Gut, 1992, **33**, 98–102

Coagulation factor V and VIII/V ratio as predictors of outcome in paracetamol induced fulminant hepatic failure: relation to other prognostic indicators

L M M B Pereira, P G Langley, K M Hayllar, J M Tredger, Roger Williams

Abstract

The value of coagulation factor V and VIII/V levels as prognostic indicators was assessed in 27 patients with fulminant hepatic failure and compared with other predictive indices. Admission factor V levels were significantly reduced in 22 patients with paracetamol induced hepatic failure compared with a healthy control group (median 9·5% *v* 103%, respectively; p<0·001) and with lower values in non-A non-B hepatitis (median 2·7%). Values in the seven patients who died after paracetamol overdose, considered together with the four who underwent liver transplantation (group median 5·1%), were significantly lower than in the 11 who survived (median 11·8%; p<0·01). Median admission factor VIII was higher in those who died or received a transplant than in those who survived (298% *v* 162%; p<0·05), with both results higher than in healthy volunteers (median 104%; p<0·01) but lower than in non-A non-B hepatitis (median 340%). The ratio of factor VIII/V on admission was <30 in all patients who survived paracetamol overdose (median 17) with corresponding values >30 in 10 of 11 of those who died (median 39). A factor V result ≤10% on admission predicted an adverse outcome in 10 of 11 fatal cases, a 91% sensitivity which was greater than for the previously defined indicator of an arterial blood pH <7·30 on admission (sensitivity 82%). Prothrombin time at admission or on day 4 did not usefully predict outcome in our series. Predictive accuracy was 73% and 82% for factor V and admission acidosis respectively and 95% for factor V in conjunction with admission coma grade III or IV and factor VIII (ratio >30). These criteria may be useful in selecting patients with paracetamol induced fulminant hepatic failure for transplantation.

In the United Kingdom paracetamol overdose is the most common single cause of fulminant hepatic failure,[1 2] and the increasing use of orthotopic liver transplantation in cases identified as having a poor prognosis (O'Grady *et al*, unpublished observations) provides a management option for which there is considerable experience in other causes of fulminant hepatic failure.[3–5] An early prediction of outcome is important in the selection of patients for liver transplantation, not only because it extends the time available for obtaining an organ but also because of worsening coagulopathy, deteriorating renal function, and progression to intractable severe cerebral oedema and infection.[6 7]

Aetiology, age, coma grade, prothrombin time, α fetoprotein, and duration of jaundice[8 9] have at various times been reported to be valuable in determining the likely prognosis of patients with fulminant hepatic failure. From this institute O'Grady *et al*[10] analysed outcome in 310 patients after paracetamol overdose and validated the following as the principal adverse prognostic indicators: an acidosis (arterial pH <7·30 on admission (median 48 hours after overdose) or the subsequent development of grade III encephalopathy, a prothrombin time >100 s, and a serum creatinine concentration of >300 μmol/l. In fulminant hepatitis B, Bernuau *et al* have identified factor V, synthesised in the liver parenchyma and vitamin K independent, as the most important single dynamic indicator of outcome.[4 11 12] In contrast, factor VIII, synthesised in the liver and endothelial cells, is increased in liver disease,[13 14] including fulminant hepatic failure.[15] In the present study we investigated the value of admission and sequential measurements of factors V and VIII as predictors of outcome in a consecutive series of patients with fulminant hepatic failure after paracetamol overdose or non-A non-B viral hepatitis. The results were compared with those prognostic indicators already referred to and on which clinical decisions are currently based in this institute.

Methods

PATIENTS

Twenty seven consecutive patients (11 men, 16 women) with fulminant hepatic failure as defined by Trey and Davidson[16] were admitted to our unit between September 1989 and March 1990 after referral for rapidly deteriorating encephalopathy, severe coagulopathy, acidosis, or renal failure. The causes were paracetamol overdose (taken with suicidal intent) in 22 (median age 27 years, range 17–60 years) and presumed non-A non-B viral hepatitis in five (median age 32 years, range 23–54 years). The median time to admission was 45 hours (range 20–60 hours) after paracetamol overdose (median 38 g, range 15–50 g), at which time 11 patients were in grade II and 11 were in grade III or IV encephalopathy and median aspartate aminotransferase activity was 3400 IU/l (range 153–23 000). *N*-acetylcysteine was administered to all patients as part of their late treatment.[17] In presumed non-A non-B viral hepatitis patients median bilirubin concentration was 300 μmol/l (range 280–592 μmol/l) and median aspartate aminotransferase activity 315 IU/l (range 200–2890 IU/l).

Institute of Liver Studies, King's College Hospital and School of Medicine and Dentistry, Denmark Hill, London SE5 9RX
L M M B Pereira
P G Langley
K M Hayllar
J M Tredger
Roger Williams

Correspondence to:
Dr Roger Williams.

