Gut, 1973, **14**, 805-815

Progress report

Acute hepatic necrosis and fulminant hepatic failure

Fulminant hepatic failure[1] 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[1,2]. Characteristic biochemical changes are increased prothrombin time, elevated serum transaminase activity, and raised blood ammonia concentration[3].

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[6]. Yet, parenteral administration of cytidine and uridine was without effect on encephalopathy in hepatectomized animals and in 10 patients with fulminant hepatic failure[7].

Or is encephalopathy brought about by accumulation of neurotoxic substances which the normal liver eliminates or detoxicates? Ammonia has been incriminated[8]: there is substantial evidence that it alters cerebral metabolism in hepatic coma but information derived from clinical studies is as yet

*In order to be included in the fulminant hepatic failure surveillance study[3], the syndrome must occur within eight weeks of the onset of illness; we, however, regard this interval as too long.

inconclusive[9]; the administration of substances reputed to lower blood ammonia concentration has been reported to have no beneficial effect in encephalopathy[10,11]. The improvement in encephalopathy which has been found to follow administration of the neurotransmitter monoamine levodopa[12–14] 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 evisceration[15].

Aetiology

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

Infections	*Poisons, Chemicals, and Drugs*[1]	*Ischaemia and Hypoxia*	*Metabolic Anomalies*
Viral hepatitis	Hepatoxicity	Ligation of hepatic artery	Acute fatty liver of pregnancy[2]
Infectious hepatitis	*Amanita phalloides* poisoning	Acute Budd-Chiari syndrome	Reye's syndrome[2]
Serum hepatitis	Paracetamol	Acute circulatory failure	
Marburg monkey disease	Tetracycline[2]	Acute pulmonary failure	
Disseminated herpes simplex virus infection	Yellow phosphorus	Heatstroke	
Reovirus infection	Certain (chiefly halogenated) hydrocarbons		
Coxsackie virus infection	Ethanol[2]		
Adenovirus infection	Hepatitis-like reaction		
Glandular fever	Halothane		
Q fever	Metahexamid		
	Zoxazolamine		
	Monoamine oxidase inhibitors		
	Hycanthone		

Table *Principal causes of fulminant hepatic failure*

[1]For an extensive list of substances liable to cause liver damage see Sicot *et al*[4] and Berthelot *et al*[5].
[2]The 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 reported[18]. There is evidence that fulminant hepatic failure is more liable to occur in virus B than in virus A infections[17]. Patients with serum hepatitis, the form of viral hepatitis with which virus B is predominantly associated[19], having a higher mean age than patients with infectious hepatitis[20], 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[16] but fulminant hepatic failure is more common in females than in males[17,21]. A study conducted in 1966[22] 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[23] and Saudi Arabia[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[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[26].

Acute hepatic necrosis, sometimes leading to fulminant hepatic failure, has been known to occur in the following infections: Marburg monkey disease[27]; disseminated herpes simplex virus infection in newborns[28] or (less commonly) in adults[29]; infections with reovirus[30], Coxsackie virus[31], or adenovirus[32]; glandular fever[33]; and Q fever[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%[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[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[35].

Overdose of paracetamol with suicidal intent has been reported from Great Britain[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[38].

Among other chemicals which have been reported from time to time as causing massive hepatic necrosis and fulminant hepatic failure are yellow phosphorus[4], contained in various rat poisons, and nitrated or halogenated hydrocarbons[4], 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[39].

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[2,3,40]. 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 fulminant 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, phenipra-zine, and phenoxypropazine[5,21,41], and hycanthone[42].

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[43] but which appears to be highly dangerous when it occurs during the performance of portacaval anastomosis for cirrhosis[44]), acute Budd-Chiari syndrome[45], acute circulatory failure with or without acute myocardial infarction[46], and acute pulmonary failure[47]. 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[48].

METABOLIC ANOMALIES

Acute fatty liver of pregnancy[49], 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 periportal areas[22]. Most of the patients reported since 1963 had taken tetracycline in unduly high dosage[38].

Reye's syndrome, or encephalopathy and fatty liver, first recognized just under 10 years ago[50], 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[51]. 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[52]. 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[53]. 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[52]. 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[44].

