New directions in acute liver failure

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This article is based on the Sir Jules Thorn lecture given at the Royal College of Physicians on 6 June 1994 by **Roger Williams,** Professor of Hepatology and Director of the Institute of Liver Studies, King's College School of Medicine and Dentistry, London.

In May 1973 the first two-bedded specifically designed unit for the treatment of acute liver failure was opened at King's College Hospital; in 1992 it was extended to a five-bedded unit, the treatment of acute liver failure (ALF) having been recognised as a supraregional specialty in 1986. The value of such a dedicated unit comes not only from the availability of all the specialised monitoring and treatment facilities that these very sick patients require, but also from the expertise of the medical and nursing staff. A 24-hour medical presence is essential. Events can happen so suddenly in these patients that intervention, if it is to be successful, has to be immediate.

Some evidence that such effort and expense are justified by an improvement in outcome is shown in Fig 1, which gives survival figures since the unit was opened. Only patients who developed grade III-IV encephalopathy are included; they are the most severely affected cases of ALF, for whom most current textbooks and review articles still quote an 80–90% mortality. Indeed, this is the justification for the increasingly early use of transplantation in these patients, an approach particularly favoured in the USA. In addition to transplantation and mannitol therapy for cerebral oedema, other developments in the intensive care regime underlying the improvement in overall results include better control of infection and management of the circulatory and metabolic disturbances. The survival figures are for all aetiologies of liver failure, and for some the outcome is even better: for instance, paracetamol overdose cases with grade III-IV encephalopathy had a survival rate of 64% in the most recent two-year period compared with 50% overall.

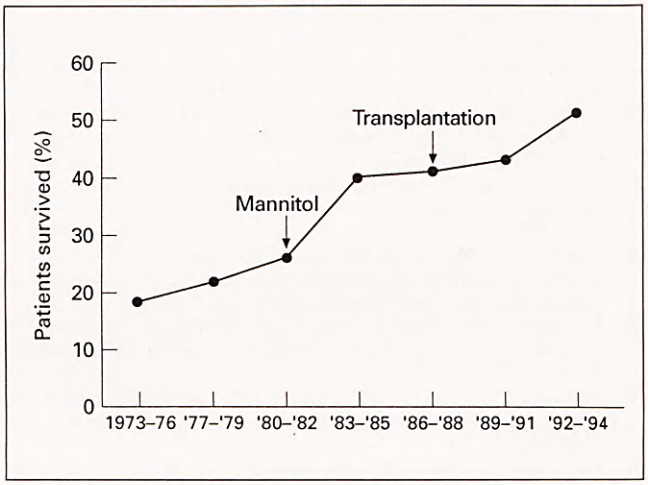

Fig 1. *Survival percentages for all aetiologies of fulminant hepatic failure in patients with grade III–IV encephalopathy only, since the liver failure unit opened in 1973; total of 1,231 patients shown.*

Classification and aetiology

Trey and Davidson in 1970 [1] were the first to describe as fulminant hepatic failure (FHF) a clinical syndrome of sudden and severe impairment of liver function characterised by the development of encephalopathy and occurring within eight weeks of the first symptoms of illness. In addition to the encephalopathy, the clinical syndrome is marked by severe coagulation and metabolic disturbance, together with cardiorespiratory and renal failure. But in those who do recover the liver, surprisingly, regains a completely normal structure. We proposed the term 'late-onset hepatic failure' (LOHF) in 1986 for agroup of patients in whom the appearance of encephalopathy is more delayed [2]. In recent years we have learned that the cases with the most rapid loss of consciousness have, paradoxically, a somewhat better chance of survival [3]. That, together with the results of a statistical analysis of data from some 600 patients with FHF and LOHF, led us to propose last year, with Schalm from Holland, a new classification to encompass both FHF and LOHF [4]. Acute liver failure is the core term and is prefixed by hyper- and sub- to describe two cohorts at the opposite ends of the clinical spectrum that exhibit significant deviations from the trends seen overall (Table 1). There is some correlation between the clinical category and the underlying aetiology. Thus 56% of the hepatitis A cases have a hyperacute course and only 14% are subacute, whereas the reverse applies to non-A non-B fulminant hepatitis where the greatest percentage follows a subacute course.