Accepted for publication
25 March 1991

All patients were in grade III or IV coma on admission.

LABORATORY ASSAYS

Blood (4·5 ml in sodium citrate) was taken daily before administration of fresh frozen plasma and vitamin K and samples were collected from the day of admission until hepatic encephalopathy resolved or death. Samples were immediately placed on ice and plasma was obtained by centrifugation at 2000 g for 10 minutes at 4°C. Levels of factors V and VIII were determined immediately or in samples stored at −70°C for a maximum of one month during which time no change in results was detected. Serum creatinine, arterial pH, prothrombin ratio, and liver function tests (serum bilirubin and aspartate aminotransferase) were measured in additional samples taken simultaneously.

Factors V and VIII were measured using one stage clotting assays. The factor V and factor VIII deficient plasma, APTT reagent (rabbit brain cephalin with ellagic acid), and thromboplastin were obtained from Sigma (Poole, Dorset). Standard human plasma was obtained from Behring (Hounslow, Middlesex), Clotting time was measured using a fibrometer (Becton Dickinson), with control values determined in 10 healthy laboratory subjects (six women, four men, median age 37 years; range 29–46 years).

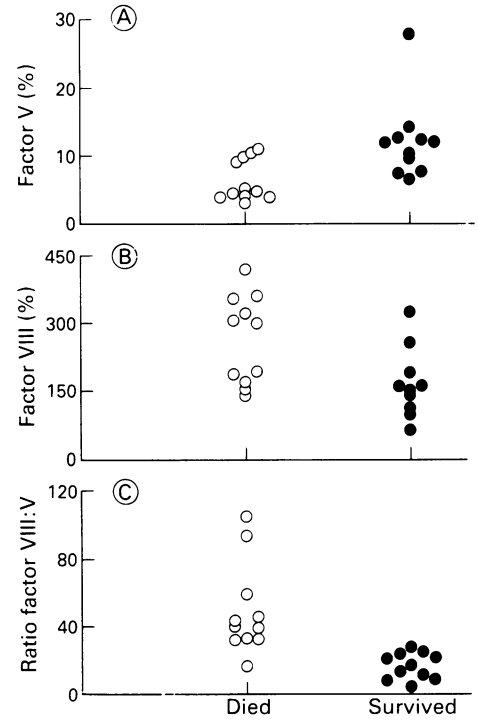

Figure 1: Admission values of Factor V (A), *VIII* (B), *and ratio VIII/V* (C) *in 22 patients with paracetamol induced fulminant hepatic failure in relation to outcome. There were significant differences between values in the 11 survivors and in the 11 patients who died for factor V* ($p<0·01$), *factor VIII* ($p<0·05$), *and ratio factor VIII/V* ($p<0·001$). *Normal ranges are presented in Table I.*

STATISTICAL ANALYSIS

Data were analysed using non-parametric ranking tests with significance accorded when $p<0·05$. The value of the prognostic indicators was judged on the basis of their sensitivity, specificity, predictive accuracy, and positive predictive value in relation to predicting an adverse outcome. Sensitivity was defined as the percentage of those patients who died showing a positive test result and specificity as that percentage of survivors with a negative test result. Predictive accuracy was the percentage of the total patient population whose outcome was correctly predicted by the test and the positive predictive value described that percentage of patients giving a positive test result who died.

Results

Seven (32%) of the 22 patients with paracetamol induced fulminant hepatic failure died 3–15 days after admission with death due to cerebral oedema in three and persistent infection in four. A further four were referred for liver transplantation at two to five days because of a predicted poor prognosis (arterial blood pH <7·30)[16] and these were considered with the seven fatal cases in the analysis of outcome. Four of the five patients with non-A non-B hepatitis died from cerebral oedema and sepsis (two to six days after admission) and the remaining patient underwent liver transplantation after two days using prognostic indicators of age over 40 years, serum bilirubin concentration >300 μmol/l, and grade IV encephalopathy.

Factor V. Levels on admission in the 22 patients with paracetamol induced hepatic failure (median 9·5%; range 3·09–27·9%) were substantially lower than in the normal control subjects (median 103%; range 45–118%; $p<0·001$). Values were significantly lower in the seven patients who died and four who underwent liver transplantation (median 5·1%) than in the 11 who survived (median 11·8%; $p<0·01$) (Fig 1A; Table I). Admission factor V results of ≤10% were recorded in 10 of the 11 patients who died or received a transplant, nine of whom were in grade III or IV encephalopathy at the time of admission. In comparison, five of the 11 patients who survived had factor V levels of ≤ 10% on admission, but in association with grade II encephalopathy.

