ACUTE LIVER FAILURE

"BE PUBLISHED OR PERISH"

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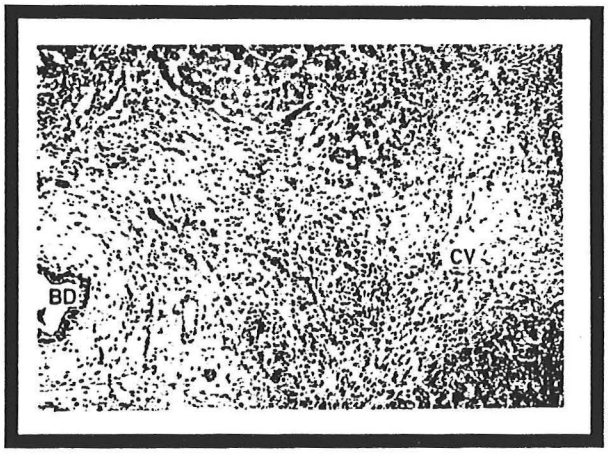

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Introduction

Few diseases in medicine are more dramatic or devastating than acute liver failure (ALF). In this condition, severe liver cell dysfunction strikes previously well individuals suddenly, and only a fraction survive. Acute liver failure embraces a great variety of conditions whose common thread is loss of hepatocyte function, usually the result of massive necrosis. Clinically, the disease is characterized by the onset of coma and a coagulopathy. Histologically, the liver is the initial site of massive destruction and chaos, regardless of the cause. This loss of hepatocyte integrity sets in motion a multi-organ response which becomes the disease itself, and leads to death in some instances even when the liver is recovering. Many patients die within two or three days of hospitalization, making the frequently used term "fulminant hepatitis" particularly apt.

Two representative cases illustrate the dramatic changes that may occur.

Case 1

This 17 yr old high school student was referred from a nearby hospital for weakness and lethargy of five days duration. The patient had been noted to be listless and "lying around the house" for the five days before her mother sought medical attention. She was thought to be febrile but her temperature had not been taken. On the day prior to admission, she was noted to be "talking out of her head," calling for her father who was dead. There was no known history of depression, viral illness or toxin exposure. Acetaminophen was specifically denied. No other family members were ill.

On exam: T 100^{o} C, P 100, BP 120/80, RR 34
Delirious, progressing to grade 3 coma, marked icterus, well-nourished.
Lungs clear, Heart RSR
Liver 3-4 cm dullness, no splenomegaly or ascites
Extremities purposeless movements, no flap, no edema

Her initial labs included: Bilirubin 68 mg/dl, AST 438, ALT 1210, Prothrombin time 24 sec, Cr 1.9 mg/dl, glucose 48, pH 7.48, pCO2 34, pO2 77. Anti-HBs pos, anti-HBc pos, acetaminophen level on day 4 was 7.6 µg/dl, ceruloplasmin 24 mg/dl.

By the third hospital day, the patient appeared more alert and the PT had diminished to 18.6 sec. However, over a five minute period during the morning hours, she developed apnea and fixed dilated pupils, and died on the sixth hospital day.

Autopsy findings disclosed only a somewhat diminished liver size (1340 gm) with evidence of severe centrilobular necrosis, plus a bronchopneumonia. The brain was not examined.

Case 2

This 60 yr old pathologist was admitted in transfer by ambulance for a PT of 61 sec. After two weeks of prodromal symptoms including fever, fatigue and RUQ pain, he noted jaundice three days pta. During the prdromal phase he had taken 2 extra strength Tylenol® capsules every four hours for the RUQ pain. On the evening prior to transfer he was admitted to his own hospital weak,

diaphoretic and dyspneic. Lab values included an ALT of 8080 IU/L, PT 61 sec, pH 7.15, and transfer was arranged.

On transfer, he was cold, clammy and ashen yellow in color but alert.

T 100.2^{0} C, BP 80 sys, P 118, rising to 148 on sitting, RR 28

Abnormal physical findings were limited to the abdomen where there was moderate abdominal distension, mostly gaseous, and no detectable liver dullness.

Intravenous fluids restored BP and corrected the acidosis. By the 2nd hospital day however, the patient had slipped to grade 3 coma, and was responsive only to strong stimuli. Large volumes of fluid were necessary to maintain urine output. By the third hospital day, he was unresponsive, with dilated but reactive pupils. Because of decerebrate posturing, and further pupillary dilation, mannitol was given. By the following morning he was calm and occasionally minimally responsive. Over the next several days, mental status improved slowly, despite the development of *E. coli* bacteremia thought secondary to Foley catheter placement.

Labs	8/6	8/10	8/15	8/20	9/3
Bilirubin	1.5	9.5	20.8	35	13.8
ALT	1527	8080	200	92	208
PT	?	61	17	14.5	14

He went on to full recovery, and after two months was back at work part-time.

Acute liver failure is defined as altered mental status and coagulopathy following an illness of less than 26 weeks, and usually less than eight weeks. A variety of terms have been applied to this condition, the most common being fulminant hepatic failure (FHF), as suggested by Trey and Davidson in 1970.[1] However, the term fulminant hepatic failure is generally applied to those patients who develop hepatic encephalopathy within eight weeks of the onset of clinical illness.[2] Gimson (Kings College Hospital, London, UK) has described a separate entity with many similar but certain unique features termed late onset hepatic failure (LOHF): those cases in whom hepatic encephalopathy develops after eight and before 26 weeks of illness.[3] LOHF resembles the more slowly progressive disease described by Benhamou (Hôpital Beaujon, Paris, France) as subfulminant hepatic failure, although the time intervals differ. For the French, fulminant hepatic failure is defined as those patients with onset of encephalopathy within two weeks of onset of jaundice, a much shorter interval, whereas subfulminant hepatic failure occurs when encephalopathy begins between 2 and 12 weeks after onset of jaundice.[4] Overall, FHF has been the most widely used term to describe this condition. Acute liver failure is now coming into use as an umbrella term, and appears the most suitable, since it encompasses all varieties, including those whose onset is not very abrupt.[2]

Table 1. Terms used for the syndrome of acute liver failure.

Shorter duration	**Longer duration**
Fulminant hepatic failure	Subfulminant hepatic failure
Massive hepatic necrosis	Submassive hepatic necrosis
Fulminant hepatic necrosis	Subacute hepatic necrosis
Acute yellow atrophy	Late-onset hepatic failure
Fulminating hepatic failure	

Needless to say, these definitions may only confuse the student of ALF, but certain generalizations hold true concerning those with slower onset of hepatic insufficiency; LOHF is clearly different in many respects. LOHF is less frequently associated with cerebral edema, for example.

Acute liver failure is uncommon but not rare, approximately 2000 cases occurring in the United States annually, with a mortality approaching 80%. The disease must have been known to the Greeks, since it is said that Euripides' wife and children died of mushroom poisoning. The first medical description was that of Morgagni who described fatal cases of jaundice in 1760, in which the patients' blood became "yellow tinged" and who developed "a kind of perturbation of the mind."[5] Rokitansky was the first to use the term "acute yellow atrophy", in 1842, and this term is still used occasionally, mostly by pathologists, but has largely been abandoned.[6]

In most instances, massive necrosis of hepatocytes has occurred prior to onset of the clinical syndrome; however, hepatocellular failure without necrosis is characteristic of fatty liver of pregnancy and Reye's syndrome, suggesting that actual death of cells is not a universal or essential feature. Regardless of the inciting event, the typical pathological picture is that of coagulative necrosis throughout the hepatic lobule, although certain conditions such as CCl_4 injury or acetaminophen poisoning 'favor' the centrilobular region. By contrast, acute fatty liver is characterized by massive accumulation of microvesicular fat in intact cells, a finding different from the large droplet fat present in the typical patient with fatty metamorphosis secondary to alcohol or poorly controlled diabetes.[7]

Etiology

Overall, viral hepatitis and drug-induced liver injury constitute the majority of cases of acute liver failure, but there are great differences between countries and continents. The common causes of ALF are listed below.

Table 2. Causes of acute liver failure.

Viral hepatitis: A,B,D,E, ?F, HSV
Drug-related liver injury
Toxins: CCl_4, *Amanita*, lead, phosphorus
Vascular: ischemic, veno-occlusive, heat stroke, malignant infiltration
Miscellaneous: Wilson's disease, acute fatty liver of pregnancy

Table 3. Prevalence of the most common etiologies of acute liver failure by country.