More information on the aetiology of ALF, as currently seen in this country, is afforded by an analysis of the 342 admissions to the liver failure unit during the

period 1992–4 (Table 2). Paracetamol overdose contributed the largest number of cases but this can no longer be described as 'the English disease' as cases are being reported from all over the world. A new feature is an increasing number of multiple drug overdoses, including two in which Ecstasy was implicated. In a considerable number of cases in the fulminant viral hepatitis group the presumed virus cause was not identified [5]. This applies also to series reported from the USA and continental Europe, although in Japan most of these cases appear to have hepatitis C infection. Dual infection with hepatitis B and C virus has been described in fulminant viral hepatitis by Benhamou's group at Clichy [6], and it is interesting to recall epidemiological evidence, from outbreaks of hepatitis in renal dialysis units in the 1970s, of an infection with an unidentified non-A non-B agent in addition to hepatitis B. This may be one of the factors responsible for acute viral hepatitis taking on a fulminant course.

The list of drugs that can cause an idiosyncratic drug reaction in presumably genetically sensitised subjects is ever lengthening. This year we have added the new anticonvulsant lamotrigine (Makin *et al*, manuscript submitted). The antituberculosis drugs are providing an increasing number of cases as a result of the re-emergence of this infection in the UK. Recognition of the variety of aetiologies in the 'others' category may allow specific therapy to be instituted, as for instance in lymphoma, which could be life-saving for the individual patient.

Assessment of prognosis

Apart from taking account of aetiology and rapidity of onset, can we assess the likely prognosis in individual cases of ALF, and with this the need for an emergency liver transplant? The decision needs to be taken as early as possible, thereby giving the best possible chance for obtaining a donor organ. The degree of prolongation of prothrombin time has been recognised for many years as a good indicator of prognosis [7]. This led to the King's College criteria for transplantation in ALF which have now been prospectively validated in a number of other centres [8]. In the non-paracetamol overdose category, a fatal outcome can be predicted with a high degree of certainty from the length of the prothrombin time alone or on the basis of three out of the five following variables: age, aetiology, jaundice to encephalopathy time, prothrombin prolongation and level of serum bilirubin. For the paracetamol overdose cases prediction of outcome is more difficult.

The Clichy group have found [9] that, along with encephalopathy, measuring Factor V is the most certain indicator. In Pittsburgh, the decision to transplant is based on the extent of reduction in the size of the liver as determined by CT scanning at the time an organ becomes available [10]. However, moving a patient with developing cerebral oedema can be dangerous and there are also risks in determining the extent of cell necrosis by liver biopsy. If submassive necrosis of 50% or more of the hepatic lobules is evident, transplantation should proceed, according to Van Thiel [10].

Multi-organ involvement in acute liver failure

As an immediate consequence of the acute liver injury, host defences to infection are severely compromised; secondary bacterial infection is associated with endotoxaemia, activation of macrophages, and release of cytokines and tumour necrosis factor, resulting in a clinical picture similar to that of septic shock, with hypotension and other circulatory changes causing tissue hypoxia and damage to a number of organs including the gut, and further ischaemic injury of the liver—a vicious cycle indeed.

With sepsis so important in pathogenesis, and with recurrent pulmonary infections and septicaemic episodes the major cause of morbidity and death in ALF, effective management or, better, prevention of infection is essential for improving survival.

Table 1. New classification of acute liver failure, based on interval between first sign of jaundice to appearance of encephalopathy, with frequency of different aetiology [4].

