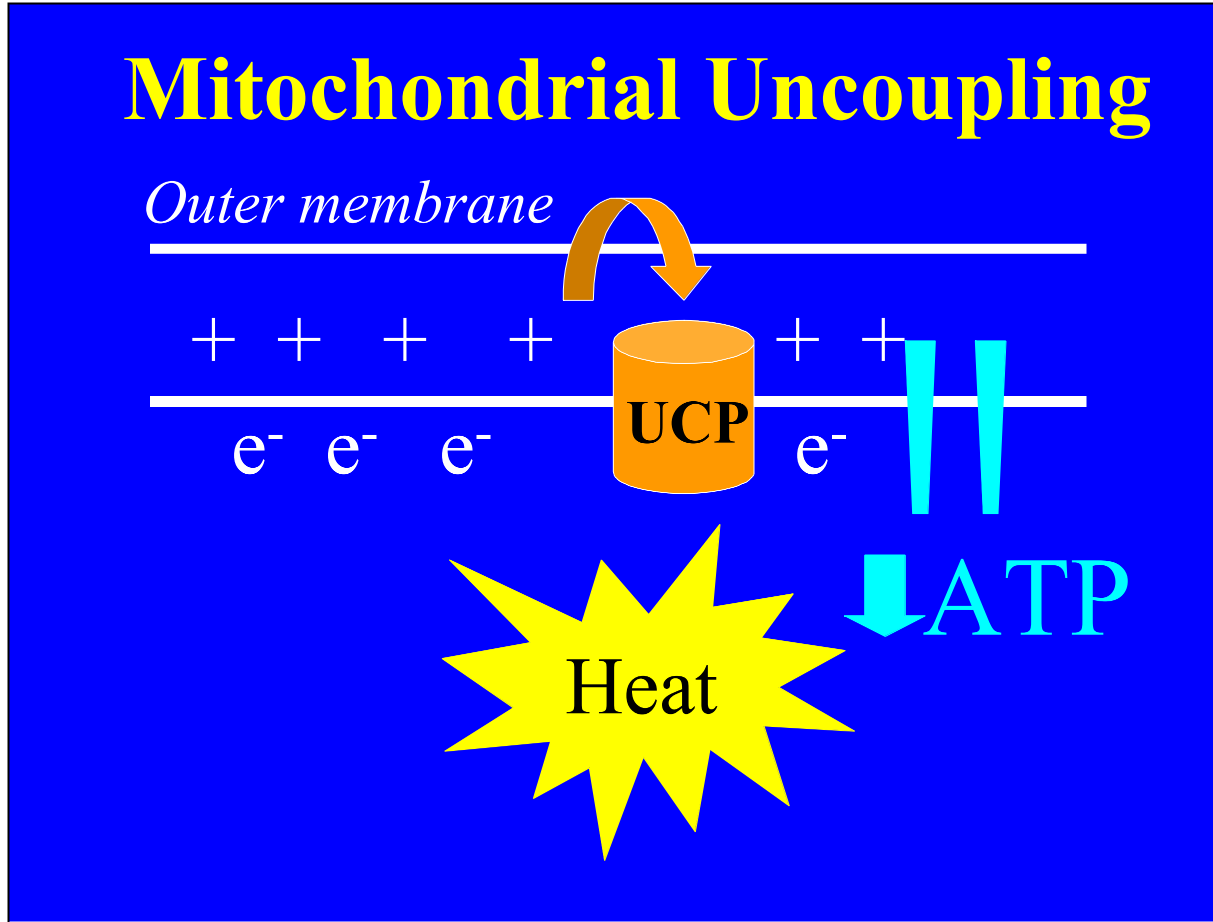
Slide 17.



The latter possibility is supported by a careful examination of hepatocytes in fatty livers, which are known to be exquisitely sensitive to various insults that partially depolarize hepatocyte mitochondria. Although fatty hepatocytes are generally viable, they have mitochondrial ultrastructural abnormalities (swelling, distruption of cristae) which suggest increased mitochondrial permeability. Mitochondrial function is also disturbed, as shown by inhibition of mitochondrial electron transport by complex 1, decreased GSH stores, and increased ROS release. Moreover, there is evidence that apoptotic signal transduction pathways have been initiated, as demonstrated by increased hepatocyte expression of Bcl-2-related proteins.