	UK	France	USA
Acetaminophen	54(%)	2	?
Acute hepatitis	37	72	60+

Table 4. Breakdown of viral hepatitis subgroups by country.

	UK	France	USA	Greece
HAV	19(%)	7	2	2
HBV	40.5	89	61	74
NANB	40.5	4	37	24

Acetaminophen poisoning with suicidal intent makes up the majority of cases in the United Kingdom, but is relatively rare elsewhere. Variation in other countries reflect in part the types of hepatitis viruses extant and their varying severity. Enterically transmitted non-A, non-B hepatitis, recently identified and termed hepatitis E, is a major cause of ALF in Asia, although virtually unknown in the Western Hemisphere.[8]

Viral Hepatitis

The foremost cause of ALF in the United States and France is acute viral hepatitis (AVH), accounting for up to 72% of all cases. AVH evolves rapidly into hepatic failure in only a small number of cases (<1%), but these serve as a reminder of the potential severity of this relatively benign condition. The reason for the development of ALF in certain individuals is not clear. Host factors as well as virulence and viral load are probably important.[9]

Hepatitis A The self-limited enteric infection typical of the hepatitis A virus (HAV) leads to hepatic failure in only 0.35% of cases, with the risk of development of ALF increasing with age.[9] New evidence that HAV persists in prolonged and severe cases has recently been described; after transplantation for ALF, the liver graft may also be infected.[10] The case fatality rate is 0.14% for all cases of HAV infection attesting to the relatively good prognosis for these patients, with more than 60% surviving (see below). Acute HAV infection is identified by the presence of IgM anti-HAV antibodies. The prevalence of acute infection among intravenous drug users (IVDA) and homosexual men seems to be increased. A recent report cited four examples of fatal fulminant hepatitis A in IVDA's, most of whom had underlying chronic liver disease. Although the underlying disease was usually alcohol-related, the role of other chronic hepatitis viruses could not be excluded.[11]

Hepatitis B The hepatitis B virus (HBV) accounts for the majority of cases of fulminant viral hepatitis in most countries, accounting for more than 70% of cases thought due to viral infection in Greece, but only 16% of cases in Britain.[9] Acute hepatitis B is more likely to evolve into a fulminant than a subfulminant course.[4] The observation that patients with fulminant hepatitis B clear HBV markers more rapidly than those with conventional acute hepatitis B has led to the speculation that an over-active immunological response produces the severe necrosis.[9,12,13] Women seem to be more at risk than men to have acute liver failure, perhaps related to their more exuberant immune response to the virus.[14] As a result, patients may become seronegative for HBsAg during the acute illness, but will still have high titer IgM anti-HBc. These HBsAg-negative cases may make up 1/3 to 1/2 of all fulminant hepatitis B.[15,16] Rapid clearance of virus due to massive immunologic assault on infected cells is an attractive hypothesis, but does not explain the fact that HBsAg-negative cases actually have a more favorable outcome than HBsAg positive ones. The survival rate in HBsAg negative cases was 47% in one large series compared to 17% for those who remained HBsAg positive.[17] Nevertheless, abnormally rapid clearance of viral antigens, including HBeAg and HBV DNA is associated with most cases of fulminant hepatitis B, and core antigen and HBsAg frequently cannot be demonstrated in liver tissue even by sensitive immunoperoxidase methods.[9] Rapid clearance of virus in the setting of ALF is a favorable sign in relation to transplantation, since fulminant hepatitis B patients appear less likely than their chronic hepatitis B counterparts to reinfect the liver graft after transplant.

Variant hepatitis B viruses incapable of secreting the hepatitis B 'e' antigen are associated with fulminant hepatitis B although this remains controversial.[18] The typical clinical picture is rapid progression of acute or chronic hepatitis B in an individual who is HBeAg negative, a paradoxical situation, since HBeAg negativity is usually associated with quiescent disease. The common finding in most cases is that of a single base pair substitution in the HBV genome. This involves the insertion of a stop codon in the precore region of the C gene, preventing production of the soluble secreted HBeAg.[19] Of 18 patients with fulminant hepatitis B seen in two centers (London or Athens), twelve were found to have the HBeAg negative mutant strain, and in those whose serum was subject to DNA sequencing, the identical base pair substitution was identified.[20] The stop codon mutation prevents synthesis and secretion of HBeAg, but does not prevent viral replication.[21] The overall prevalence of HBV mutants has not been described.

Non-A, non-B hepatitis Patients whose ALF is attributed to non-A, non-B hepatitis are those in whom no viral markers are detected and no history of toxin or drug exposure can be found. In this 'wastebasket' group, parenteral exposure is seldom elicited. Most studies have not implicated the hepatitis C virus, although the antibody to hepatitis C might not appear so early in the illness.[25,26] Suspicion of a distinct sporadically-transmitted virus associated with fulminant hepatitis has been raised by these cases. Viral particles resembling toga viruses have been identified by electronmicroscopy in the liver of a single patient with FHF who had returned to England from Africa just before becoming ill.[27] When

she died of recurrent ALF after liver transplantation, similar particles were identified in the transplant liver she had received. This may constitute the best-described case of hepatitis "F"; however, because of the unusual travel history, a unique virus limited to Africa is also a possibility.

Hepatitis D (delta hepatitis, HDV) This passenger virus which travels within an HBsAg envelope can only infect individuals who are chronic HBV carriers or who become simultaneously co-infected with HBV. Intravenous drug abusers are the main reservoir of infection. In the United States, either delta co-infection or super-infection of a carrier is involved in only 10-20% of all B-related hepatitis, but accounts for more than half the cases of ALF in B positive individuals.[22] (These were formerly considered to represent hepatitis B infection, prior to the discovery of the delta agent.) The delta virus is thought to be cytotoxic to liver cells and inhibits HBV replication. For this reason, fulminant superinfection of a carrier (as opposed to co-infection) may be more lethal, since hepatitis B virus is already well established in the carrier patient. It is occasionally necessary to screen HBsAg negative individuals for evidence of (past) delta infection, since inhibition of replication may result in negative HBsAg testing.[9] Delta antigen can be detected in the nuclei of hepatocytes in infected individuals.[23] Unfortunately, in ALF, this is usually determined only at autopsy. A recent report from Taiwan implicates chronic HBV carriers as having an increased incidence of ALF, most of which is not related to delta.[24] Is there yet another passenger virus, or are these individuals simply more prone to acute exacerbation of their chronic disease?

Hepatitis E, an enteric virus which occurs in epidemics due to food or water contamination, primarily in India and in Mexico, has recently been identified. This differs from previous known viruses in causing epidemics in which a high incidence of fulminant hepatitis is seen. The case fatality rate is increased to 40% in pregnant women.[28] Although hepatitis E has not been identified in the United States, serologic tests are just beginning to become available. It is possible that some cases of fulminant non-A, non-B hepatitis may actually be isolated examples of sporadic hepatitis E occurring here at home.

Other viruses Herpes virus, CMV and EBV lead the list of those implicated in an occasional case of fulminant hepatic necrosis. The herpes viruses produce disease usually in association with immunosuppressive therapy.[29,30] ALF is particularly lethal in this group, but can be treated with acyclovir if early identification can be made. Characteristic inclusion bodies are seen in liver tissue, usually at autopsy. Fulminant hepatitis has now been reported in association with herpes viruses 1,2 and 6.[31]

Drugs and Toxins

A wide variety of toxins and therapeutic agents have been responsible for ALF. Virtually all xenobiotics are metabolized at least in part by the liver. Liver injury due to drugs can be divided into two categories: predictable and idiosyncratic. Those agents always cause liver injury in a uniform dose-response fashion have an intrinsic toxic effect on the liver, and a similar pattern of liver injury can be reproduced in animals. Agents in which injury occurs occasionally

or rarely are considered idiosyncratic, and most therapeutic drugs which produce hepatic damage fall in this latter category.