	Hyperacute 0–7 days	Acute 7–28 days	Subacute 5–26 weeks
Hepatitis A	55.2%	31%	13.8%
Hepatitis B	62.5%	29.9%	8.3%
Non-A non-B hepatitis	13.6%	38.8%	47.6%
Idiosyncratic drug reactions	35.2%	52.9%	11.7%

Table 2. Aetiology of 342 cases of acute liver failure admitted to the liver failure unit at King's College Hospital during 1992–4.

Overdose		*Other causes*	
Paracetamol	250	Wilson's	3
Ecstasy	2	Fatty liver of pregnancy	7
		Lymphoma/	
Viral hepatitis		malignant infiltration	7
A	8	Sepsis	2
B	8	Budd-Chiari	5
Non-A, B, C, D, E	28	Ischaemic hepatitis	9
		Miscellaneous	6

Idiosyncratic drug reactions
Lamotrigine, cyproterone, non-steroidal anti-inflammatory drugs, chloroquine, rifampicin/isoniazid, halothane, flucloxacillin 7

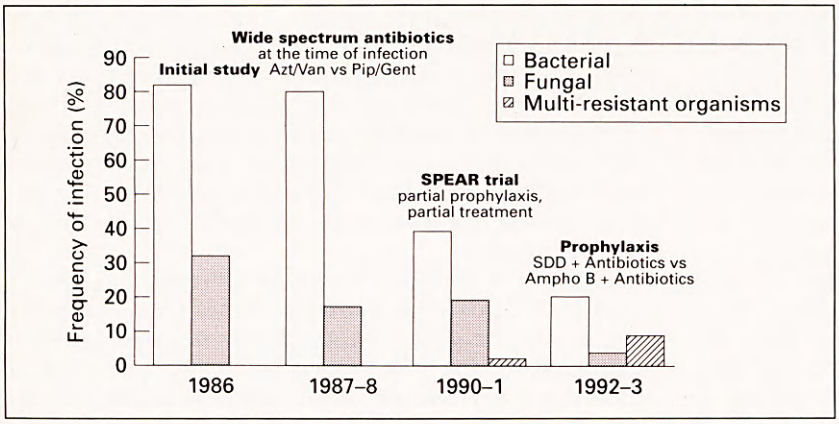

Fig 2. *Results of controlled clinical trials carried out in the liver failure unit, showing reduced incidence of bacterial and fungal infections with various treatment regimes.* Data of Rolando *et al* [12–14].

Fig 2 shows the results of a series of clinical trials at King's College Hospital. The initial study in 1986 [11,12] confirmed the high frequency of bacterial infections, and of fungal infections which appear later in the clinical course (80% and 30% of cases respectively). In the second study [13], wide-spectrum antibiotics were used at the first signs of infection, the patients being randomised to two antibiotic regimens. Little difference was observed between them, and the overall frequency of infection remained high. We then undertook a trial of prophylaxis with SPEAR (systemic parenteral and enteral antimicrobial regime) [14]. This reduced the frequency of infection to 30% overall, and it was further reduced in the most recent trial (manuscript in preparation), in which prophylaxis with the full SDD (selective decontamination of digestive tract) regime was compared with the effect of amphotericin B alone, both groups of patients also getting intravenous antibiotics at the first signs of an infection. A worrying development in this trial was the emergence of a significant number of infections from multiple resistant strains, especially *Enterococcus faecium* and *Klebsiella*. This may hamper further improvements to antibiotic regimes. Our latest trial is based on the use of granulocyte colony stimulating factor (G-CSF) administration to improve host defences in these patients. Defects in neutrophil adherence, migration and opsonisation were well demonstrated in the laboratory by Wyke some years ago [15,16], and against all these G-CSF has some action.