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[55]; spontaneous ventilation is preserved; in half the cases convulsions, generally of Jacksonian type, occur[52,56].

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[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[3], following Adams and Foley[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[49,58]. The changes occur early and have been observed by Trey and Davidson[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*[59] 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[21,56,60–62]. 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[62]; (2) more rapid decrease in clotting factors than can be accounted for by arrested synthesis alone[60]; (3) increase in the plasma disappearance rate of ^{125}I-labelled fibrinogen[61]; and (4) the presence in the blood of fibrin-degradation products in the absence of circulating activator of plasminogen[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

fibrin-degradation products in the blood occurs, but is unusual[62]. Plasma factor VIII activity is elevated in viral hepatitis[56,62,63], normal or moderately depressed in the hepatitis of *A. phalloides* poisoning[60].

Despite the coagulation defects, haemorrhage is not always life-threatening[17,62,64]. It was the cause of death in five only of a series of 60 patients with viral fulminant hepatic failure[52]; 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[65] has reported major bleeding as directly responsible for death in 21 of a series of 30 patients, while Saunders *et al*[66] 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[52]. 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[52]. 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[56,65]. We have seen spontaneous regression of hyperlactacidaemia in three patients with viral fulminant hepatic failure.

CARDIOVASCULAR DISORDERS

Tachycardia, low blood pressure[17,52], and reduced total blood volume[67] are the characteristic cardiovascular features of fulminant hepatic failure. Cardiac output is usually high[3,68]. 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[64]. Weight increase by about 0·5 kg per day is frequent and is probably due to salt and water retention. Hypokalaemia is present early[65]. 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[65]; in children it is often early and severe. It can be reversed by intravenous glucose, of which very large amounts may be needed[69]. Polymorphonuclear leucocytosis is practically always present. Moderate elevation of serum amylase is the rule, and acute pancreatitis has been reported[56,65].

Prognosis

The mortality rate of fulminant hepatic failure is of the order of 80 to 90% in adults[3,70] and 50% in children[70]. 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; hypocapnia 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[70,71]. No single one of these features necessarily presages a fatal outcome and all have been observed in patients who got better[70]. On the other hand we have never known a patient over 60 recover. Like other workers[71] we have seen irreversible coma develop in the presence of laboratory and histological evidence of liver regeneration.

Some investigators[71,72] 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 significant but individual exceptions occur.

The first signs of a favourable outcome in our patients have been improvement in deficiencies of coagulation factors, especially of factor V, and the appearance, or increase, of alpha-1 fetoprotein in the serum[73]. Neuropsychiatric 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[3,65,66,74,75], 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 corticosteroids and by exchange transfusion to justify an adverse verdict on these forms of therapy[65,74]; in the case of exchange transfusion, such a verdict has been confirmed in a recent controlled trial[76]. 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[77] but that at higher exchange rates it may possibly be beneficial[78]. Fatal bone marrow aplasia in a healthy voluntary donor immediately after cross circulation has been reported[79] and it is safer to use as partners either patients in irreversible coma or baboons[80–82].

Intensive therapy with heparin aimed at controlling intravascular coagulation has been proposed[61], and encouraging results reported[65,83]. 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[84]. It is too early yet to assess the usefulness of exchange transfusion followed by infusion of human anti-hepatitis B antigen plasma in patients with fulminant hepatitis B antigen-positive viral

hepatitis[85]. Liver transplantation has been performed in six patients with fulminant hepatic failure[86–89] but, so far as our knowledge goes, with success in one case only[87]. Promising results have been reported with total body washout[90–92].

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[93,94].

B. RUEFF[1] AND J.-P. BENHAMOU

Unité de Recherches de Physiopathologie Hépatique (INSERM), and Centre de Réanimation des Maladies du Foie et des Hémorragies Digestives, Hôpital Beaujon, Clichy, France

[1]Please address requests for reprints to Dr Bernard Rueff, Hôpital Beaujon, 100, Boulevard du Général Leclerc, 92110 Clichy, France.