Toxins The fluorinated hydrocarbons, carbon tetrachloride and tetrachlorethane produce centrilobular necrosis in a predictable fashion and cause a similar lesion in renal tubular epithelial cells. Most commonly, toxicity is seen in "glue sniffers" or those exposed to cleaning solvents.[32,33]

Amanita phalloides, the "death cap" mushroom, is still responsible for a significant number of deaths annually in France and in the United States, in amateur mushroom fanciers. The clinical syndrome is quite specific and early identification may be helpful if antidotes are used and if latent hepatic injury can be anticipated.[34] Successful liver transplantation has been performed.[34,35]

Drugs with intrinsic toxicity Acetaminophen (paracetamol) remains the most common agent for suicidal ingestion in Britain, and continues to claim lives annually despite the availability of N-acetylcysteine as an antidote. The clinical syndrome following acute ingestion may be characterized by modest nausea and vomiting or none, followed 24-72 hours later by altered mental status and rapid progression to coma and complications. The acetaminophen metabolic pathway elucidates the reasons for its toxic effects and for the efficacy of sulfhydryl group donors such as cysteamine or N-acetylcysteine.

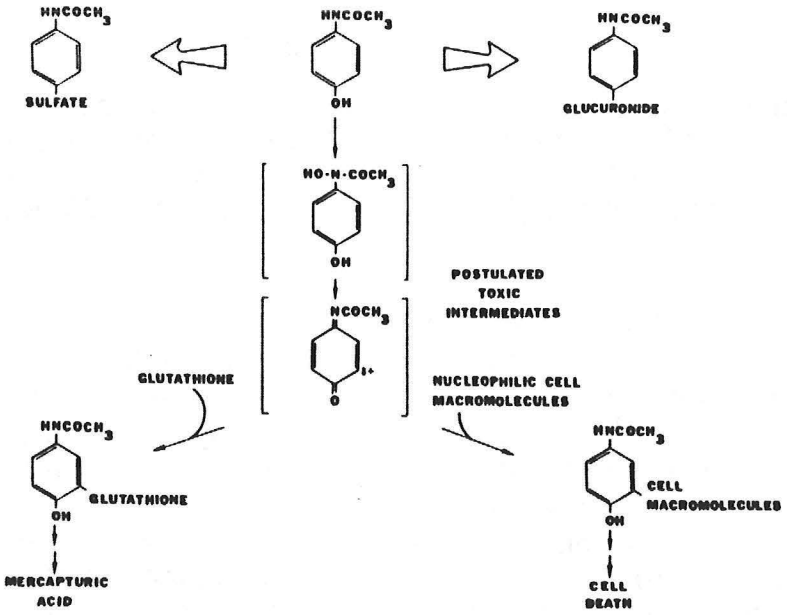

Figure 1. Acetaminophen metabolic diagram[37]

Formation of toxic intermediates which bind macromolecules occurs when the capacity of sulfation and glucuronidation is exceeded and glutathione as a reducing agent is exhausted.[36] Sulfhydryl donors such as N-acetylcysteine reconstitute glutathione and the formation of the harmless by-product, mercapturic acid, then occurs. The lesion observed is similar to that seen in CCl_4 poisoning: confluent centrilobular necrosis which is clearly dose-related. A nomogram has been developed to predict severity of liver damage, based on blood level and in-

terval between ingestion and sample collection, but this is a guide and is not invariably correlated with outcome.

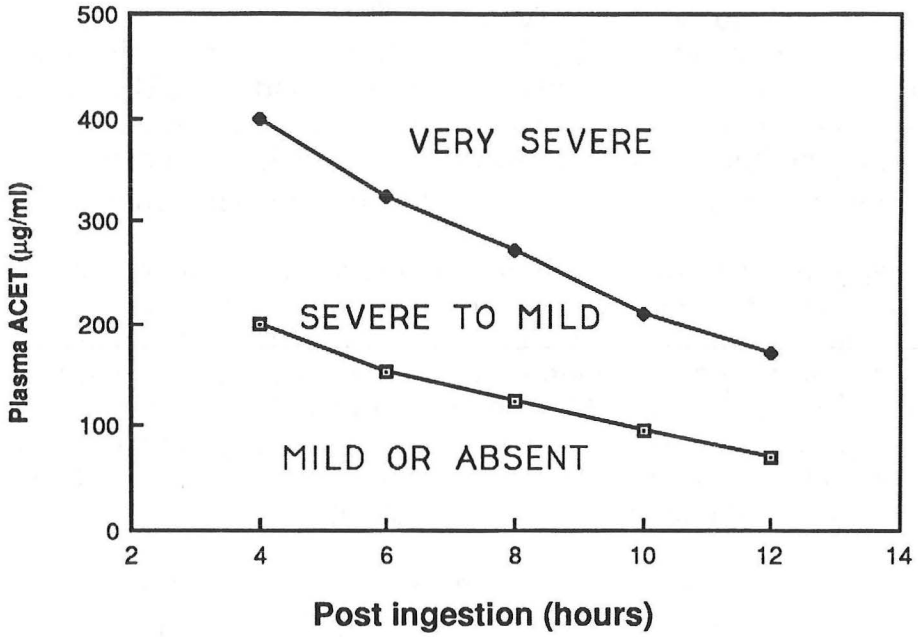

Figure 2. Nomogram for determining likelihood of serious acetaminophen hepatic injury using plasma levels. Levels falling in the lowest zone indicate liver damage will be mild, while levels in the uppermost zone are predictive of serious liver damage and mandate N-acetylcysteine even at more than 20 hours post ingestion.[37]

Cysteamine was first suggested as an antidote to acetaminophen poisoning in 1976,[38] but N-acetylcysteine (NAC) has become the more common antidote in use, either intravenously as used in the United Kingdom or by mouth in the United States.[39,40] Giving NAC early is optimal but the question frequently arises, how late is too late? Many patients appear to have a beneficial effect even as late as 36 hours after ingestion.[41]

The effect of a given dose of acetaminophen is exaggerated in the presence of starvation, drugs which enhance the cytochrome P 450 system, and particularly alcohol. This potentiation effect is most pronounced in alcoholics or binge drinkers who take Tylenol® in therapeutic or supra-therapeutic doses but without suicidal intent.[42-45] The striking clinical features are extraordinarily high aminotransferase levels, usually greater than 4000 IU/L and often higher than 10,000 IU/L.

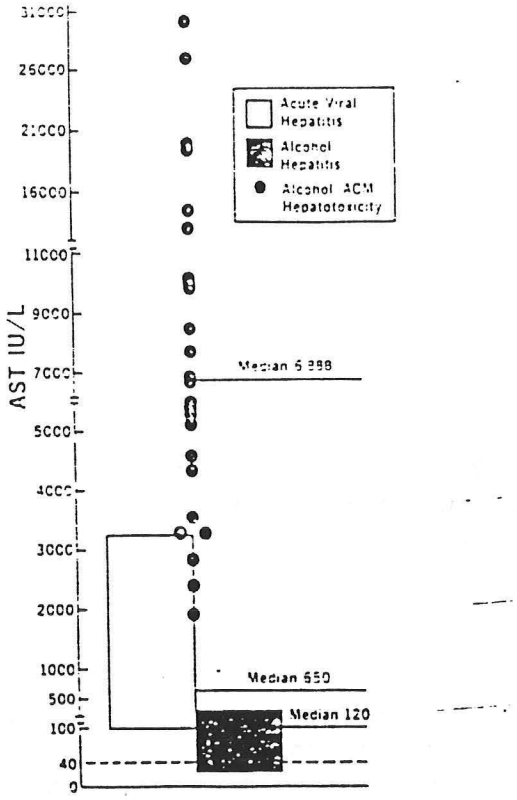

Figure 3. Peak AST values in persons with alcohol and acetaminophen hepatotoxicity, compared to values seen in alcoholic or viral hepatitis.[43]

The case fatality rate may be lower than that observed in suicidal acetaminophen ingestion, but is at least 20% in most reviews. A national survey of these cases, dubbed 'therapeutic misadventures', is underway; this relatively new entity appears on the rise and may be the most common single cause of ALF in Dallas in 1992.

Idiosyncratic drug reactions Most xenobiotic agents are quite lipophilic, and are therefore oxidized and subsequently conjugated by the liver prior to renal excretion of more water soluble metabolites. While many pharmacologic agents cause mild aminotransferase level increases, a large number produce rare catastrophic insults to hepatocytes by a process which is poorly understood. In some instances, e.g., halothane, sulfonamides and dilantin, hypersensitivity plays a role. It is postulated that neo-antigens are created which are presented on the hepatocyte surface, invoking the immune attack.[46]

Table 5. Drugs implicated in acute liver failure, with references.