Hypotension and other circulatory changes

The severity of the vasodilatation and associated circulatory disturbances is closely related to the extent of underlying hepatic damage (Table 3). The non-survivors have lower mean arterial pressure and systemic vascular resistance. Oxygen consumption and oxygen extraction is decreased, much as found in other critically ill patients. As a consequence of the tissue hypoxia, there is a switch to anaerobic metabolism with a build-up of lactate in the serum. Bihari was the first to draw attention to the importance of microcirculatory disturbance in ALF and showed that an infusion of prostacyclin (a microcirculatory vasodilator) resulted in a significant increase in oxygen consumption consequent on the increase in oxygen delivery [17]. Wendon, continuing these studies, has shown that both adrenaline and noradrenaline are effective in maintaining systemic blood pressure. Their use is, however, accompanied by a fall in oxygen consumption, presumably as a result of an effect on tissue perfusion, and can be prevented by giving prostacyclin at the same time. The vasopressor agent angiotensin is of value as it allows noradrenaline requirements to be reduced whilst maintaining blood pressure and increasing oxygen consumption. Angiotensin may preferentially constrict microcirculatory shunts rather than the nutrient vessels.

In septic shock there is a massive release of nitric oxide, largely due to endotoxin-induced expression of the inducible nitric oxide synthase in vascular endothelial cells and smooth muscle cells. Infusion of low doses of LNMMA—a competitive antagonist—restores the blood pressure and responsiveness to pressor agents, and the same mechanisms probably pertain in the circulatory disturbance of ALF. Recent studies by Wendon have shown that large doses of LNMMA do have a pressor effect and have a detrimental effect on oxygen consumption despite protec-

Table 3. Haemodynamic measurements in survivors and non-survivors of acute liver failure [20].

	Survivors	Non-survivors	
MAP (mmHg)	92	77	
CI (l/min/m^2)	5.9	6.6	(2.5–3.6)
SVRI (dyne.sec.cm^5.m^2)	1268	825	(1200–2000)
VO_2 (ml/min/m^2)	135	108	(110–150)
OER (%)	2.4	4.9	(20–30%)
Lactate (mmol/l)	2.4	4.9	< 2.5

tion in these patients by pre-dosing with prostacyclin and acetylcysteine.

Of considerable importance was the demonstration by Harrison and Wendon that infusion of *N*-acetylcysteine improves blood flow as well as oxygen delivery and extraction by the tissues in both the systemic and the cerebral circulations [18]. The clinical benefits of such an infusion were shown in a controlled clinical trial carried out in ALF due to paracetamol overdose: the decreased frequency of multi-organ failure, particularly cerebral oedema, hypotension and renal failure, and the greater survival in the treated group was statistically highly significant [19]. The patients had grade III-IV encephalopathy and these important effects are quite separate from the better known antidote action of *N*-acetylcysteine when given within 12–15 hours of taking the overdose of paracetamol. Similar beneficial effects on the circulatory disturbances have been demonstrated in cases of ALF from fulminant viral hepatitis. We have postulated that the improvement is due to an enhancement of endothelial-derived relaxant factor (nitric oxide) at tissue level.

Cerebral oedema and ischaemia

The occurrence of cerebral oedema as an almost inevitable part of the progressive encephalopathy of ALF was recognised in the 1940s, and since then many experimental and clinical studies have been directed to the mechanisms involved, in particular whether it is predominantly the result of toxic damage to cell membranes or consequent to an increase in permeability of the cerebral blood vessels. If the accompanying elevation in intracranial pressure cannot be controlled, brain stem coning is likely as a terminal event. Sadly, there are instances of cerebral death from this cause in cases when the liver has begun to recover, and in patients who have undergone an otherwise successful liver transplantation.

Although it has been suggested that patients with grade IV encephalopathy have an elevated cerebral blood flow, thereby contributing to the rise in intracranial pressure, our most recent studies have shown that cerebral blood flow is almost invariably reduced [20]. Of note in Fig 3 are the two patients with very low values, for such reductions have been thought to be incompatible with neurological recovery; both patients survived. The cerebral metabolic rate for oxygen is greatly reduced, more than can be accounted for by the decreased metabolic requirements of coma. This is evident from the lower cerebral lactate production and greater cerebral oxygen consumption obtained when cerebral blood flow is increased by infusion of *N*-acetylcysteine or mannitol.

