Progress report
Acute hepatic necrosis and fulminant hepatic failure

Fulminant hepatic failure is defined as severe, acute impairment of hepatic function culminating in hepatic encephalopathy, the encephalopathy being the result of hepatocellular failure and supervening within three weeks of the onset of symptoms*. This definition excludes the hepatic encephalopathy of hepatic cirrhosis and of chronic hepatitis, which produces a slightly different clinical picture, but fulminant hepatic failure as defined here may of course occur as a superimposed phenomenon in patients with these conditions. Likewise excluded is encephalopathy caused by sedatives in patients with viral hepatitis or by a direct cerebral action of certain halogenated hydrocarbons in subjects whose livers are already damaged by these compounds.

The clinical features of a typical attack of fulminant hepatic failure are progressive jaundice of acute onset, shrinkage of the liver, foetor hepaticus, and hepatic coma. Characteristic biochemical changes are increased prothrombin time, elevated serum transaminase activity, and raised blood ammonia concentration.

Pathogenesis

The morbid anatomical basis of most cases or fulminant hepatic failure is hepatic necrosis. Acute hepatic necrosis and fulminant hepatic failure are not coextensive terms, since the former may not be sufficiently massive to precipitate the latter, while in fulminant hepatic failure from certain causes (see table) there is little or no hepatic necrosis and the hepatic failure seems to result from inhibition of hepatocyte function.

The pathogenesis of the encephalopathy of fulminant hepatic failure is still the subject of speculation.

Is encephalopathy due to the absence or short supply of materials needed for normal brain function and normally secreted by the liver into the blood stream? It has been shown in perfusion experiments on cats (1) that cerebral carbohydrate metabolism and the survival of the brain depend on substances released by the liver and (2) that in the absence of the liver small amounts of cytidine and uridine added to the perfusion fluid maintain normal cerebral carbohydrate metabolism and electrical activity. Yet, parenteral administration of cytidine and uridine was without effect on encephalopathy in hepatectomized animals and in 10 patients with fulminant hepatic failure.

Or is encephalopathy brought about by accumulation of neurotoxic substances which the normal liver eliminates or detoxicates? Ammonia has been incriminated: there is substantial evidence that it alters cerebral metabolism in hepatic coma but information derived from clinical studies is as yet incomplete.

*In order to be included in the fulminant hepatic failure surveillance study, the syndrome must occur within eight weeks of the onset of illness; we, however, regard this interval as too long.
inconclusive⁶; the administration of substances reputed to lower blood ammonia concentration has been reported to have no beneficial effect in encephalopathy¹⁰,¹¹. The improvement in encephalopathy which has been found to follow administration of the neurotransmitter monoamine levodopa¹²–¹⁴ has been ascribed to restoration in the brain of normal neurotransmitter amines; hypothetically, these could have been displaced by false neurochemical transmitters. Possible amino acid precursors of false neurochemical transmitters are produced from protein in the gut by the action of bacterial amino acid decarboxylases, and normally are cleared from the portal blood by the liver. However, against the implication of intestinal factors, and of ammonia in particular, in the mechanism of the cerebral disorder of fulminant hepatic failure is the observation that electroencephalographic changes in rats with total hepatectomy and total evisceration respectively are similar, while blood ammonia levels are elevated in the hepatectomized animals but normal in those with total evisceration¹⁵.

**Aetiology**

The principal causes of fulminant hepatic failure are summarized in the table.

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Table  **Principal causes of fulminant hepatic failure**

¹For an extensive list of substances liable to cause liver damage see Sicot et al⁴ and Berthelot et al⁴.

²The hepatic lesion is a fatty change, not acute hepatic necrosis.

**Infections**

By far the commonest cause of fulminant hepatic failure is viral hepatitis, in its two forms, infectious hepatitis and serum hepatitis. The incidence of fulminant hepatic failure in infectious hepatitis is of the order of 0.2 to 1.0%¹,¹⁶,¹⁷. In serum hepatitis case-fatality rates ranging from 0 to 60% have been reported¹⁸. There is evidence that fulminant hepatic failure is more liable to occur in virus B than in virus A infections¹⁷. Patients with serum hepatitis, the form of viral hepatitis with which virus B is predominantly associated¹⁹, having a higher mean age than patients with infectious hepatitis²⁰, it is difficult to say whether the greater frequency of fulminant hepatic failure is related to the virus or to age. The sexes are equally susceptible to infectious hepatitis but fulminant hepatic failure is more common in females than in males¹⁷,²¹. A study conducted in 1966²² indicated that in Europe and North America the mortality from viral hepatitis was the same in pregnant women as in the general population, but that in Asia and the Mediterranean area the mortality during pregnancy was higher.
More recently a strikingly high incidence of fulminant hepatic failure among pregnant women has been reported in Morocco\textsuperscript{28} and Saudi Arabia\textsuperscript{24}. The common belief that physical exercise during infectious hepatitis increases the risk of the onset of fulminant hepatic failure has been challenged by Chalmers\textsuperscript{25}. A comparative study between patients with acute viral hepatitis treated with corticosteroid drugs and patients not so treated revealed no significant difference in the incidence of fulminant hepatic failure between the two groups\textsuperscript{26}.