Frequent offenders
Isoniazid[47,48]
valproate[49-51]
halothane[46,52,53]
phenytoin[54]
sulfonamides[55]
propylthiouracil[56]
amiodarone[57,58]
disulfiram[59,60]
dapsone[61]

Rare but memorable
carbamazepine[62]
ofloxacin[63]
ketoconazole[64]
lisinopril[65]
nicotinic acid[66,67]
labetalol[68]
etoposide (VP-16)[69]
imipramine[70]
alpha interferon[71]

Table 6. Drug combinations with apparent synergistic toxicity

Trimethoprim-sulfamethoxazole[72]
Rifampicin-isoniazid[37]
Acetaminophen-isoniazid[73]
Alcohol-acetaminophen[42-45]

These lists are not all inclusive. In many instances, compounds similar to the index drug have been reported to cause similar patterns of toxicity. For example, enflurane and isoflurane toxicity resembles halothane but is less frequent.[74]

Vascular Etiologies

Cardiac-related hepatic ischemia produces profound aminotransferase elevations, centrilobular necrosis and a syndrome of acute liver failure. Causes include myocardial infarction, cardiac arrest/resuscitation, cardiomyopathy and pulmonary embolism.[75,76] Renal failure is frequently present, and the underlying cardiac abnormality is not always obvious initially.[77] Sinusoidal obstruction with subsequent ischemia or interruption of sinusoidal flow has been described in metastatic gastric carcinoma,[78] carcinoid,[79] breast, oat cell carcinoma[80] amyloid and blastic infiltration with leukemic cells.[81] Occlusion of hepatic venous outflow may occasionally produce a similar picture, either as the Budd-Chiari syndrome,[82] or as veno-occlusive disease in the setting of intensive cytolytic therapy for cancer chemotherapy or bone marrow transplantation.[83,84]

Miscellaneous causes of acute liver failure

Wilson's Disease ALF is one of the unique presentations of Wilson's disease and is nearly always fatal without hepatic transplantation.[85] The special identifying features of this rapidly deteriorating condition is the presence of hemolysis and a decreased serum alkaline phosphatase. A ratio of alkaline phosphatase to bilirubin of less than 2.0 accurately distinguishes cases of Wilsonian liver failure from other causes.[86]

Acute fatty liver of pregnancy (AFLP), occurs in the last trimester and typically presents as sudden onset of jaundice and altered mental status, often accompanied by hypoglycemia.[87] Signs of pre-eclampsia are also frequently present.[88,89] Although patients may have relatively normal aminotransferase levels, hepatic dysfunction as measured by prothrombin time may be severe. Alternatively, transaminase levels may be very high and hemolysis and thrombocytopenia more evident (the HELLP syndrome).[90] Management of the mother includes delivery of the infant but fetal demise occurs in about 40% before delivery can be accomplished. AFLP may be managed successfully with transplantation, if resolution of the condition does not follow delivery of the infant.[91]

Other rare causes of ALF include amebic abscesses,[92,93] disseminated tuberculosis,[94] recrudescence of hepatitis B after withdrawal of cancer chemotherapy,[95] and following bone marrow transplantation.[96]

Clinical Features of ALF

Regardless of etiology, ALF has a unique constellation of clinical features which are distinct from those seen with chronic hepatic insufficiency. Perhaps because of the relative rarity of the condition, the diagnosis is often missed by the first medical contact. Typically, a young patient develops flu-like symptoms and jaundice over several days, followed by rapid onset of altered mental status proceeding to coma within 48 hours. Central hyperventilation and elevated ammonia levels are present. Many of the features of ALF are similar to those of septic shock and these conditions can occasionally be confused.[97] Patients with LOHF differ in some respects from those with FHF, but there is considerable overlap. In general, LOHF patients have a more gradual onset of encephalopathy and rarely have cerebral edema, although ascites is a more prominent symptom. Careful management of ALF in most instances demands an intensive care unit setting, and specialized expertise.

Encephalopathy/cerebral edema The hallmark of acute hepatic insufficiency, the onset of encephalopathy, is often abrupt and may actually precede the appearance of jaundice. Unlike encephalopathy associated with chronic liver disease, agitation, delusional ideas and hyperkinesis are common, but give way to somnolence and coma eventually. Coma is graded from 0 to 4 in similar fashion to that for chronic hepatic encephalopathy. The overall prognosis for survival for those who reach only grades 1 or 2 coma is good, while that for patients proceeding to coma grades 3 or 4 is much poorer. Benzodiazepine-like substances have been implicated in the pathogenesis of the encephalopathy of ALF.[98] Elevated concentrations of 1,4 benzodiazepines have been detected in brain tissue in animal models[99] and in humans with ALF.[100] These substances cause somnolence by augmenting GABA-ergic tone through a receptor-mediated mechanism. It may soon be possible to use benzodiazepine receptor antagonists such as flumazenil, recently released for use in the United States, both as a test for the presence of hepatic encephalopathy and as treatment.

Cerebral edema, a cardinal feature of ALF, develops in 75-80% of those who progress to Grade 4 encephalopathy, and is the leading cause of death in these patients.[101,102] Cerebral edema was found at autopsy in half the patients in one study, although uncal or cerebellar herniation was only present in one-eighth.[103] Cerebral blood flow is markedly reduced in patients with acute and chronic hepatic encephalopathy, but cirrhotic patients very rarely have edema.[104] Cerebral oxygen consumption was low in all twelve patients with ALF in grade 4 coma, and cerebral venous blood demonstrated increased lactate levels in half.[105] The cause of the rapid increase in brain water content is unclear and controversial--increased brain water content may occur through alteration in permeability of the blood-brain barrier, so-called vasogenic edema,[106] or by loss of cell membrane transport leading to swelling of astrocytes, termed cytotoxic edema.[107] It has been suggested that ammonia

may be involved in the inhibition of membrane Na^+-K^+ ATPase but other toxins are likely, since ammonia toxicity is not associated with the degree of brain edema seen in FHF.[108] Cerebral edema in the confinement of the cranial vault results in intracranial hypertension, and a decrease in intracerebral perfusion.[109] Cerebral perfusion pressure (CPP) is the mean arterial pressure minus the intracerebral pressure and must be maintained above 40 mm Hg to sustain adequate intracerebral blood flow. Since mean arterial pressure is often low in FHF, many patients may die of intracerebral ischemic injury the result of inadequate cerebral blood flow in this setting. This provides a plausible explanation for the demise of those patients in whom herniation cannot be demonstrated. Permanent brain damage is occasionally noted in patients who recover.[110]

Clinically, patients with cerebral edema initially develop systemic hypertension (Cushing's reflex) and increased muscle tone, progressing to decerebrate rigidity and posturing, with abnormal pupillary reflexes (usually dilatation), and finally brain stem respiratory patterns and apnea. Signs of increased intracranial pressure are not a reliable guide, since pressure changes occur rapidly and require rapid responses to maintain cerebral perfusion. Nor is CT scan a valid guide to management, although it is useful in excluding intracerebral hemorrhage in any patient who shows a rapid change in mental status.[111] Intracranial pressure monitoring may be performed using subdural or epidural transducers. Although placement of an ICP monitor is invasive and bleeding is a potential complication, monitoring is particularly helpful for patients undergoing transplantation, since rapid changes in ICP occur under these circumstances.[112] Acute high pressure waves may herald imminent herniation, and can guide management.[113,114] If ICP monitoring is not available, continuous measurement of systemic blood pressure is the best guide for detection of paroxysmal rises in ICP. Transfer of patients to transplant facilities may be necessary but is hazardous in those in coma with elevated intracranial pressure, since pressure changes in flight and even rapid positional changes in an automobile increase intracranial pressure.[115]

For signs of cerebral edema, mannitol (0.3-0.4 gm/kg) is given, usually 100-200 ml of a 20% solution by rapid IV infusion and this may be repeated at least once. If renal failure is present or the serum osmolality is above 310 mosm, mannitol will have little effect and may be contra-indicated.[102] Hemofiltration may be used in combination with mannitol to prevent the hyperosmolar state but rapid osmotic shifts can be expected. Combined measurement of ICP and CPP has demonstrated that head-up tilt as high as 45°, as had been suggested previously, is probably deleterious, since CPP is actually diminished when the head is elevated > 20°.[116] Dexamethasone, useful in head injury, is of no value in cerebral edema due to ALF.[117] Hyperventilation may be of some value in an acute crisis but chronic use did not appear of benefit in a large controlled trial.[118] Similarly, thiopental infusion was suggested as therapy for cerebral edema following on the experience in head trauma patients.[119] However, thiopental decreases cerebral blood flow: initial enthusiasm for this has since waned. N-acetylcysteine has recently been shown to have a beneficial effect on cerebral (and systemic) blood flow and oxygen consumption,[105] regardless of etiology of

the ALF (see discussion below). Hypothermia dramatically lowers ICP in rats with cerebral edema but this has not been attempted in humans with ALF.[120]