Monitoring of the cerebral state requires an appreciation not only of a rise in intracranial pressure but also of the dangers of ischaemia resulting from the decreased cerebral blood flow and oxygen delivery. An additional clinical event, recently demonstrated, is epileptiform activity. This is difficult to detect clinically in the paralysed, ventilated patient, and an EEG monitor is a valuable addition to the cerebral monitoring. The early recognition of this complication and its control by diazemols and/or phenytoin is of vital importance in minimising the likelihood of secondary cerebral oedema. During fits the jugular bulb oxygen saturation drops as a result of an increase in blood flow and oxygen consumption in the brain. Sequential measurements are of particular value; in an illustrative case, such treatment improved oxygen saturation (from 59% to 89%) and cerebral perfusion pressure (from 53 to 61 mmHg), and pupillary reactivity was restored.

In clinical practice, mannitol given in bolus doses has shown its value over and over again in the treatment of individual episodes of raised intracranial pressure: reduction in brain water consequent on the osmotic effect of mannitol is largely responsible for this effect. Once renal failure has developed, the administration of mannitol is coupled with the removal of two to three times the administered volume by ultrafiltration over 30 minutes. Although *N*-acetylcysteine has no effect on intracranial pressure, the increase in cerebral blood flow produced may prevent

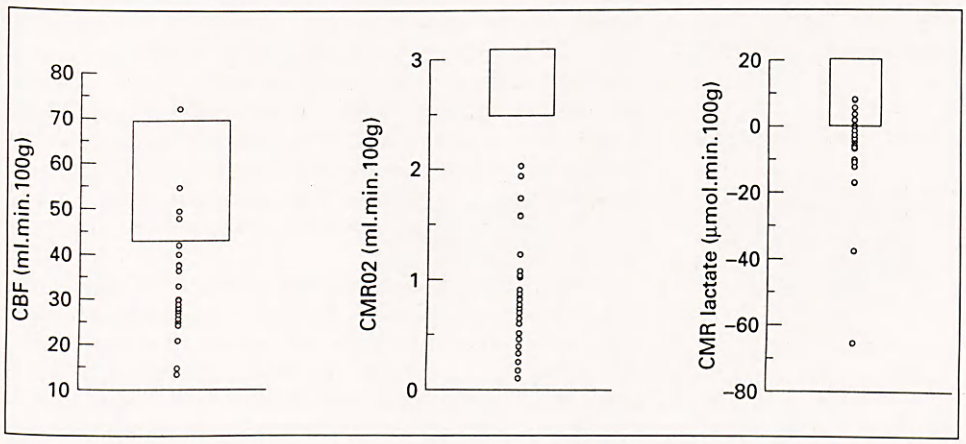

Fig 3. *Results of studies of cerebral circulation in 30 patients with grade IV coma.* Data from Wendon *et al* [20].

or delay the development of cerebral oedema. Hyperventilation has the opposite effect, with a decrease in cerebral blood flow, and should be avoided.

Other aspects of intensive liver care

Kidney impairment and fluid imbalance are best managed by pumped continuous veno-venous haemodiafiltration. Coagulation disturbances are complex, with impaired synthesis of both pro- and anticoagulation factors along with latent disseminated intravascular coagulation (DIC), but management options are limited to blood transfusion with or without fresh frozen plasma, and platelet concentrate if a bleeding diathesis develops. Of the many metabolic disturbances, particularly those of glucose homeostasis, hypophosphataemia and hypomagnesaemia must always be borne in mind so that specific replacement is not delayed.