References

[1]Lucké, B., and Mallory, T. (1946). The fulminant form of epidemic hepatitis. *Amer. J. Path.*, **22**, 867-945.
[2]Trey, C., Lipworth, L., Chalmers, T. C., Davidson, C. S., Gottlieb, L. S., Popper, H., and Saunders, S. J. (1968). Fulminant hepatic failure. Presumable contribution of halothane. *New Engl. J. Med.*, **279**, 798-801.
[3]Trey, C., and Davidson, C. S. (1970). The management of fulminant hepatic failure. In *Progress in Liver Diseases*, edited by H. Popper and F. Schaffner, Vol. 3, pp. 282-298. Grune and Stratton, New York, and Heinemann, London.
[4]Sicot, C., Bismuth, C., Fréjaville, J. P., Berthelot, P., Rueff, B., and Benhamou, J. P. (1969). Les hépatites toxiques. *Rev. franç. Étud. clin. biol.*, **14**, 192-212.
[5]Berthelot, P., Sicot, C., Benhamou, J. P., and Fauvert, R. (1965). Les hépatites médicamenteuses. II. Étude analytique des médicaments responsables. *Rev. franç. Étud. clin. biol.*, **10**, 140-179.
[6]Geiger, A., and Yamasaki, S. (1956). Cytidine and uridine requirement of the brain. *J. Neurochem.*, **1**, 93-100.
[7]Sicot, C., Degos, J. D., and Rueff, B. (1970). Unpublished data.
[8]Walker, C. O., and Schenker, S. (1970). Pathogenesis of hepatic encephalopathy—with special reference to the role of ammonia. *Amer. J. clin. Nutr.*, **23**, 619-632.
[9]Davidson, C. S., and Gabuzda, G. J. (1969). Hepatic coma. In *Diseases of the Liver*, 3rd ed., edited by L. Schiff, pp. 378-409. Lippincott, Philadelphia.
[10]Reynolds, T. B., Redeker, A. G., and Davis, P. (1958). A controlled study of the effects of L-arginine on hepatic encephalopathy. *Amer. J. Med.*, **25**, 359-367.
[11]Schwartz, R., Lehman, E., Hammond, J., Seibel, J. M., and Goldson, F. (1956). The failure of monosodium glutamate in the treatment of hepatic coma. *Gastroenterology*, **30**, 869-881.
[12]Parkes, J. D., Sharpstone, P., and Williams, R. (1970). Levodopa in hepatic coma. *Lancet*, **2**, 1341-1343.
[13]Sarrazin, A., Emerit, J., Olivier, L., Rebelo, F., and Bousquet, O. (1971). Traitement du coma hépatique par la L-Dopa: premiers résultats. *Presse méd.*, **79**, 2226-2227.
[14]Fischer, J. E., and James, J. H. (1972). Treatment of hepatic coma and hepatorenal syndrome: mechanism of action of L-dopa and aramine. *Amer. J. Surg.*, **123**, 222-230.
[15]Pujol, J. P., Prandi, D., Roche, J., Degos, F., Degos, J. D., Marleau, D., Bleichner, G., Weiss, Y., Rueff, B., and Sicot, C. (1971). The role of the intestine in experimental acute hepatic encephalopathy. (Abstr.) *Gut*, **12**, 769.
[16]Rowland, A. J., and Skone, J. F. (1972). Epidemiology of infectious hepatitis. *Brit. med. Bull.*, **28**, 149-155.
[17]Boughton, C. R. (1968). Viral hepatitis in Sydney: a review of fatal illnesses in a hospital series. *Med. J. Aust.*, **2**, 343-350.
[18]Chalmers, T. C., Koff, R. S., and Grady, G. F. (1965). A note on fatality in serum hepatitis. *Gastroenterology*, **49**, 22-26.
[19]Blumberg, B. S., Sutnick, A. I., and London, W. T. (1970). Australia antigen as a hepatitis virus: variation in host response. *Amer. J. Med.*, **48**, 1-7.
[20]Mosley, J. W., and Galambos, J. T. (1969). Viral hepatitis. In *Diseases of the Liver*, 3rd ed., edited by L. Schiff, pp. 410-497. Lippincott, Philadelphia and Toronto.
[21]Cook, G. C., and Sherlock, S. (1965). Jaundice and its relation to therapeutic agents. *Lancet*, **1**, 175-179.
[22]Haemmerli, U. P. (1966). Jaundice during pregnancy with special emphasis on recurrent jaundice during pregnancy and its differential diagnosis. *Acta med. scand.*, Suppl. no. **444**.
[23]Delons, S., Berbich, A., Reynaud, R., and Lebon, P. (1968). Contribution à l'étude des ictères graves de la femme enceinte au Maroc. *Rev. méd.-chir. Mal. Foie*, **43**, 117-130.