Coagulopathy Profound changes in clotting are typical in ALF, only partly due to the role of the liver in synthesizing clotting factors. Platelet counts are diminished below 100,000/mm^3 in 2/3 of patients at some point in their clinical course and platelet function is altered.[121] Decreased levels of factors II, V, VII, IX, and X account for the prolonged prothrombin time and partial thromboplastin time observed.[122] Measurement of the prothrombin time is the most widely used test to follow the patient's clinical condition, although Factor V levels are used in some centers.[8] Factor VIII levels are generally increased. Because of the various clotting defects observed, disseminated intravascular coagulation (DIC) was postulated to occur, leading to the use of heparin in these patients with catastrophic results.[123] Bleeding is common in ALF patients and low-grade fibrinolysis and intravascular coagulation may be contributing factors, but they are hard to distinguish from the changes wrought by the liver synthetic failure.[124] Anti-thrombin III levels are decreased and the level of thrombin-antithrombin complexes is increased.[125] Heparinization for hemodialysis is difficult in FHF because of the lack of anti-thrombin III, and supplementation has recently been shown to correct the defect if hemodialysis is needed.[126] Bleeding most often correlates with platelet count, and platelet supplementation may be necessary for counts < 50,000. Fresh frozen plasma has not been shown to be of value in the absence of bleeding but is given routinely when blood is being transfused.[104,108]

Renal and cardiovascular changes The circulatory changes in ALF resemble those seen in cirrhosis in some respects, but differ in certain ways as well. Hypotension is the rule, with hypovolemia, greatly decreased systemic vascular resistance (SVR), a compensatory increase in cardiac output, cardiac index and increased interstitial edema. All these features resemble the sepsis syndrome. Endotoxemia is common but probably not the entire explanation of these complex metabolic changes.[127] Tumor necrosis factor (TNF) levels are elevated in ALF as are IL-1 levels.[128] TNF is an important endogenous mediator of septic shock and would be likely to play a role here. However, although TNF levels are elevated with infection, either viral or bacterial, they are normal in patients after acetaminophen overdose, even though these patients display the same clinical syndrome. TNF is not, therefore, the single mediator of the hemodynamic changes observed in ALF.[129]

Oliguric renal failure is a common complication, occurring in approximately half the patients, depending somewhat on the etiology.[130] Renal failure worsens the prognosis as shown below.

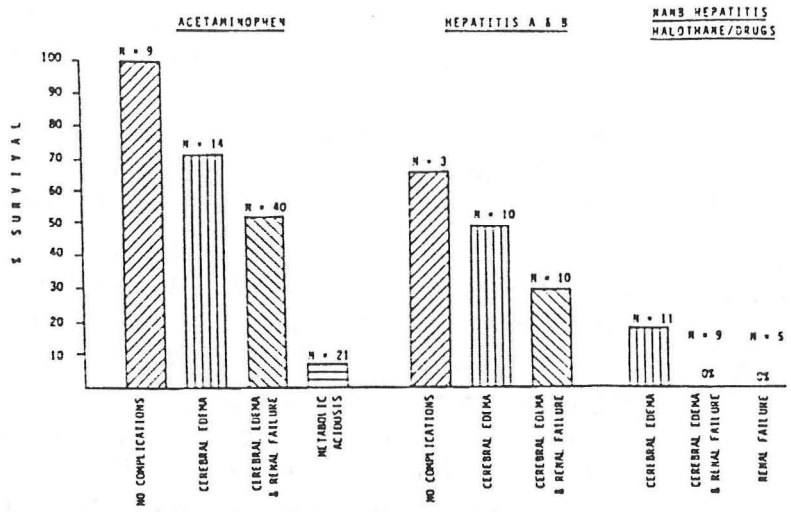

Figure 4. Survival rates in acetaminophen, hepatitis A & B, correlate with the pattern of complications present.[162]

Functional renal failure, also called the hepatorenal syndrome, is seen primarily, but acute tubular necrosis is also found.[131] Occasionally, acetaminophen or carbon tetrachloride will be responsible for renal failure, which is out of proportion to that usually seen in ALF, due to direct toxic effects.[132-133] Reduced renal blood flow can be demonstrated, and renin and aldosterone levels are increased,[134] while levels of atrial natriuretic factor are normal.[135] Dialysis is now routinely used in those with significantly elevated serum creatinine, however performing hemodialysis is difficult due to hypotension, bleeding, heparinization difficulties and the likelihood of precipitation of increased ICP.[130]

Oxygen transport and utilization The circulatory changes seen in ALF which are characterized by severe peripheral shunting have been difficult to understand.[136] Many patients in the latter stages of their illness develop lactic acidosis, a bad premonitory sign.[137] Patients with ALF develop pathologic oxygen supply-dependency, since they appear to extract oxygen from the blood over a wider range of oxygen delivery than is normally observed.[138]

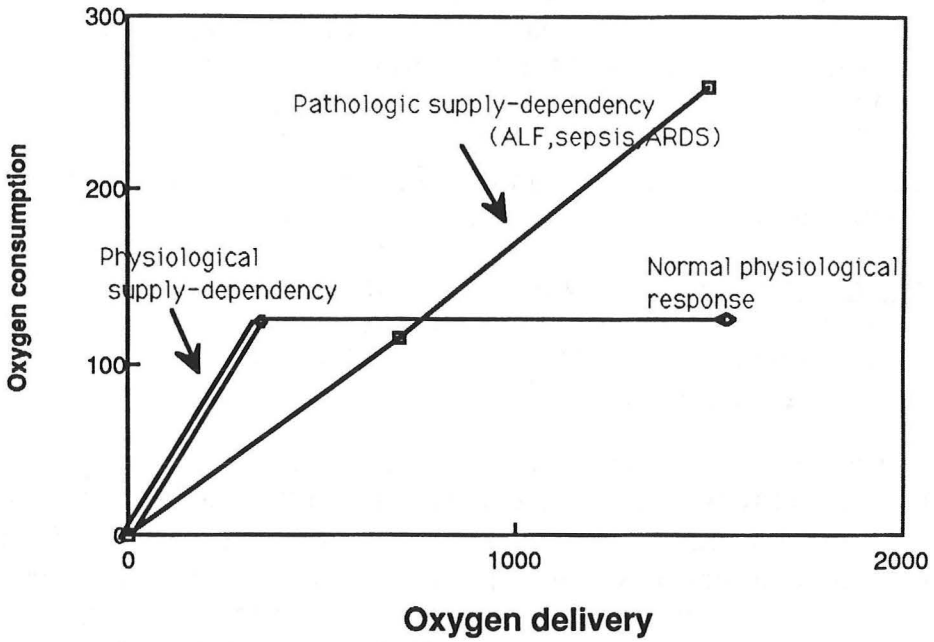

Figure 5. Oxygen dissociation curve, both normal and pathologic.

This same abnormal supply-dependency curve is seen in adult respiratory distress syndrome.[139] Changes in peripheral oxygenation are the result of vasodilatation, platelet plugging of small vessels and interstitial edema. A rightward shift in the oxyhemoglobin dissociation curve also occurs, allowing greater delivery of oxygen at peripheral sites. In all studies, oxygen extraction is abnormal in ALF patients and particularly in non-survivors. Peripheral shunting with tissue hypoxia is virtually universal, and a major part of the multiple organ failure syndrome seen in these patients.