TABLE I *Liver function test results at admission in 22 patients with fulminant hepatic failure due to paracetamol overdose*

Liver function test	*Survived (n=11)*	*Died (n=11)*	*p*
Arterial blood pH			
Median	7·40	7·10	0·01
Range	7·15–7·40	7·04–7·37	
Creatinine (μmol/l)			
Median	145	289	0·01
Range	66–415	121–897	
Prothrombin ratio			
Median	5·5	7·4	NS
Range	1·7–8·3	2·9–12·9	
Factor V (%)			
Median	11·8	5·1	0·01
Range	6·5–28·0	3·1–10·9	
Factor VIII (%)			
Median	162	298	0·01
Range	65–324	141–360	
Ratio Factor VIII/V			
Median	17	39	0·001
Range	4·08–27·6	16·4–104·5	

Reference ranges of normal values were: pH 7·35–7·45, creatinine 45–105 μmol/l, prothrombin ratio 0·9–1·1, factor V 60–150%, factor VIII 70–150%, ratio factor VIII:V 0·64–3·19.

Admission factor V results in the five patients with non-A non-B fulminant viral hepatitis were the lowest recorded (median 2·7%; range 1·7–4·1%. Sequential factor V results in the paracetamol overdose patients who survived showed a return to the normal range within four days of admission. In those patients who died no significant change was observed, with mean values remaining below 17% at four days (Fig 2). Trough factor V results in survivors were significantly higher than in patients who died (median 11·7% *v* 4·4%; $p<0·01$). Sequential factor V results continued to fall after admission in four of five patients with non-A non-B hepatitis.

Factor VIII and factor VIII/V ratios. Median factor VIII on admission in paracetamol induced fulminant hepatic failure was higher in patients who died or received a transplant than in survivors (298% *v* 162%; $p<0·05$), (Fig 1B; Table I). Both results were significantly higher than for the control group (median 104%; range 72–144%; $p<0·01$). Sequential factor VIII results fell consistently only in survivors, with peak factor VIII significantly lower than in those who died (median 233 *v* 335; $p<0·01$). In the five patients with non-A non-B hepatitis, factor VIII was again appreciably increased (median 340%, range 290–620%; $p<0·01$ *v* control), although not significantly higher than in the fatal paracetamol overdose cases. Using the ratio of factor VIII/V, there was greater discrimination between results in patients with paracetamol induced hepatic failure who died (median 39) and those who survived (median 17; $p<0·001$) (Fig 1C; Table I). Ten of 11 fatal cases showed a ratio >30 on admission. Sequential values for the ratio showed a steady fall in patients who survived but an increase in those who died. Admission ratios were even higher in the five patients with fulminant viral hepatitis (median 165, range 76–226; $p<0·001$ *v* control). In contrast to the paracetamol overdose cases, sequential factor VIII/V results decreased in these patients, even though four of the five patients died.

Of the additional laboratory variables determined on admission, only serum creatinine results differed significantly between patients who died and those who survived after paracetamol overdose (median 289 *v* 145 μmol/l, $p<0·01$; Table I). There were no corresponding differences in the admission prothrombin time ratio (Table I), serum aspartate aminotransferase (median 412 IU/l, range 189–17 980 IU/l in survivors *v* 324 IU/l, range 153–23 000 IU/l) and serum bilirubin concentrations (median 108 μmol/l, range 41–198 μmol/l in survivors *v* μmol/l, range 82–284 μmol/l).

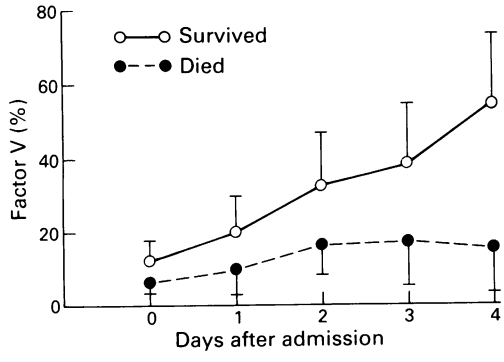

Figure 2: Sequential measurements of factor V levels in 22 patients with paracetamol induced fulminant hepatic failure in relation to outcome. Results are mean (SD) of 5–11 determinations. The normal range of factor V concentrations is 60–150%.