[34]Gelpi, A. P. (1970). Fatal hepatitis in Saudi Arabian women. *Amer. J. Gastroent.*, **53**, 41-61.
[35]Chalmers, T. C. (1969). Rest and exercise in hepatitis. *New Engl. J. Med.*, **281**, 1421-1422.
[36]Blum, A. L., Stutz, R., Haemmerli, U. P., Schmid, P., and Grady, G. F. (1969). A fortuitously controlled study of steroid therapy in acute viral hepatitis. I. Acute disease. *Amer. J. Med.*, **47**, 82-92.
[37]Martini, G. A., Knauff, H. G., Schmidt, H. A., Mayer, G., and Baltzer, G. (1968). Über eine bisher unbekannte, von Affen eingeschleppte Infektionskrankheit: Marburg-Virus-Krankheit. *Dtsch. med. Wschr.*, **93**, 559-571.
[38]Miller, D. R., Hanshaw, J. B., O'Leary, D. S., and Hnilicka, J. V. (1970). Fatal disseminated herpes simplex virus infection and hemorrhage in the neonate: coagulation studies in a case and a review. *J. Pediat.*, **76**, 409-415.
[39] *British Medical Journal* (1973). Editorial. Herpes hepatitis in adults. *Brit. med. J.*, **1**, 248.
[40]Joske, R. A., Keall, D. D., Leak, P. J., Stanley, N. F., and Walters, M. N. I. (1964). Hepatitis-encephalitis in humans with reovirus infection. *Arch. intern. Med.*, **113**, 811-816.
[41]Benirschke, K., Kibrick, S., and Craig, J. M. (1958). The pathology of fatal Coxsackie infection in the newborn. *Amer. J. Path.*, **34**, 587.
[42]Wigger, H. J., and Blanc, W. A. (1966). Fatal hepatic and bronchial necrosis in adenovirus infection with thymic alymphoplasia. *New Engl. J. Med.*, **275**, 870-874.
[43]Allen, U. R., and Bass, B. H. (1963). Fatal hepatic necrosis in glandular fever. *J. clin. Path.*, **16**, 337-341.
[44]Alkan, W. J., Evenchik, Z., and Eshchar, J. (1965). Q fever and infectious hepatitis. *Amer. J. Med.*, **38**, 54-61.
[45]Sicot, C., Bismuth, C., Pébay-Peyroula, F., Fréjaville, J. P., and Rueff, B. (1969). Eléments du pronostic des intoxications phalloïdiennes. *J. europ. Toxicol.*, **2**, 250-253.
[46]Sicot, C., Bismuth, C., Fréjaville, J. P., Rueff, B., Boivin, P., and Benhamou, J.-P. (1968). Intérêt des dosages répétés de la transaminase glutamo-pyruvique pour le pronostic des intoxications phalloïdiennes. *Rev. franç. Étud. clin. biol.*, **13**, 1022-1024.
[47]Proudfoot, A. T., and Wright, N. (1970). Acute paracetamol poisoning. *Brit. med. J.*, **3**, 557-558.
[48]Combes, B., Whalley, P. J., and Adams, R. H. (1972). Tetracycline and the liver. In *Progress in Liver Diseases*, edited by H. Popper and F. Schaffner, Vol. 4, pp. 589-596. Grune and Stratton, New York, and Heinemann, London.
[49]Galambos, J. T. (1972). Alcoholic hepatitis: its therapy and prognosis. In *Progress in Liver Diseases*, edited by H. Popper and F. Schaffner, Vol. 4, pp. 567-588. Grune and Stratton, New York, and Heineman, London.
[50]Sherlock, S. (1971). Halothane hepatitis. *Gut*, **12**, 324-329.
[51]Klatskin, G. (1969). Toxic and drug-induced hepatitis. In *Diseases of the Liver*, 3rd ed., edited by L. Schiff, pp. 498-601. Lippincott, Philadelphia.
[52]Lapierre, J., Holler, C., Saison, E., and Tran Vinh Hien. (1973). La bilharziose: soixante-seize cas traités par l'hycanthone. *Nouv. Presse méd.*, **2**, 901-905.
[53]Brittain, R. S., Marchioro, T. L., Hermann, G., Waddell, W. R., and Starzl, T. E. (1964). Accidental hepatic artery ligation in humans. *Amer. J. Surg.*, **107**, 822-832.