Studies of the circulatory abnormalities in ALF make a strong case for pulmonary artery pressure monitoring in these patients.[136] Because of the profound shifts in fluid and vasomotor tone, fluid replacement and use of pressors becomes difficult, and it may be impossible to tell with central venous pressure monitoring alone whether there is adequate left ventricular filling. Pulmonary artery monitoring also allows for optimization of oxygenation. Additionally, use of pressors for improvement in mean arterial pressure may actually aggravate peripheral oxygen consumption.[136] Conventional pressor treatment for shock such as dobutamine or dopamine is relatively ineffective. Prostacyclin, (PGI_2), which has microcirculatory vasodilatory effects, has been shown to increase peripheral oxygen utilization.[140] An unexpected finding was that N-acetylcysteine, used as an acetaminophen antidote, appears also to enhance oxygen delivery and consumption, possibly by "opening" the microcirculation via an effect on nitric oxide control of vasomotor tone.[105] A further understanding of the role of peripheral vasodilation and the proper management of the ALF patient's hemodynamics should improve survival.[142]

Metabolic changes in ALF Hypoglycemia is common and may be the cause of altered mental status in a small proportion of individuals. Hypoglycemia is the result of defective gluconeogenesis in the failing liver, and increased insulin levels due to inadequate insulin uptake. Blood glucose levels need close monitoring and 10% glucose is given intravenously as needed. Hyperkalemia occurs and requires massive replacement in some patients, as much as 600 mEq per day. This is due in part to the respiratory alkalosis, with renal excretion of K^+ in exchange for H^+ ions. Hyponatremia usually is on a dilutional basis, and hypophosphatemia is common for unclear reasons.

Cardiac abnormalities Rarely is an important cardiac problem encountered in ALF since the patients are frequently young and otherwise fit. If major electrolyte imbalance is seen, then arrhythmias may occur; EKG changes are occasionally reported with cerebral edema alone.[143]

Septicemia Among the complications of ALF, bacterial and fungal infections are common, for many reasons. Patients with ALF have diminished opsonic activity in serum,[144] faulty polymorphonuclear leukocyte function,[145] and impaired cell-mediated and humoral immunity.[9] In addition, they are comatose, with numerous indwelling catheters, and may be receiving H_2 blockers, steroids or broad spectrum antibiotics. Systemic bacteremia may in part be due to intestinal entry of bacteria as a result of faulty Kupffer cell function similar to that observed with gram negative infection in cirrhosis.[146] However, in studies of large numbers of consecutive patients, gram positive organisms, mainly streptococci and *Staphylococcus aureus* predominated, suggesting that skin entry sites are equally important.[147] In one prospective study of 50 patients, 80% of patients had culture-proven infection and half of the remaining patients had suspected infection but were culture-negative.[148] Two thirds were gram positive isolates, and several patients had more than one infection. Most infections occurred within three days of admission and 32% had additional fungal infection (15 with *Candida*, 1 with *Aspergillus*). Gram positive pneumonia was the most common infection, accounting for 50% of the episodes. Twenty eight percent had bacteremia. The role of endotoxemia in worsening renal function and peripheral vasodilatation may be significant in certain patients, and infection undoubtedly plays a significant role in mortality. Regular microbial surveillance, and aggressive treatment of presumed infection is essential. Disseminated fungemia is particularly ominous.[149] Topical therapy directed at *Candida* may be helpful, and controlled trials of enteral decontamination regimens are underway.

Pathogenesis of Acute Liver Failure

Although the etiologic agent is usually known, a full understanding of the pathogenesis of ALF eludes us. There are many common pathophysiologic changes, including the shock-like state, and the frequent occurrence of cerebral edema that suggest a unified pathogenetic mechanism. Stated a different way: Is ALF simply an extension of liver injury to a point of no return (quantitatively more of the same kind of damage) or does a second process ensue, in which released substances from the damaged liver or the stimulation of the cytokine response

further injure the liver and other organs? A corollary: why do some individuals get ALF and others do not, with the same viral infection or drug-induced injury?

Table 7: Factors increased and decreased in ALF patients.

Increased	**Decreased**
Renin	Fibronectin
Aldosterone	Gc protein
Tumor necrosis factor	Coagulation factors
IL-1	Thrombin-antithrombin
Interferon (viral hepatitis)	
PGE_2, TXA_2, PGI_2	

Whether levels of factors are elevated because of *de novo* stimulation, or because of failure of hepatic clearance remains uncertain. As will be seen from the discussion of treatment options below, attempts at removal of unknown toxins using hemodialysis or other means has not proved to be particularly successful. Disturbances of the homeostatic mechanism are dramatic, but which part of the disturbance is crucial to survival?

One serum protein which is markedly diminished in fulminant hepatic failure is Gc protein. This alpha-2-globulin is the principal vitamin D-binding protein and is important in binding and sequestering actin released from hepatocytes during hepatic necrosis.[150-151] Survival of patients with ALF, and of experimental animals with ALF after acetaminophen, correlates well with the level of Gc and the presence of complexes with actin.[152,153]

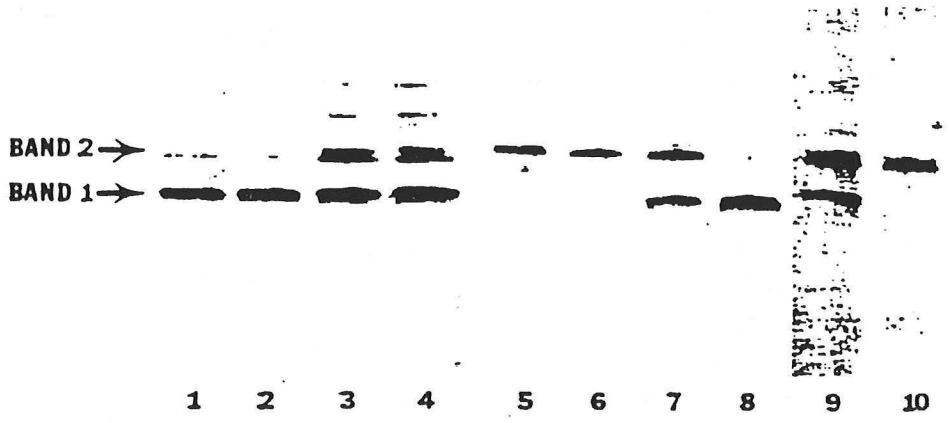

Figure 6. Polyacrylamide Gel Electrophoresis of Serum Followed by Western Blotting with Anti-Human Gc Protein. Band 1 represents native uncomplexed Gc protein, while band 2 represents Gc protein-G-actin complexes. Lanes 1 and 2, serum samples from normal subjects. Lanes 3,4 and 7,8, consecutive serum samples from 2 patients with severe hepatitis who recovered. Lanes 5,6 and 9,10, consecutive serum samples from 2 patients with fulminant hepatitis who died. Gc protein is predominantly in native configuration (band 1) in normal subjects, but the complexed configuration (band 2) was prominent in the patients,

particularly in those who died. The total quantity of Gc protein in those patients with fulminant hepatitis was diminished, and native Gc protein totally absent in some serum samples from the patients who died.[152]

Depletion of Gc protein might have pathogenetic significance since exhaustion of this actin scavenger mechanism enhances precipitation of actin filaments (and platelets) in the micro-circulation.[154] Evidence in experimental animals suggests that ARDS and death result from exhaustion of the scavenger mechanism.[155] Of interest, similar changes in Gc level and appearance of complexes has been shown in patients with gram negative sepsis and in an animal model of septic shock.[156,157] Additional studies suggest that complexes of fibronectin with an unknown substance are also present and this additional high MW complex might further contribute to microcirculatory blockade.[145]

It is unlikely that TNF is the principal mediator of the shock syndrome since it was not shown to be elevated except in the presence of viral or bacterial infection. Similarly, prostaglandin metabolism is clearly affected, and may be important in production of tissue hypoxia, but is unlikely to have such a catastrophic effect on the entire organism. Studies in mice given acetaminophen have suggested that PGE_2, TxA_2, and PGI_2 levels are all increased in this animal model of ALF. Nevertheless, prostacyclin, (PGI_2) a vasodilator and inhibitor of platelet aggregation, given shortly after acetaminophen protected against the liver injury. Whether this was due to some direct effect on cellular membrane stabilization, or to microcirculatory improvement could not be determined. Infusion of prostacyclin in patients with ALF has been shown to improve hemodynamics in terms of cardiac output and oxygen delivery, probably by improvement in microcirculatory flow.[138] It seems unlikely that a single pathogenetic mechanism can explain all the abnormal events. Nevertheless, basic studies are particularly necessary, since intuitive treatment schemes have thus far been of limited value.

Prognosis

Predicting outcome is of particular importance, because transplantation has become an option, at least for some patients. Single tests or clinical factors such as age, sex, time from onset of jaundice and height of bilirubin are of little overall value, and a search for a discriminant function which would identify survivors has been undertaken.[159,160] Many studies have suggested a dismal overall outcome, with survival as low as 6% in an American series from the 70's to early 80's.[161] Part of the problem in most centers is that the relative rarity of ALF makes large series and controlled observations nearly impossible. It also means that a critical mass of investigators or skilled clinicians is rarely available.