Acute hepatic necrosis, sometimes leading to fulminant hepatic failure, has been known to occur in the following infections: Marburg monkey disease\textsuperscript{27}; disseminated herpes simplex virus infection in newborns\textsuperscript{28} or (less commonly) in adults\textsuperscript{29}; infections with reovirus\textsuperscript{30}, Coxsackie virus\textsuperscript{31}, or adenovirus\textsuperscript{32}; glandular fever\textsuperscript{33}; and Q fever\textsuperscript{34}.

**Toxins, Chemicals, and Drugs**

Hepatic damage caused by toxins, chemicals, or drugs is much less common than viral hepatitis.

Substances liable to produce fulminant hepatic failure may be studied under two headings: (1) those which are directly hepatotoxic and (2) those which produce a hepatitis-like reaction.

1. The effect produced by poisons which act on the liver cell directly depends on the amount ingested. The special interest of the resultant hepatic damage is that it affords an opportunity to study, under what is tantamount to experimental conditions in human subjects, the effects of agents of known composition acting on hepatocytes at a known point in time.

Poisoning by Amanita mushrooms, most commonly *A. phalloides*, is more frequent in France, Germany, and the Benelux countries than in Britain or the USA. Some 50 cases occur in France every year with a mortality of about 30\%\textsuperscript{35}. Toxins present in these mushrooms cause massive hepatic necrosis. Hepatocellular failure can be detected as early as 24 hours after ingestion of the poison, by demonstration of raised serum glutamic pyruvic transaminase (SGPT) levels, whereas clinical evidence of liver cell damage rarely appears before the fourth day. The SGPT concentration has prognostic as well as diagnostic value. Sicot and his colleagues\textsuperscript{36} measured SGPT activity eight-hourly in 14 patients. In 10 patients the maximal level of SGPT reached during the first three days did not exceed 9000 units of pyruvic acid, and none of these 10 patients subsequently had encephalopathy. The SGPT levels were in excess of 9000 units in four patients; encephalopathy developed in all four and two died. If fulminant hepatic failure is to develop it generally does so towards the fifth day and culminates in death on the seventh day. Some 50\% of deaths, however, are not due to fulminant hepatic failure but to disorder of water and electrolytes resulting from diarrhoea and vomiting and leading to circulatory and renal failure\textsuperscript{35}.

Overdose of paracetamol with suicidal intent has been reported from Great Britain\textsuperscript{37}; the most striking necropsy feature in all fatal cases has been acute hepatic necrosis.

The intravenous administration of tetracycline in excessive dosage may lead to a fatal liver disease characterized clinically by progression to stupor and coma and pathologically by fatty change in liver cells without significant necrosis. Most but not all of the known cases have occurred during pregnancy\textsuperscript{38}.
Among other chemicals which have been reported from time to time as causing massive hepatic necrosis and fulminant hepatic failure are yellow phosphorus, contained in various rat poisons, and nitrated or halogenated hydrocarbons, which are used in a variety of industrial processes. The fulminant hepatic failure of yellow phosphorus poisoning is often accompanied by acute circulatory failure.

Fulminant hepatic failure may develop in alcoholic (ethanol) hepatitis; the pathological lesion is massive steatosis, resembling the fatty change induced by tetracycline.

2 Drug-produced hepatitis-like reactions are hypersensitivity reactions, unrelated to dosage or to duration of administration.

Prominent in this category is the acute hepatic necrosis which the anaesthetic halothane causes in a very small proportion of the cases in which it is administered. It is usually heralded by unexplained pyrexia about a week after the anaesthesia; jaundice does not appear until some days or weeks later, if it appears at all. Halothane hepatitis is more frequent after multiple than after single exposure, but its occurrence is unrelated to the duration of the anaesthesia. We have seen fatal hepatitis in a child who had received halothane for less than three minutes. The mortality is high and death occurs in fulfilment hepatic failure. Light and electron microscopy have revealed similarity, but not identity, between the pathological changes in the liver and those of acute viral hepatitis.