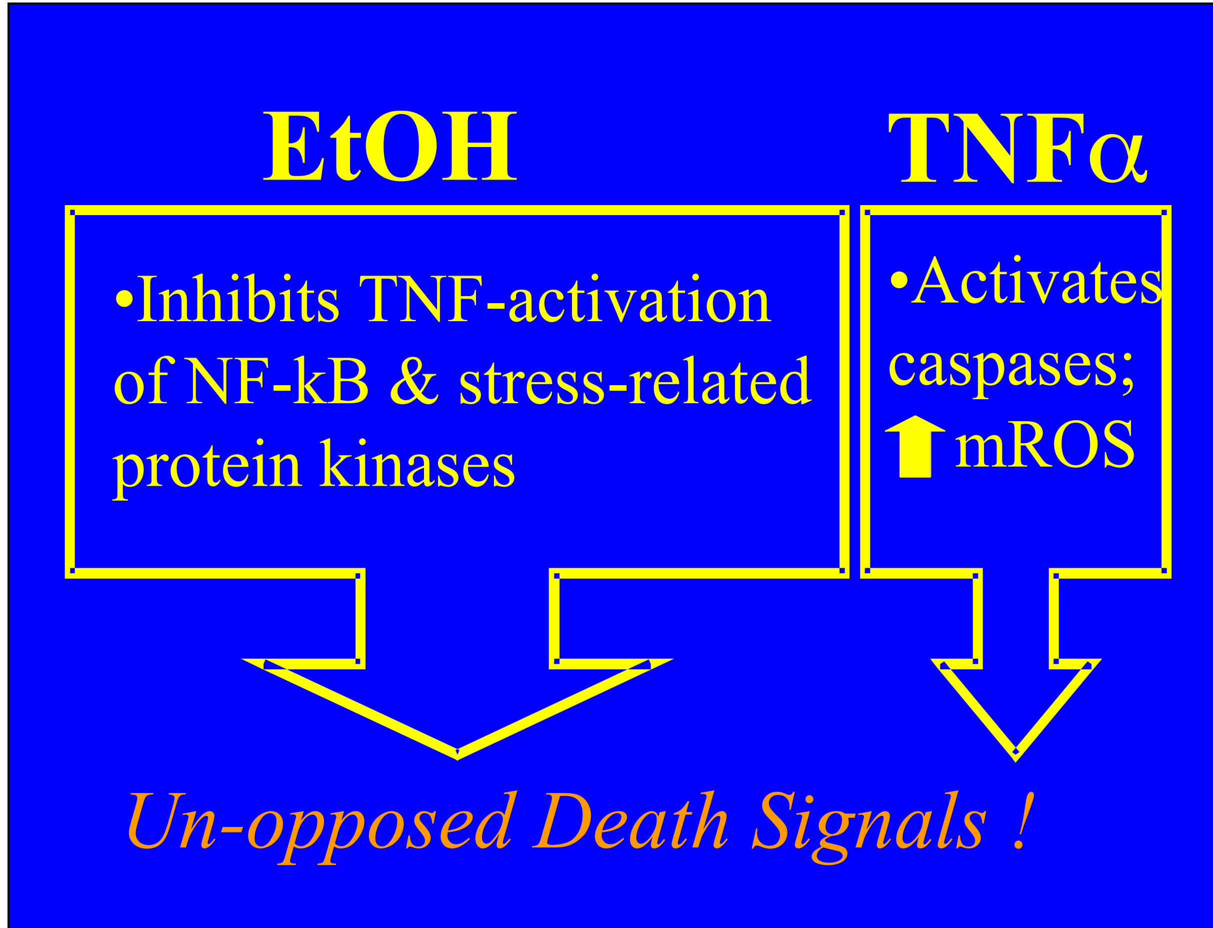
Surprisingly, however, when viable primary hepatocytes that were exposed to ethanol *in vivo* are challenged by TNFa *in vitro*, death occurs as a result of necrosis (not apoptosis). Such necrosis might result, at least partially, from ethanol-related depletion of mitochondrial GSH, which limits detoxification of TNF-induced ROS). Indeed, agents that replenish mitochondrial GSH stores are somewhat protective. However, necrosis is ultimately the consequence of cellular ATP depletion, and there is human, animal and cell culture data which indicate that chronic ethanol exposure reduces hepatocyte ATP stores.

Slide 18.