The one exception to this is the Acute Liver Failure Unit at Kings College Hospital, London where most of the observations on natural history and prognosis have been made. This unique unit receives ALF referrals from the United Kingdom and Europe. Ironically, the evaluation of charcoal hemoperfusion as a therapeutic option over a fifteen year period at Kings, produced the most information about prognosis.[162,163] The use of historic controls and a gradual improvement in overall prognosis of ALF at Kings resulted in an initial impression that the column was efficacious.[164] These historically-controlled studies showed dramatic improvement in survival with the charcoal column, although a controlled

trial was not performed. What became apparent with further review was that a greater understanding of the intensive management of such patients (not the columns), had improved survival considerably. When a controlled trial was performed, efficacy of charcoal hemoperfusion was not demonstrable. Survival had improved specifically in certain etiologic groups, particularly hepatitis A and acetaminophen.[165] While overall survival was limited at about 20% in 1973, by 1988, it had improved to greater than 50%, a least for certain groups.

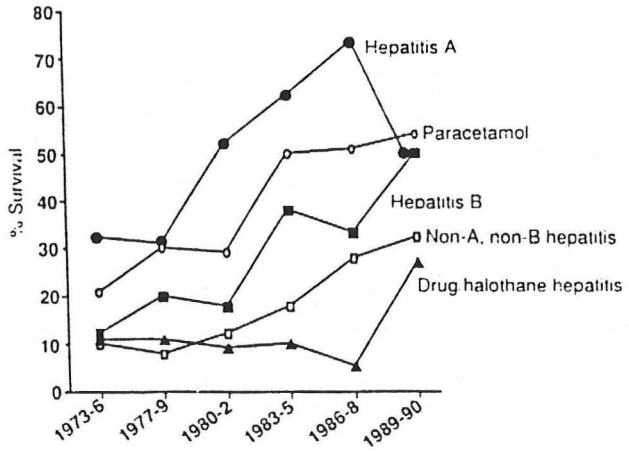

Figure 7. Improvements in survival according to etiology in patients with ALF (grades 3 and 4 encephalopathy) at Kings College Hospital, London.[166]

Statistical analysis of 588 patients seen at Kings during the period 1973-1985 was used to identify factors associated with a poor prognosis demonstrated a dichotomy. Survival indicators were different for acetaminophen-induced ALF and for non-acetaminophen cases. Etiology has the most important variable for predicting survival. Criteria for predicting survival were then adopted, and when applied (retrospectively) to the 175 patients seen after 1985, good predictive value was found.

Table 8. Criteria for non-survival (consideration of liver transplantation) at Kings College Hospital, London.[165]

Acetaminophen

pH < 7.3 (irrespective of grade of encephalopathy)

or

prothrombin time >100 sec and serum creatinine >300 µmol/L in patients with grade III or IV encephalopathy

Non-acetaminophen patients

Prothrombin time > 100 sec (irrespective of grade of encephalopathy)

or

Any 3 of the following variables (irrespective of grade of encephalopathy)

Age < 10 or > 40

Etiology non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions

Duration of jaundice before onset of encephalopathy > 7 days

Prothrombin time 50 sec

Serum bilirubin > 300 µmol/L

In summary, acetaminophen overdoses carry a reasonably good prognosis overall, as do hepatitis A, and to a lesser extent, hepatitis B. Dismal survival seems to be the rule in non-A, non-B hepatitis and the idiosyncratic drug reactions, although recent improvement in these categories is tantalizing. The upward curve of survival at Kings for all groups emphasizes once again the importance of skilled care, and may not be easily duplicated elsewhere.[166]

Therapy

The list of primary therapies attempted in ALF is long and discouraging. Heroic measures are indeed used for desperate situations, but seem to be of little value. Each time, a new treatment demonstrates early promise only to be discarded when subsequent results are as dismal as before.[167] This prompted the wise Professor Jean-Pierre Benhamou to say in 1972, regarding ALF, and its treatment:

> "Table II reflects a significantly higher recovery rate in the publications dealing with single cases than in those based upon two or more cases and shows a significantly lower recovery rate in our personal series than in the published cases. It would thus appear that authors tend to publish isolated cases with a favourable outcome attributed to a given therapy, but not to publish cases in which therapy has failed. In fact it might be argued that the best future one can wish for a sufferer from SAHF [ALF] is to undergo a new treatment and have his case published--"be published or perish!"[167]

Table 9. List of ineffective treatments for the overall condition, ALF.

Corticosteroids
Exchange transfusions
Pig perfusions
Total body washout
Spouse cross-transfusions
Heparin infusions
Hemodialysis, hemoperfusion
Charcoal hemoperfusion
Dialysis plus activated charcoal in series
Insulin/glucagon infusions

Randomized controlled trials of steroid therapy showed no efficacy and possible harm in their use.[168,169] Exchange transfusions showed early promise as did 'total body washout,' a process whereby cardiopulmonary bypass was used to substitute saline for blood briefly.[170,171] A recent study has raised the option of intensive plasmapheresis.[172] Pig cross-perfusion has been largely unsuccessful and those techniques using humans for cross perfusion are highly hazardous.[173,174] Heparin treatment was initially shown to improve survival in four cases, only to be later discarded.[123] Hemodialysis with large pore membranes showed early promise in improving mental status but could not improve survival.[175] The ALF Unit at Kings has a long experience with charcoal hemoperfusion. A column of coated activated charcoal will remove a variety of toxic substances and appeared in early testing to show significant promise.

Difficulties with platelet removal by the column were encountered and eventually overcome, but the use of controlled trials failed to show efficacy.[162-165] Post-dilution hemofiltration[176] and hemodialysis in combination with charcoal[177] may also merit further trials. One obvious lesson from the experience with those modalities which remove toxins is that patients may show improvement in coma grade with these techniques, but long term survival mandates improvement in liver mass by some means, and toxin removal does not accomplish this. Insulin and glucagon which in combination appear to be hepatotrophic, were thought to have a beneficial effect in early trials,[178] only to fail when subjected to controlled trials.[179]

Recent interest in using prostaglandin analogues as treatment for ALF was stimulated by demonstrated efficacy of PGE_1 in a mouse model of viral hepatitis.[180] An uncontrolled trial of PGE_1 demonstrated an improved survival compared to historic controls (12 of 17, 71%), but when examined closely this study fails to meet the minimum standards for proving effectiveness.[181] Sharp drops in aminotransferase levels with clinical improvement suggested that stabilization of the necrotic process had occurred, and further experience in controlled trials are necessary. A recent report of a negative uncontrolled trial has also appeared. This repetitive pattern of successful pilot studies and unsuccessful large trials affirms the message Professor Benhamou told us twenty years ago. Most of the therapies so far considered can at times awaken the patient briefly, but full recovery is dependent on rapid regeneration of liver cell mass.

Therapy Guidelines

Lacking specific medications of proven efficacy, the hallmark of therapy in ALF is good intensive care of the comatose patient. Every effort must be made to elucidate the etiology, since therapy may depend on this. All patients should have serological evaluation for acute hepatitis viruses, acetaminophen levels, ceruloplasmin (under age 50), and toxicological screen if indicated. Initial emergency room management includes obtaining blood glucose (and beginning 10% dextrose if necessary), prothrombin time, as well as other routine studies. H_2 blockers are routinely given. Close followup of mentation, blood pressure, and urine output are rudimentary. An antidote may be indicated and should be given without delay if its need is suspected. Consideration should be given to the question of candidacy for liver transplantation on admission, since transfer to a specialized center is best accomplished when the patient is only experiencing grade 1 or 2 encephalopathy. If the patient progresses to grade 3 or 4 coma, intensive care unit is mandated with careful monitoring of pulmonary artery pressure and oxygenation where feasible. Aggressive treatment for evidence of cerebral edema, bleeding, infection and changes in blood pressure or oxygenation must be undertaken, and all those caring for the patient must be alerted to signs of impending herniation and the possibility of full recovery with thoughtful aggressive management. Although there may be a place for PGI_2, PGE_1 or NAC as primary therapy for ALF in the future, there is no basis for their use at present, except in controlled trials.