Other drugs liable to cause hepatitis-like liver injury and fulminant hepatic failure include: metahexamid; zoxazolamine; hydrazine-type monoamine oxidase inhibitors such as iproniazid, isocarboxazid, phenelzine, pheniprazine, and phenoxypropazine, and hycanthone.

Ischaemia and Hypoxia

Certain conditions causing hepatic ischaemia or hypoxia lead to acute hepatic necrosis and, if the necrosis is extensive enough, to fulminant hepatic failure. They include accidental ligation of the hepatic artery (which is not ordinarily fatal in patients with normal hepatic function but which appears to be highly dangerous when it occurs during the performance of portacaval anastomosis for cirrhosis), acute Budd-Chiari syndrome, acute circulatory failure with or without acute myocardial infarction, and acute pulmonary failure. In these last two conditions hepatic necrosis even when present is not necessarily the ultimate cause of death. The hepatic necrosis of heatstroke is likely to be due to hepatic hypoxia secondary to circulatory collapse, although direct thermal injury may be a contributory factor.

Metabolic Anomalies

Acute fatty liver of pregnancy, a rare condition believed to be related to depressed protein anabolism, occurs almost exclusively in primiparae, generally during the last month of gestation, and usually terminates in fatal fulminant hepatic failure. Clinically it may be indistinguishable from acute viral hepatitis, although the serum transaminase and alkaline phosphatase values are only moderately raised. The histological change consists in multiple intracellular fat droplets without significant necrosis and affects the whole liver lobule except a thin rim of cells in the perportal areas. Most of the patients reported since 1963 had taken tetracycline in unduly high dosage.
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Reye’s syndrome, or encephalopathy and fatty liver, first recognized just under 10 years ago, is placed here for convenience under ‘metabolic anomalies’. In fact its aetiology is uncertain and it may be that the metabolic anomaly is triggered by virus infection or by toxins. It occurs in children under the age of 15 years and is characterized by a prodromal illness with vomiting followed by lethargy, convulsions, coma, and death in 50% of cases. Jaundice is absent or mild, but the liver is usually enlarged. Elevated serum glutamic oxaloacetic transaminase activity and prolonged prothrombin time are constant features. The principal histological finding is fine fat globules in the parenchymal cells of the liver; they are also found in other organs, especially the heart and the kidneys. In the brain there is oedema and neurone degeneration, and the neuropsychiatric manifestations are probably the joint product of cerebral damage and hepatocellular failure.

Clinical Manifestations

Liver
Jaundice, deep and progressive, is usual but not constant. It precedes encephalopathy, only exceptionally appearing after its onset. The liver is small, but when hepatic necrosis is massive there may be hepatomegaly. Fulminant hepatic failure due to poisoning by Amanita mushrooms or to acute Budd-Chiari syndrome is associated with abdominal pain, generally referred to the right upper abdominal quadrant but sometimes to the right lower quadrant, and may therefore simulate an acute abdominal emergency. In viral fulminant hepatic failure the liver is rarely painful. Ascites occurs in some 10% of cases of fulminant hepatic failure from any cause, mainly in patients who have survived for five days or more. Foetor hepaticus is usually pronounced.

The laboratory findings are those of hepatic cell damage. Hyperbilirubinaemia, with serum bilirubin levels generally over 20 mg per 100 ml and conjugated bilirubin predominating in a ratio of 4:1, is the rule. Serum transaminase values are markedly raised in all cases of fulminant hepatic failure associated with hepatic necrosis; they are moderately raised or, exceptionally, normal in fulminant hepatic failure associated with fatty change. Serum alkaline phosphatase activity is normal or moderately elevated. Serum albumin levels are usually normal but may fall in patients who survive with fulminant hepatic failure for over a week. Blood ammonia concentration is elevated, but normal values have been observed.

Neuropsychiatric Changes
In the progression of fulminant hepatic failure we distinguish three stages of neuropsychiatric deterioration.

Stage I
Reduced mental alertness, with asterixis and/or flapping tremor.*

Stage II
Mental confusion manifested as disorientation in time and space and palilalia. In some 50% of cases confusion is associated with restlessness.

*These two conditions are often confused. Asterixis is intermittent sustained muscle contraction; flapping tremor is a coarse tremor resembling that of Parkinson’s disease but occurring only when the limbs are held in certain postures.
Stage III

This stage in turn has been divided into three stages.

In stage IIIa coma is shallow; some spontaneous movement still occurs; the tendon, corneal, and light reflexes are normal; the plantar response is present, but may be in extension.