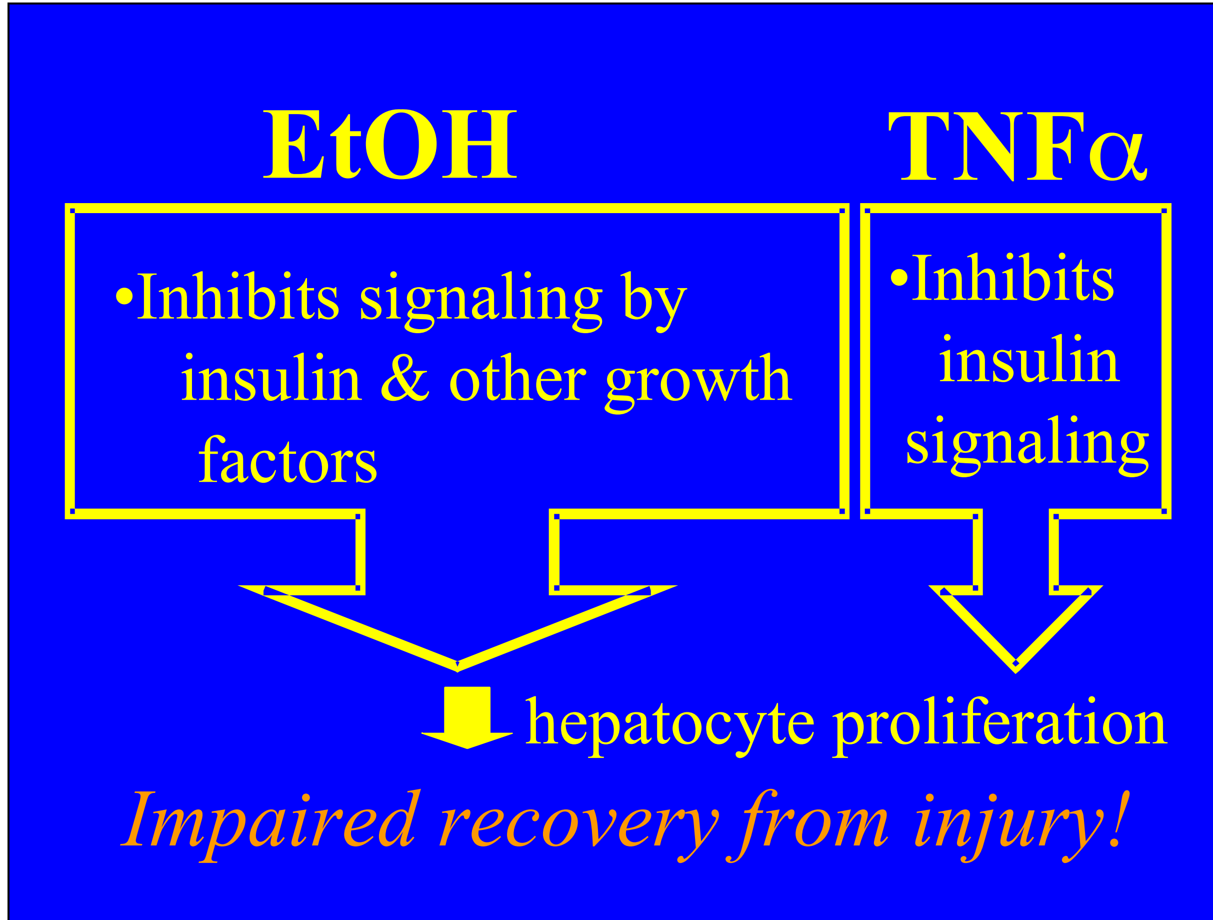
In this regard it is interesting to note that TNFa up-regulates hepatocyte expression of an inner mitochondrial membrane protein, uncoupling protein (UCP)-2, which partially dissipates the proton gradient across the inner mitochondrial membrane. Increases in UCP-2 are not fatal per se, but do reduce the efficiency of mitochondrial ATP synthesis and, thus, are predicted to potentiate necrosis when UCP-2 expressing cells are challenged by other insults (e.g., ethanol, hypoxia) that interfere with electron transport chain activity (slide 17). The latter suggests another molecular mechanism that might contribute to the synergy between ethanol- and TNF-induced hepatotoxicity.

Slide 19.