[54]Maillard, J. N., Huguier, M., and Rueff, B. (1971). Interruption of the hepatic artery: accidental in the course of portacaval anastomosis. *Minnesota Med.*, **54**, 81-85.
[55]Berthelot, P., Mignon, F., and Maillard, J. N. (1969). Syndrome aigu de Budd-Chiari. I. Aspects cliniques et biologiques de deux observations. *Rev. méd.-chir. Mal. Foie*, **44**, 25-28.
[56]Bang, N. U., Iversen, K., Jagt, T., and Tobiassen, G. (1959). Serum glutamic-oxaloacetic transaminase activity as an index of centrilobular liver cell necrosis in cardiac and circulatory failure. *Acta med. scand.*, **164**, 385-393.
[57]Refsum, H. E. (1964). Severe arterial hypoxemia and liver-cell necrosis in patients with pulmonary insufficiency. *Acta med. scand.*, **176**, 473-478.
[58]Kew, M., Bersohn, I., Seftel, H., and Kent, G. (1970). Liver damage in heatstroke. *Amer. J. Med.*, **49**, 192-202.
[59]Sherlock, S. (1968). *Diseases of the Liver and Biliary System*, 4th ed., pp. 548-550 and 106-107. Blackwell Scientific Publications, Oxford and Edinburgh.
[60]Reye, R. D. K., Morgan, G., and Baral, J. (1963). Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood. *Lancet*, **2**, 749-752.
[61]Schubert, W. K., Partin, J. C., and Partin, J. S. (1972). Encephalopathy and fatty liver (Reye's syndrome). In *Progress in Liver Diseases*, edited by H. Popper and F. Schaffner, Vol. 4, pp. 489-510. Grune and Stratton, New York, and Heinemann, London.
[62]Rueff, B., Sicot, C., and Benhamou, J.-P. (1969). Les hépatites aiguës comateuses: sémiologie et évolution. In *Journées de réanimation de l'Hôpital Claude-Bernard*, Part I, pp. 131-143. Arnette, Paris.
[63]Rolett, E. L., and Sleisenger, M. H. (1959). The diagnosis of acute viral hepatitis simulating an abdominal emergency: a case report. *Ann. intern. Med.*, **51**, 1071-1077.
[64]Victor, M., Adams, R. D., and Cole, M. (1965). The acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. *Medicine (Baltimore)*, **44**, 345-396.
[65]Conomy, J. P., and Swash, M. (1968). Reversible decerebrate and decorticate postures in hepatic coma. *New Engl. J. Med.*, **278**, 876-879.
[66]Opolon, P., Hecht, Y., Theodoropoulos, G., Hadchouel, P., Grynblat, A., and Caroli, J. (1969). Ictères graves par nécrose hépatique aiguë. I. Étude clinique, biologique et anatomique de 48 cas. *Rev. méd.-chir. Mal. Foie*, **44**, 251-279.
[67]Ware, A. J., D'Agostino, A. N., and Combes, B. (1971). Cerebral edema: a major complication of massive hepatic necrosis. *Gastroenterology*, **61**, 877-884.
[68]Adams, R. D., and Foley, J. M. (1953). The neurological disorder associated with liver disease. *Res. Publ. Ass. nerv. ment. Dis.*, **32**, 198-237.
[69]Parsons-Smith, B. G., Summerskill, W. H. J., Dawson, A. M., and Sherlock, S. (1957). The electroencephalograph in liver disease. *Lancet*, **2**, 867-871.
[70]Ménaché, D., Guillin, M. C., Rueff, B., Bismuth, C., Fréjaville, J. P., Sicot, C., and Benhamou, J. P. (1968). Etude de l'hémostase au cours des hépatites phalloïdiennes. In *Problèmes de Réanimation*, 5th Series, edited by A. Larcan, pp. 449-512. S.P.E.I., Paris.
[71]Rake, M. O., Flute, P. T., Pannell, G., and Williams, R. (1970). Intravascular coagulation in acute hepatic necrosis. *Lancet*, **1**, 533-537.
[72]Guillin, M. C., Ménaché, D., Barge, J., Rueff, B., and Fauvert, R. (1971). Les troubles de l'hémostase au cours des hépatites virales graves: Etude clinique, anatomique et biologique. *Ann. Méd. interne*, **122**, 605-612.