In stage IIIb coma deepens; the tendon, corneal, light, and plantar reflexes become lost; decerebrate and decorticate postures may develop\textsuperscript{55}; spontaneous ventilation is preserved; in half the cases convulsions, generally of Jacksonian type, occur\textsuperscript{55,56}.

Stage IIIc is irreversible coma. It may set in gradually, or be ushered in by a 'crisis' which may be the expression of cerebral oedema or of cerebellar or uncal herniation\textsuperscript{57}. Such crises may take the form of convulsions, exacerbation of hyperventilation, rise in blood pressure, or rise in body temperature.

The above classification of the stages in the neuropsychiatric aberration of fulminant hepatic failure differs from the classifications proposed by other investigators. Trey and Davidson\textsuperscript{8}, following Adams and Foley\textsuperscript{58}, distinguish: stage I, with euphoria, confusion, mental slowness, and slurred speech; stage II, accentuation of stage I plus improprieties of behaviour; stage III, somnolence and incoherent speech; and stage IV, coma.

Fulminant hepatic failure is almost invariably accompanied by abnormalities in the electroencephalogram\textsuperscript{49,58}. The changes occur early and have been observed by Trey and Davidson\textsuperscript{3} at their stage II. The usual pattern of electrical activity consists of slow waves of high amplitude, and severe cases may show paroxysms of bilaterally synchronous delta waves. The terminal stage is marked by gradually fading low-voltage activity. Multiple spikes occur, especially, but not exclusively, during convulsions. Unexplained improvement in the electroencephalographic pattern is not necessarily of good prognostic significance; it may be transitory, and has been encountered in cases in which the outcome was fatal. In a five-grade classification of electroencephalograms from patients with liver disease Parsons-Smith et al\textsuperscript{99} found a good correlation between neuropsychiatric aberrations and severity of electroencephalographic changes.

Disorders of coagulation

Thrombocytopenia, prothrombin deficiency expressed as prolonged prothrombin time, and depression of plasma fibrinogen and of plasma factors II, V, VII, IX, and X are almost constant features of fulminant hepatic failure\textsuperscript{51,56,60–62}. Deficiencies in the clotting factors are generally attributed to reduced synthesis by the damaged liver, but there is evidence that in at least a third of patients utilization of these factors also is accelerated and is related to intravascular coagulation. Pointers to the occurrence of intravascular coagulation are: (1) thrombocytopenia in the blood with no reduction of megakaryocytes in the bone marrow\textsuperscript{62}; (2) more rapid decrease in clotting factors than can be accounted for by arrested synthesis alone\textsuperscript{60}; (3) increase in the plasma disappearance rate of \textsuperscript{125}I-labelled fibrinogen\textsuperscript{61}; and (4) the presence in the blood of fibrin-degradation products in the absence of circulating activator of plasminogen\textsuperscript{62}. In the remaining two-thirds of patients plasminogen activator is found in the blood and one cannot know whether fibrinolysis is primary or secondary to intravascular coagulation. Fulminant hepatic failure with no reduction in fibrinogen and no
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fibrin-degradation products in the blood occurs, but is unusual. Plasma factor VIII activity is elevated in viral hepatitis, normal or moderately depressed in the hepatitis of A. phalloides poisoning.

Despite the coagulation defects, haemorrhage is not always life-threatening. It was the cause of death in five only of a series of 60 patients with viral fulminant hepatic failure; three had gastrointestinal haemorrhage and two had massive postpartum uterine bleeding; a large haematoma developed in the brain stem in one of these patients. On the other hand, Williams has reported major bleeding as directly responsible for death in 21 of a series of 30 patients, while Saunders et al. encountered life-threatening haemorrhage in more than half the adults and 70% of the children of their large series.

We have observed fulminant hepatic failure without pronounced coagulation-factor deficiencies, but this is exceptional.

Disorders of Ventilation and of Acid-Base Balance

Nearly all patients with fulminant hepatic failure show hyperventilation with consequent hypocapnia. A patient with hypercapnia is unlikely to have fulminant hepatic failure, unless the hypercapnia can be accounted for by obstruction to the respiratory passages. Moderate depression of serum bicarbonate level is the rule, with pH in the range 7.40-7.60. In the rare cases with markedly lowered serum bicarbonate concentration and pH below 7.10, lactic acid accumulates in the blood with resultant metabolic acidosis.

We have seen spontaneous regression of hyperlactacidaemia in three patients with viral fulminant hepatic failure.

Cardiovascular Disorders

Tachycardia, low blood pressure, and reduced total blood volume are the characteristic cardiovascular features of fulminant hepatic failure. Cardiac output is usually high. Two of our patients had sinus bradycardia with a pulse rate of around 40 per minute but recovered none the less.