Overall outcome and results of transplantation

Table 4 shows what happened in 344 cases of ALF admitted over the past two years to our unit. Of the 252 cases of paracetamol overdose, 44 fulfilled transplant criteria, the percentage being higher in fulminant viral hepatitis (27/46) and lower in the idiosyncratic drug reaction and 'others' category (6/46). Of the 77 cases fulfilling transplant criteria, 53 were listed on the super-urgent priority list to await organ donation. Apart from the small number of paracetamol overdose cases for whom transplantation was contraindicated on psychiatric grounds, the main reason for not listing was the presence of other serious medical problems, for instance heart disease, or the occurrence, as part of the ALF, of uncontrollable sepsis, refractory hypotension or an apparently irretrievable cerebral state. The latter reasons also explain why not all those listed were finally transplanted (39/53).

The survival (79%) of those who were transplanted is excellent considering how ill they were at the time of operation. The figure is only 10% lower than that obtained for an elective transplant in our programme. The survival figure alone does not adequately reflect the effort and time taken in their care before their final recovery; these patients stay for a mean of 21 days in the liver failure unit following the transplant, compared with 3–4 days for an elective transplant. Four of the 24 cases fulfilling transplant criteria but not listed, and one of the 12 listed but not transplanted, survived (5/38; 13%); the latter is further evidence of the accuracy of the King's College criteria in determining a poor prognosis without transplantation. That some people from those two groups did survive also makes the point that one should not give up on treatment in these cases. The 61% survival for those not reaching transplant criteria suggests that if less severe criteria with good predictive value could be identified, the survival overall might be further increased.

Table 4. Outcome of 344 admissions with acute liver failure during 1992–4.

	Admissions	Fulfilled criteria	Listed	Transplanted
Paracetamol/ drug overdose	252	44	29	21
Viral hepatitis	46	27	18	13
Idiosyncratic reactions/others	46	6	6	5

One approach that can be utilised for patients whose condition becomes too unstable for transplantation is the removal of the necrotic liver by surgical hepatectomy and a portacaval anastomosis. The patients can improve to a remarkable extent, presumably because toxic substances are no longer being released from the liver into the circulation; the mean arterial pressure, oxygen extraction and systemic vascular resistance increase (Wendon *et al*, manuscript submitted), and cerebral oedema usually becomes more easily controllable. The window of opportunity thereby obtained for transplantation is limited to 24–36 hours.

Use of bioartificial liver

Two devices are currently undergoing clinical trial; that pioneered by Demetriou in the USA is based on culture of porcine hepatocytes. Separated plasma is first passed through an adsorbent charcoal column to remove toxic substances that might otherwise damage the cultured hepatocytes, and then through the hollow fibres in the device containing the cultured hepatocytes. Patients treated in this way were successfully maintained until a transplant could be carried out; improvement in encephalopathy grade along with normalisation of intracranial pressure were among the striking benefits claimed by the investigators [21]. The other device, known as ELAD (extracorporeal liver assist device), the one that we are now evaluating, is based on cultured human hepatoblastoma cells. It was developed by Sussman and colleagues in Houston [22]. Each column contains 200 g of cells so that a circuit based on a perfusion of two columns should give approximately 20–30% of normal liver function. Ultrafiltrate is drawn into extracapillary space containing the hepatocytes at about 20 ml/min and reinfused into the return blood line after passing through a filter system to prevent passage of the hepatoblastoma cells into the patient.