[63]Meili, E. O., and Straub, P. W. (1970). Elevation of factor VIII in acute fatal liver necrosis. *Thrombos. Diathes. haemorrh. (Stuttg.)*, **24**, 161-174.
[64]Ritt, D. J., Whelan, G., Werner, D. J., Eigenbrodt, E. H., Schenker, S., and Combes, B. (1969). Acute hepatic necrosis with stupor or coma: an analysis of thirty-one patients. *Medicine (Baltimore)*, **48**, 151-172.
[65]Williams, R. (1972). Problems of fulminant hepatic failure. *Brit. med. Bull.*, **28**, 114-119.
[66]Saunders, S. J., Hickman, R., Macdonald, R., and Terblanche, J. (1972). The treatment of acute liver failure. In *Progress in Liver Diseases*, edited by H. Popper and F. Schaffner, Vol. 4, pp. 333-344. Grune and Stratton, New York, and Heinemann, London.
[67]Hecht, Y., Combrisson, A., Opolon, P., Boustani, R., and Caroli, J. (1970). Les troubles tensionnels et volémiques de l'insuffisance hépatique aiguë par nécrose aiguë du foie. *Rev. méd.-chir. Mal. Foie*, **45**, 7-12.
[68]Rueff, B., Roche, J., Hoanca, O., and Sicot, C. (1970). Le débit cardiaque au cours des hépatites graves. (Abstr.) *Biol. Gastro-ent.*, **2**, 177.
[69]Samson, R. I., Trey, C., Timme, A. H., and Saunders, S. J. (1967). Fulminating hepatitis with recurrent hypoglycemia and hemorrhage. *Gastroenterology*, **53**, 291-300.
[70]Rueff, B., Sicot, C., Benhamou, J. P., and Fauvert, R. (1971). Le pronostic des hépatites virales graves. *Ann. Méd. interne*, **122**, 373-380.
[71]Caroli, J., Opolon, P., Scotto, J., Hadchouel, P., Thomas, M., and Lageron, A. (1971). Eléments du pronostic au cours des comas par atrophie hépatique aiguë. *Presse méd.*, **79**, 463-466.
[72]Paliard, P., Patricot, F., and Grimaud, J. A. (1972). Les altérations histologiques des hépatites graves et leur évolution: à propos de 45 observations suivies par biopsie. *Ann. Gastroent. Hépat.*, **8**, 133-150.
[73]Schlegel, N., and Rueff, B. (1973). Unpublished data.
[74]Benhamou, J. P., Rueff, B., and Sicot, C. (1972). Severe hepatic failure: a critical study of current therapy. In *Liver and Drugs*, edited by F. Orlandi and A. M. Jézéquel, pp. 213-228. Academic Press, London and New York.
[75]Sherlock, S., and Parbhoo, S. P. (1971). The management of acute hepatic failure. *Postgrad. med. J.*, **47**, 493-498.
[76]Redeker, A. G., and Yamahiro, H. S. (1973). Controlled trial of exchange-transfusion therapy in fulminant hepatitis. *Lancet*, **1**, 3-6.
[77]Sicot, C., Fréjaville, J. P., Roche, J., Rueff, B., Benhamou, J. P., and Fauvert, R. (1971). Six cas d'hépatite grave traitée par circulation croisée interhumaine. *Ann. Méd. interne*, **122**, 381-387.
[78]Roche, J., Sicot, C., Rueff, B., Prandi, D., Degos, F., Degos, J. D., Weiss, Y., Pujol, J. P., and Benhamou, J.-P. (1972). The effect of cross-circulation on the encephalopathy of the liverless rat. The importance of the exchanged blood flow rate. (Abstr.) *Digestion*, **6**, 245-246.