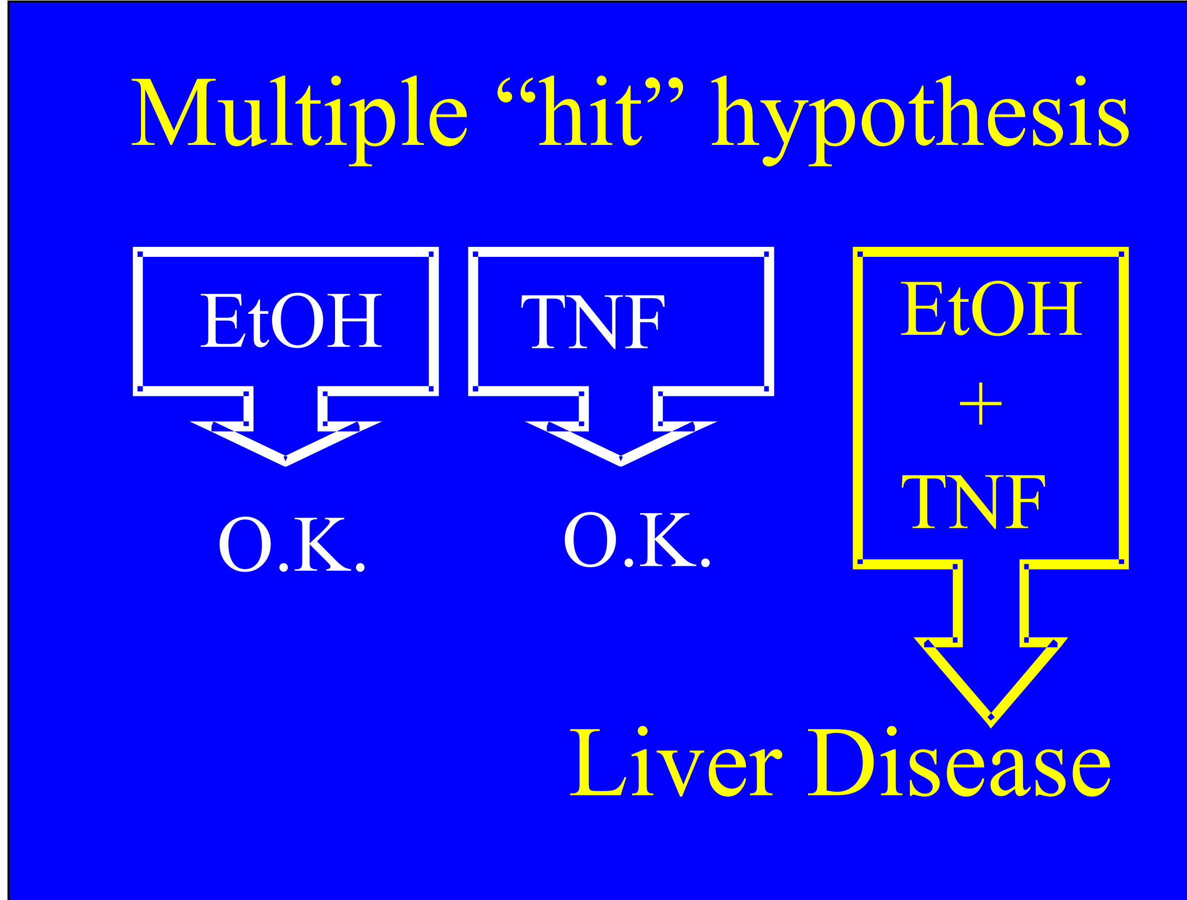
Thus, there are at least two ways that ethanol and TNFa might interact to kill hepatocytes: 1st , the cumulative actions of ethanol and TNFa on hepatocyte mitochondria might produce overwhelming ROS release and ATP depletion and 2nd, lethality results because ethanol has inhibited normal cellular anti-oxidant and anti-apoptotic defenses.

Slide 20.



Finally, while much attention is being focused on the TNFa signaling pathways that lead to cell death, we must not forget that this cytokine can also interrupt the viability signals that are initiated by growth factors, such as insulin, that hepatocytes require for survival.

Slide 21.