A controlled clinical trial is under way to determine just how much additional hepatic function is achieved with this device, and its overall benefit in patient management. Fig 4 gives one illustration of its use in a 14-year-old boy with acute liver failure from non-A non-B fulminant hepatitis. Both the international normalised

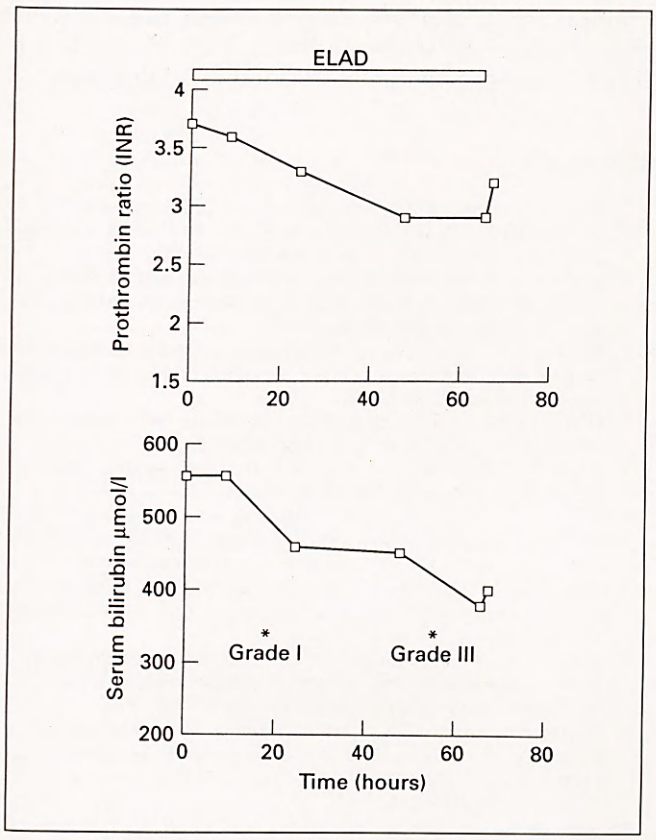

Fig 4. *Improvement in INR (prothrombin ratio) and serum bilirubin in a 14-year-old boy with non-A non-B acute liver failure while on the extracorporeal liver assist device (ELAD).*

ratio (INR) (formerly prothrombin time) and serum bilirubin level improved on the device during some 66 hours. His encephalopathy grade nevertheless showed some deterioration, but as he still did not fulfil transplant criteria it was decided to proceed with a partial rather than complete orthotopic liver transplantation. In this procedure the left lobe of the patient's own liver is removed and the comparable part of the donor organ is placed in the same situation. The potential for complete recovery of the patient's own liver remains; if and when this occurs, the graft can be allowed to atrophy by withdrawing immunosuppression, or it can be removed surgically. Worldwide at least ten cases have now been treated by auxiliary liver transplantation, and in a number of them the patient's own liver has recovered [23,24]. What happened to our own patient? First, he recovered clinically and is now out of hospital with virtually normal liver function tests; second, his own liver is recovering; the hepatobiliary isotope scan at four weeks showed similar uptake of colloid in both the recipient right and donor left lobe (Fig 5). The histological appearances of the patient's own liver, as shown by liver biopsy, are also indicative of the recovery phase.

Hepatic regeneration

In many of the patients who come to transplantation, particularly after some duration of illness, substantial areas of regeneration are found in the explanted liver. Had regenerative activity been 10–20% greater, the transplant might have been avoided. This raises ques-