Renal Disorders

Renal abnormality with oliguria as the presenting symptom has been reported. Weight increase by about 0.5 kg per day is frequent and is probably due to salt and water retention. Hypokalaemia is present early. Hyponatraemia is common, probably because water retention exceeds sodium retention. In patients who survive for four days or longer oliguria may become intense, even in the presence of a normal blood pressure.

Other Disorders

Profuse sweating in the absence of fever, hypercapnia, or hypoglycaemia is seen in some 25% of cases. Hypoglycaemia may occur; in children it is often early and severe. It can be reversed by intravenous glucose, of which very large amounts may be needed. Polymorphonuclear leucocytosis is practically always present. Moderate elevation of serum amylase is the rule, and acute pancreatitis has been reported.

Prognosis

The mortality rate of fulminant hepatic failure is of the order of 80 to 90% in adults and 50% in children. Statistical studies have shown that in
viral fulminant hepatic failure the following elements are of significantly bad
prognostic omen: age over 40 years; clinically detectable reduction in liver
volume; hypcapnia with partial pressure of carbon dioxide in arterial blood
inferior to 30 mmHg; pulse rate over 120 beats per minute; convulsions
and/or decerebrate postures; one-stage prothrombin time over 50 seconds;
blood ammonia level above 2 μg per ml. No single one of these features
necessarily presages a fatal outcome and all have been observed in patients
who got better. On the other hand we have never known a patient over
60 recover. Like other workers we have seen irreversible coma develop in
the presence of laboratory and histological evidence of liver regeneration.

Some investigators have proposed histological criteria as guides to
prognosis; it has been claimed that where necrosis affects more than 70%
of hepatocytes the outlook is poor. Such criteria may be statistically signifi-
cant but individual exceptions occur.

The first signs of a favourable outcome in our patients have been improve-
ment in deficiencies of coagulation factors, especially of factor V, and the
appearance, or increase, of alpha-1 fetoprotein in the serum. Neuropsy-
chiatric disturbance subsides within a week or 10 days and leaves no sequelae,
but jaundice persists for an additional two to six weeks. In our experience
the liver invariably returns to complete normality.

Treatment

For fulminant hepatic failure to be treated effectively the encephalopathy
has to be reversible and the liver capable of regenerating. But in a given
case we have no means of assessing either the reversibility or otherwise of
encephalopathy or the regenerative potential of the liver.

Many forms of treatment have been proposed, and success in
individual cases has led to unfounded claims of efficacy. Corticosteroid drugs,
exchange blood transfusion, haemodialysis, extracorporeal liver perfusion,
and cross circulation have been tried, but neither review of the literature nor
our own experience gives grounds to believe that they have made a significant
impression on recovery rates. Enough patients have been treated by corti-
costeroids and by exchange transfusion to justify an adverse verdict on these
forms of therapy; in the case of exchange transfusion, such a verdict has
been confirmed in a recent controlled trial. Judgment on the other methods
mentioned above must be suspended meantime, because of the paucity and
the heterogeneity of the reported cases and the absence of controlled studies.
There is evidence that cross circulation has a negligible effect at exchange
rates between 100 and 200 ml per minute but that at higher exchange
rates it may possibly be beneficial. Fatal bone marrow aplasia in a healthy
voluntary donor immediately after cross circulation has been reported
and it is safer to use as partners either patients in irreversible coma or
baboons.

Intensive therapy with heparin aimed at controlling intravascular coagula-
tion has been proposed, and encouraging results reported. However, of
seven patients with fulminant hepatic failure recently treated with high doses
of heparin combined with replacement therapy, only one recovered and three
had massive gastrointestinal bleeding. It is too early yet to assess the useful-
ness of exchange transfusion followed by infusion of human anti-hepatitis B
antigen plasma in patients with fulminant hepatitis B antigen-positive viral
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hepatitis. Liver transplantation has been performed in six patients with fulminant hepatic failure but, so far as our knowledge goes, with success in one case only. Promising results have been reported with total body washout.

General supportive measures, indispensable whatever be the type of specific therapy favoured, include a daily intake of 2 l of water, 1 to 2 l of blood and/or plasma, 200 g of glucose, and 50 m-equiv of potassium. Antibiotics should be given to combat the risk of infection from intravenous tubes and urinary catheters. Endotracheal intubation and assisted respiration may be necessary. Heart failure will call for the administration of lanatoside C, convulsions for chloral or diazepam, and water and sodium retention for the intravenous administration of frusemide. Since even small doses of narcotics or sedatives may precipitate deep coma in patients with fulminant hepatic failure it may be safer to control restlessness by physical restraint than by the administration of these agents.

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