The importance of TNFa in the pathogenesis of insulin-resistance is well-recognized in human beings and experimental animals with obesity and type 2 diabetes. It is known that ethanol also interferes with the propagation of signals from hepatocyte insulin receptors, and inhibition of insulin signaling is thought to be important for the anti-proliferative actions of ethanol. However, it is not clear if ethanol-associated insulin-resistance is mediated by ethanol-induction of TNFa. Insulin-resistance appears to play a major role in the pathogenesis of nonalcoholic (i.e., obesity and diabetes-related) fatty liver disease because, in certain animal models, the liver pathology is decreased by various treatments that improve insulin-sensitivity. However, the molecular mechanisms that benefit the liver are uncertain and currently, it is not known if ethanol-related inhibition of insulin signaling contributes to alcoholic liver damage. Never-the-less, it is likely that interactions between ethanol and factors (such as TNFa and insulin) that are produced by other cells cooperate to damage the liver. This model is consistent with the clinical observations which indicate that multiple "hits" are required to develop serious liver damage from alcohol exposure

Slide 22.

Therapy

Rx	Efficacy	
	Patients	Animals
Abstinence	Y(incomplete)	Y
Nutrition	Y/N	??
Antibiotics	??	Y
Anti-TNF	??(steroids)	Y
Anti-oxidants	Maybe	Y
Insulin sensitizers	??	??

Therapy for Alcoholic Liver Disease

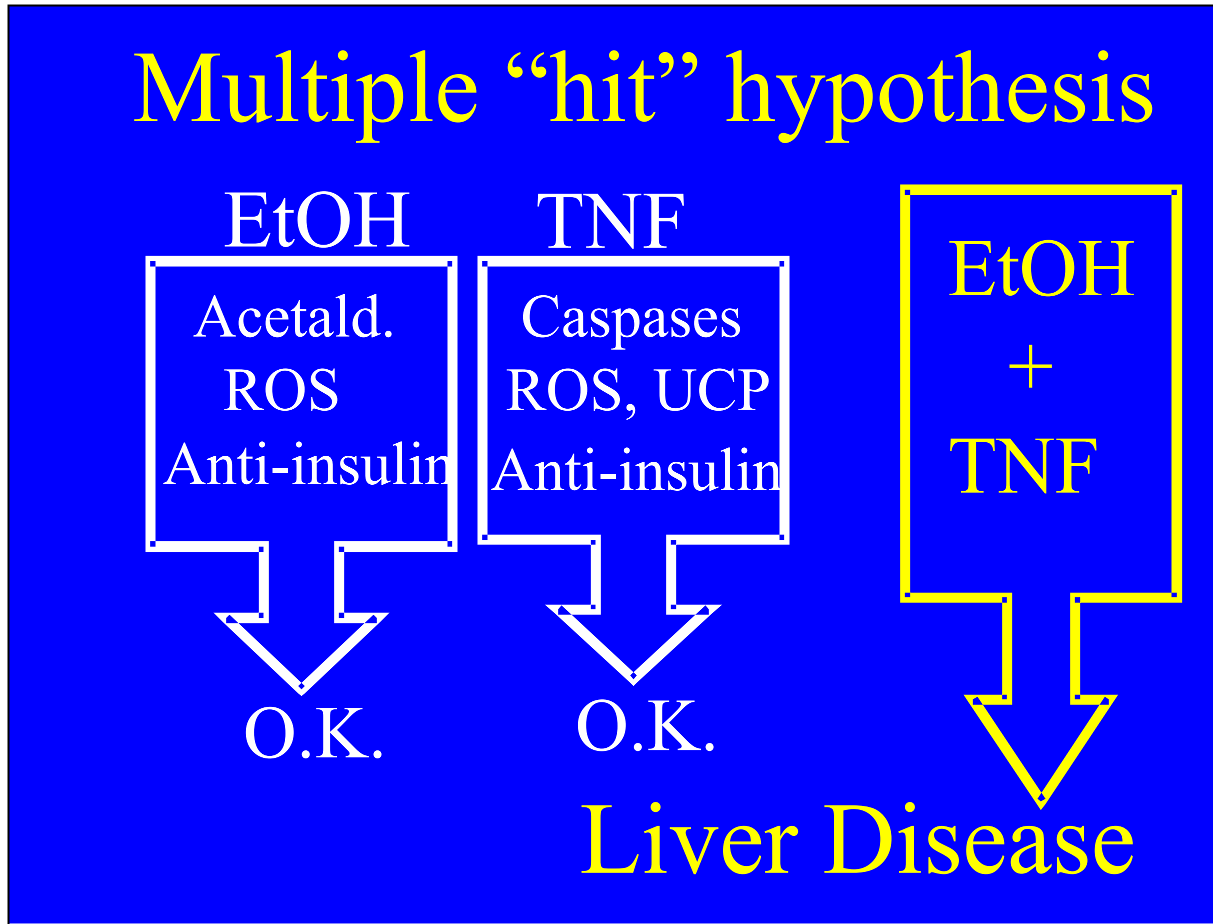
Abstinence from alcohol is a central component of treatment for all stages of alcohol-induced liver disease. Indeed, sobriety improves the survival of both non-cirrhotic and cirrhotic patients with alcoholic liver damage. However, abstinence does not assure a good outcome for all patients with alcoholic liver injury. Complete recovery from hepatic steatosis occurs within 1-.2 weeks of discontinuing alcohol ingestion. Liver damage resolves much more gradually (over months) in a minority of patients with alcoholic steatohepatitis. However, in almost 90% of patients who stop drinking after developing steatohepatitis, hepatic inflammation and injury persist. At least one quarter of these individuals become cirrhotic within 5 years.