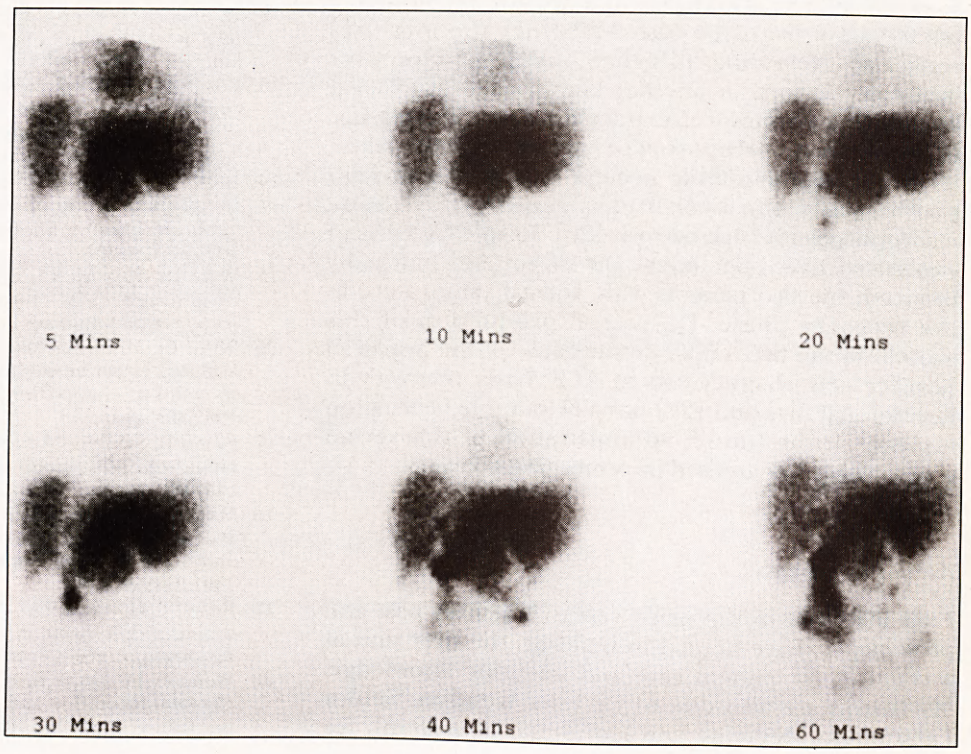

Fig 5. *Serial hepatobiliary isotope scans at 4 weeks in the same patient after auxiliary liver transplantation.* Courtesy of Dr M Buxton-Thomas.

tions as to how effective are the processes of regeneration in ALF, and whether the extent of the necrosis is so great in some instances that regeneration cannot even be initiated.

Regeneration of the liver is controlled by a balance between stimulatory growth factors released in response to hepatocyte loss, and inhibitory factors, either physiological liver growth inhibitors or toxins in the circulation not cleared by the failing liver. Stimulatory factors include epidermal growth factor, transforming growth factor-α and hepatocyte growth factor (HGF) [25]. In ALF, irrespective of aetiology or outcome, serum HGF levels are much higher than in normal controls and in patients with other types of liver disease, indicating that there is no deficiency of this potent hepatocyte mitogen. Of the various inhibitors, transforming growth factor-β (TGF-β) is the best characterised member of a family of five closely related multifunctional polypeptides that regulate cell proliferation, function and differentiation.

Recent work at King's College has involved measurements of TGF-β mRNA and levels of H3 histone mRNA in specimens of explanted liver from patients with ALF (Harrison *et al*, submitted). H3 histone is a marker of DNA synthesis and cell proliferation. High levels of histone mRNA expression were found in the liver of most of the paracetamol overdose cases. Levels were lower in the non-A non-B group, consistent with other observations indicating poorer hepatic regeneration in these patients. Of interest was the inverse correlation with the serum bilirubin level, for other experimental evidence suggests that cholestasis can inhibit hepatic DNA synthesis. As for TGF-β, its mRNA levels were increased, again to a greater extent in the paracetamol overdose cases. Whether the increases reflect an overriding influence of regeneration over inhibitory factors, or another known action of TGF-β in inducing synthesis of extracellular matrix proteins, is uncertain. 'Hepatocyte growth factor-like/macrophage stimulating protein' is a serum protein produced in the liver and is required by tissue macrophages for phagocytosis [26]. Its mRNA levels in explanted liver specimens are in general markedly reduced; the two patients with normal values were in the recovery phase. Decreased production of this protein in the liver could be the cause of the impaired Kupffer cell phagocytosis in ALF. Early recovery in Kupffer cell function [27] has a favourable bearing on survival; in the future, administration of this serum protein might be utilised in promoting recovery.

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