[79]Muller, J. M., Guignier, M., Couderc, P., Debru, J. L., Franco, A., Cordonnier, D., Motin, J., Paliard, P., Robert, D., Petit, P., and Cuche, M. (1971). Les méthodes d'assistance hépatique: étude critique de leurs possibilités actuelles dans le traitement des insuffisances hépatiques aiguës d'origine virale ou toxique. *Ann. Gastroent. Hépat.*, **7**, 25-52.
[80]Muller, J. M., Guignier, M., Debru, J. L., Motin, J., Paliard, P., Robert, D., Petit, P., and Cuche, M. (1972). Application de la circulation croisée au traitement de l'insuffisance hépatique aiguë (I.H.A.) d'origine virale. *Sem. Hôp. Paris*, **48**, 2963-2969.
[81]Saunders, S. J., Terblanche, J., Bosman, S. C. W., Harrison, G. G., Walls, R., Hickman, R., Biebuyck, J., Dent, D., Pearce, S., and Barnard, C. N. (1968). Acute hepatic coma treated by cross-circulation with a baboon and by repeated exchange transfusions. *Lancet*, **2**, 585-588.
[82]Hume, D. M., Gayle, W. E., Jr., and Williams, G. M. (1969). Cross circulation of patients in hepatic coma with baboon partners having human blood. *Surg. Gynec. Obstet.*, **128**, 495-517.
[83]Rake, M. O., Flute, P. T., Shilkin, K. B., Lewis, M. L., Winch, J., and Williams, R. (1971). Early and intensive therapy of intravascular coagulation in acute liver failure. *Lancet*, **2**, 1215-1218.
[84]Guillin, M. C., Rueff, B., and Ménaché, D. (1972). Coagulation disorders in fulminant viral hepatitis: a therapeutic trial. (Abstr.) In *Proceedings of the Fifth International Meeting of the Association for the Study of the Liver*, Abstracts Book, p. 12. Éditions Médicales et Universitaires, Paris.
[85]Gocke, D. J. (1971). Fulminant hepatitis treated with serum containing antibody to Australia antigen. (Letter). *New Engl. J. Med.*, **284**, 919.
[86]Starzl, T. E., and Marchioro, T. L. (1967). Open discussion. *Transplantation*, **5**, 820-823.
[87]Bertoye, A., Marion, P., Mikaeloff, P., and Bolot, J. F. (1969). Essais de traitement de certaines insuffisances hépatiques graves aiguës par greffe hépatique temporaire hétérotopique hétérologue (foie de babouin). *Lyon méd.*, **222**, 347-374.
[88]Léger, L., Chapuis, Y., Lenriot, J. P., and Deloche, A. (1970). Transplantation hétérotopique d'un foie de babouin à l'homme. *Presse méd.*, **78**, 429-430.
[89]Chapuis, Y., and Huault, G. (1972). Personal communication.
[90]Klebanoff, G., Hollander, D., Cosimi, A. B., Stanford, W., and Kemmerer, W. T. (1972). Asanguineous hypothermic total body perfusion (TBW) in the treatment of stage IV hepatic coma. *J. surg. Res.*, **12**, 1-7.
[91]Klebanoff, G. (1973). Early experience with total body washout for hepatic coma. (Abstr.) *Gastroenterology*, **64**, 156.
[92]Tobias, H., and Isom, W. (1973). Total body perfusion in the treatment of hepatic coma secondary to fulminant hepatitis. (Abstr.) *Gastroenterology*, **64**, 157.
[93]Laidlaw, J., Read, A. E., and Sherlock, S. (1961). Morphine tolerance in hepatic cirrhosis. *Gastroenterology*, **40**, 389-396.
[94]*British Medical Journal* (1973). Editorial. Safe prescribing in liver disease. *Brit. med. J.*, **2**, 193-194.