Other New Modalities..Toward a liver machine

Hepatic assist devices that employ living hepatocytes would be more than detoxifiers, and would perform more of the complex hepatic functions than is possible with a simple toxin removal process. One such machine, the extracorporeal liver assist device (ELAD), has been used in dogs and one patient with some promise.[182] C3A cells from a human hepatoblastoma line are grown in hollow fiber cartridges to confluency, and can be maintained for an indefinite period of time at high density. These cells metabolize ammonia and aromatic amino acids, synthesize clotting factors, and have high levels of cytochrome P 450 enzymes. Whole blood is perfused through channels between the cell-containing tubes and exchange of toxins and nutrients can occur. In the one patient studied so far, bilirubin improved dramatically, as did level of consciousness, while on ELAD. She died of septic shock three days after discontinuation of the machine. Liver cell transplantation via microcarriers into the abdominal cavity of rats has shown some success.[183] Collagen-coated microbeads were used to stabilize rat liver cells prepared by collagenase perfusion of normal rat liver. Cells were implanted in Gunn rats which do not conjugate bilirubin, and conjugated bilirubin subsequently demonstrated. Similarly, analbuminemic rats could be shown to synthesize albumin.[184] Problems encountered with this technique include rapid rejection of transplanted cells. Nevertheless, a bridge of even a few days might be enough to allow regeneration of the native liver to occur. Auxiliary partial liver transplants have been performed in emergency situations with reasonable results.[185] Eventually, the graft may be rejected by which time the native liver should be fully regenerated.[186,187]

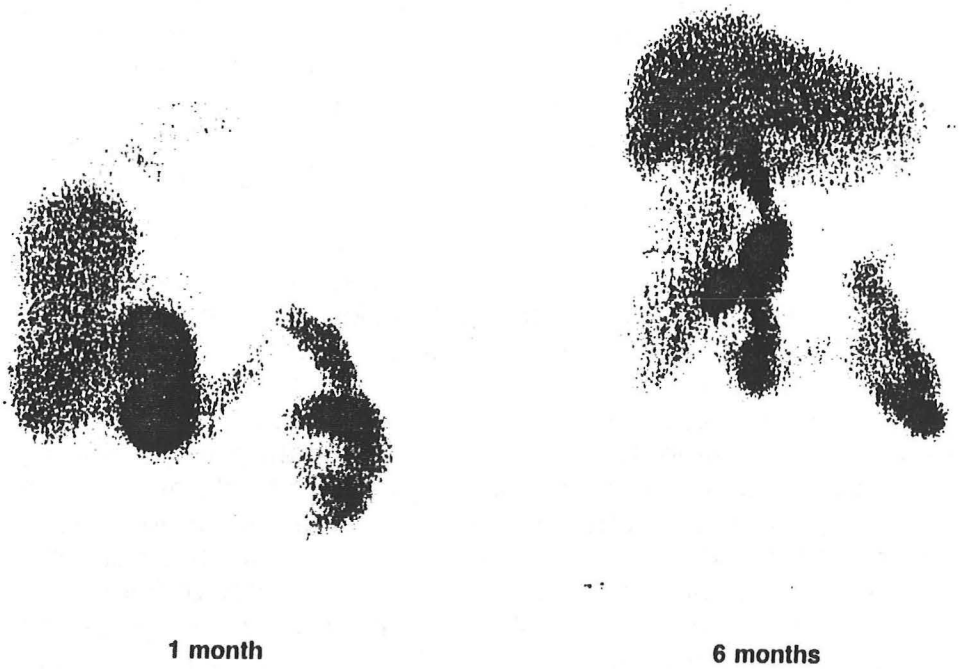

Figure 8. DISIDA scintigraphy one and six months after auxiliary partial liver transplantation. At one month, uptake is by the graft, whereas the regenerated host liver takes up the DISIDA at six months.[186]

Liver Transplantation

Orthotopic liver transplantation offers the ultimate fix to the problem of sudden loss of hepatocytes. However, like an amputation, a surgical solution selected for an acute problem which may be self-limited invites a lifetime of regret. Surgery in young, well-nourished patients who have not suffered the ravages of chronic liver disease is somewhat easier, and, where prognostic information suggests less than 20% chance of survival without transplantation,[188] liver grafting can be performed. However, problems encountered include transportation of the ALF patient with cerebral edema to the transplant center, and the inability to obtain a suitable organ in an appropriate time interval. Transplantation across ABO blood groups has been performed with reasonable success, but demonstrates the compromises one may have to make to accomplish the transplant.[189] Nevertheless, overall one year survival of transplanted ALF patients during the 1980's was generally 60% in a wide group of centers,[190-198] and results are likely to be even better in the 1990's. Specific problems will still be encountered with recurrence of disease in some of the viral syndromes.[10,27,199]

Table 10. Spectrum of hepatic substitution schemes.

Hemoperfusion/hemodialysis
Extracorporeal liver assist device
Hepatocyte transplantation
Auxiliary heterotopic transplant
Orthotopic liver transplant

Hepatocyte growth factors

More appealing and less traumatic than organ transplantation would be the induction of rapid hepatocyte regeneration by appropriate hepatocyte growth factors. Several candidate substances have been identified in serum of patients or animals following liver resection or ALF.[200,201] These include human hepatocyte growth factor (hHGF, also called hepatopoietin A),[202] epidermal growth factor (EGF),[203] transforming growth factor alpha, (TGF),[204] and hepatocyte stimulatory substance (HSS).[205] Best characterized is hHGF,[206,207] which has been purified from blood of patients with ALF, and has now been sequenced.[208] The primary structure of rat HGF, elucidated from cDNA, contains four "kringle" units and resembles plasmin in some respects.

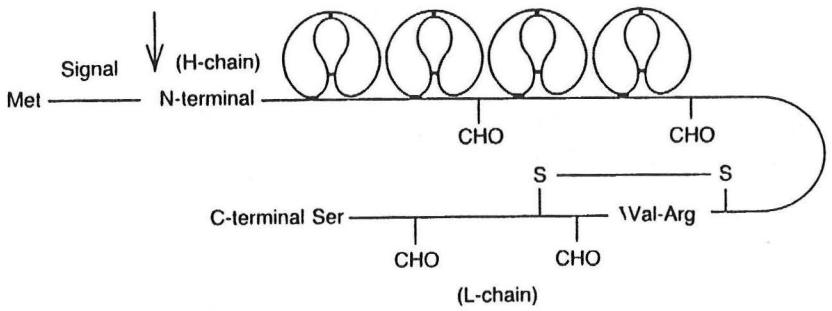

Figure 9. The structure of hHGF.[208]

On the basis of Northern blot analysis of mRNA, rat HGF is expressed in a variety of tissues, including liver, kidney, lung and brain. Serum hHGF levels in patients with FHF were ten to 16 times that found in normal individuals.[209,210] Levels were particularly high in patients with grade 3 or 4 encephalopathy. In survivors. the levels decreased to normal rapidly, but no correlation of levels of hHGF at time of admission with survival could be made. The c-*met* oncogene appears to be the HGF cell surface receptor.[211] Clinical studies of hHGF supplementation in patients with ALF have not been performed. The failure of hepatic regeneration in many patients with ALF and the high levels of HGF in ALF patients suggests the possibility that loss of hepatocytes beyond a certain point may be irremediable.

Table 11. Therapy on the horizon or in use

Agent	**Comment**
N-acetylcysteine	for acetaminophen but also ? for all
Prostacyclin, PGI_2	needs wider application in controlled trials
PGE_1	may fail the controlled trial test
Transplantation	useful but problematical
Hepatocyte growth factors	untried but a possible option

Summary

Acute liver failure represents a challenge to our highest levels of thought, action and intensive care research. Since the mortality is high, and the patients usually under 30, the stakes are high as well. Sudden loss of hepatocyte function involves a complex syndrome necessitating some form of temporary liver support while hepatocyte regeneration takes place. The best plan for management of such patients includes: 1) a careful search for etiology, since antidotes may be indicated and prognosis depends in part on etiology, 2) aggressive intensive care directed at the specific problems associated with ALF--cerebral edema, bleeding, infection, renal failure, 3) early consideration of the need for transplantation. There are no miracle cures for this condition.

Acknowledgment

The recent explosion of information concerning the pathophysiology and management of ALF is in large measure the result of the work of one man, Dr. Roger Williams, and the Liver Unit at Kings College Hospital. Fifty of the 211 references in this review represent papers from the Acute Liver Failure Unit at Kings and this achievement in itself is worthy of mention.

Thanks for suggestions to Drs. Burton Combes, Jennifer Cuthbert, Willis Maddrey, Caroline Riely and Roger Williams.

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