Efforts to optimize caloric intake to achieve a positive nitrogen balance is about the only other intervention that has been consistently associated with improved liver tests and protein balance in patients with alcoholic liver injury. However, such results are difficult to interpret because it might be argued that the former is a consequence (rather than a cause) of the latter. It remains possible that manipulation of diet composition will be a useful strategy for treating alcoholic liver disease. For example, it has been reported that diets enriched with saturated fatty acids decrease alcohol-related liver damage in rodent models of alcoholic liver injury.

Fortunately, studies in animal models of alcoholic liver injury are beginning to suggest new therapeutic targets. In experimental animals, various strategies that decrease the absorption of intestinal endotoxin or which prevent increases in the activity of TNFa, an endotoxin-inducible cytokine, inhibit alcohol-induced liver disease. However, apart from the proven utility of corticosteroids in highly-selected subsets of patients with severely decompensated steatohepatitis, there is little information about the efficacy of any other anti-inflammatory/cytokine modulatory treatments in the prevention or treatment of alcoholic liver disease in humans.

Increased production of reactive oxygen species by hepatic mitochondria and microsomes occurs in experimental models of alcoholic liver damage. Treatment with various anti-oxidants decreases liver injury in these systems. Benefits have been inconsistent in the small groups of patients who have been treated with similar agents. Precursors of methionine, including S-adenosyl-methionine and phosphatidylcholine, are most promising membrane-stabilizing anti-oxidants, and larger studies with these agents are underway. As mentioned earlier, treatments that improve hepatic insulin-resistance reverse nonalcoholic fatty liver disease in some animal models of that disease. However, it is not known if insulin-resistance is important in the pathogenesis of alcoholic liver injury. Moreover, enthusiasm for treatment with the most promising insulin-sensitizing agents is tempered by growing evidence that at least one of these (i.e., troglitazone) causes ideosyncratic acute liver failure.

Slide 23.



Multiple mechanisms are likely to be involved in the pathogenesis of alcoholic liver injury. The metabolism of alcohol by hepatocyte enzyme systems probably contributes to hepatotoxicity by generating reactive metabolites and oxygen species that damage vital molecules and tax hepatocyte defense mechanisms. However, these responses are generally not sufficient to kill hepatocytes, as demonstrated by observations that serious liver damage is infrequent in most humans and experimental animals that consume large amounts of alcohol for long periods of time. Indeed, work in animal models of alcoholic liver injury indicates that TNFa, a proinflammatory cytokine, is necessary for alcohol to injure the liver. However, this finding is also curious because TNFa does not usually kill hepatocytes. Thus, although the specific mechanisms remain poorly understood, it is likely that TNFa and ethanol cooperate to produce liver injury.

Emerging evidence suggests that chronic alcohol consumption inhibits some of the protective and proliferative responses that normally occur in hepatocytes that have been exposed to TNFa. In addition, alcohol and TNFa also interfere with the actions of growth and viability factors, such as insulin. The cumulative effects of these processes cause hepatocyte death while impairing the liver's normally robust regenerative response, and then, serious liver damage occurs.

References

Epidemiology of Alcoholic Liver Disease
(SLIDES 1-3)

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Histologic Spectrum of Alcoholic Fatty Liver Diseases
(SLIDE 4)

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(SLIDE 5)

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Clinical Features and Prognosis of Alcoholic Liver Disease
(SLIDES 6 -8)

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