RELATION TO OTHER PROGNOSTIC INDICATORS IN PARACETAMOL OVERDOSE

Arterial blood pH on admission was significantly lower in the patients who died or received a transplant than in those who survived (median 7·10 *v* 7·40, respectively, $p<0·01$; Table I). When compared to factor V ≤10%, which predicted death in 10 of the 11 fatal cases (91% sensitivity), acidosis on admission (pH <7·30) was observed in nine of these 11 (sensitivity 82%) (Fig 3A). In neither of the two patients who died without systemic acidosis were the prognostic criteria of coma grade >II, prothrombin time >100 s, and serum creatinine >300 μmol/l satisfied.[10] Thus the predictive sensitivity for an adverse outcome of a factor V result of ≤10% on admission (91%) was the same as that of the two major prognostic indicators of O'Grady *et al* combined (91%) (Table II). It was greater than for the predictive sensitivity of 20% for a prothrombin time on day 4 of >180 s.[18] Five of 11 survivors had a factor V result of ≤ 10% (55% specificity) but this specificity and the corresponding positive predictive value increased substantially (both to 91%) when an admission factor V result of ≤10% was taken in conjunction with grade III or IV encephalopathy. These results were greater than the corresponding specificity and positive predictive value for admission pH <7·30 (both 82%). The sensitivity for a poor prognosis of an admission factor VIII/V ratio of >30 was the same as factor V ≤10% (91%) and this ratio showed the greatest accuracy in correctly predicting outcome in 21 of 22 cases (95%) compared with values for admission factor V ≤10% (73%) or admission pH <7·30 (82%) (Table II). No false positive results were observed using the indicator factor VIII/V ratio >30 (positive predictive value=100%), although a corresponding frequency of 5/15 was seen for an admission factor V level of ≤10% (positive predictive value=67%).

Discussion

Plasma factor V concentrations were not only substantially reduced when the patients were admitted to the unit (usually during the second day after the paracetamol overdose), but values of ≤10% also showed a high sensitivity for predicting an adverse outcome. This rapid diminution of factor V levels probably reflects the decrease over two to three half-lives (12–24 hours each) with synthesis largely inhibited as a result of the rapidly developing liver damage. Substantial decreases have also been shown in such cases for other clotting factors synthesised in the liver including factor VII,[19] protein C,[20] and antithrombin III.[21] A prolonged inhibition of factor V synthesis was also a poor prognostic sign, with factor V levels remaining below 17%

TABLE II *Assessment of prognostic indicator in 22 patients with paracetamol induced fulminant hepatic failure*

Prognostic indicator	*Sensitivity (%)*	*Predictive accuracy (%)*	*Positive predictive value (%)*	*Specificity (%)*
Admission factor V <10%	91	73	67	55
Factor V <10% in grade III-IV encephalopathy	91	95	91	91
Factor VIII/V ratio >30	91	95	100	100
Grade III-IV encephalopathy on admission	82	86	90	91
Prothrombin time on day 4, rising or >180 s	20	71	40	91
Admission pH <7·30*	82	82	82	82
Together with serum creatinine >300 μmol/l and prothrombin time >100 s in grade III–IV encephalopathy†	91	86	83	91

*Includes one patient with acidosis at the referring hospital; †criteria in patients without acidosis.[10]

in those who died and returning to normal within four days in those patients who survived.

The use of a factor V level of ≤10% as a prognostic indicator in paracetamol induced fulminant hepatic failure compares with a value of <20% suggested by Bernuau and colleagues[22] for patients with fulminant hepatic failure due primarily to viral hepatitis and idiosyncratic drug reactions.[4] If we had taken factor V results of <20% in our paracetamol cases a poor prognosis would have been predicted in 10 of 11 patients who survived and may also have selected the 10 cases for treatment by transplantation unnecessarily. On the basis of factor V levels of ≤10%, an adverse outcome was predicted in fewer cases. In emphasising the value of factor V as a prognostic indicator our experience suggests that aetiology may be as important in determining that level of factor V which is valuable for predicting outcome as it is in determining prognosis.[10] No direct comparison between prognostic levels of factor V in paracetamol overdose or viral hepatitis induced hepatic failure was possible in our study because none of the non-A non-B hepatitis patients survived. However, factor V levels were lower overall in the viral hepatitis patients, perhaps as a result of the more protracted course and this may reflect their worse prognosis (9% survival *v* 39% after paracetamol overdose) as determined in a large series from this institute.[10]

When taken in conjunction with grade III or IV encephalopathy on admission or with factor VIII results (expressed as a ratio factor VIII:V >30), admission factor V ≤10% correctly predicted outcome in all but one of the 22 patients. The exception was a young woman who died of sepsis 10 days after an overdose and whose death was not predicted with any of the prognostic indicators currently in use in our institute – namely, an arterial blood acidosis on admission or progression to grade III encephalopathy with a serum creatinine >300 μmol/l and a prothrombin time >100 s,[10] or a prothrombin time rising or exceeding 180 s on day 4 after overdose.[18] In comparisons with these prognostic indicators, factor V results of ≤10% on admission showed the highest sensitivity for predicting an adverse outcome (91%) in our series of 22 patients. Predictive accuracy was as high (around 75%) as acidosis on admission or the prothrombin time on day four, but positive predictive value was slightly lower than for the former (67% *v* 82%).

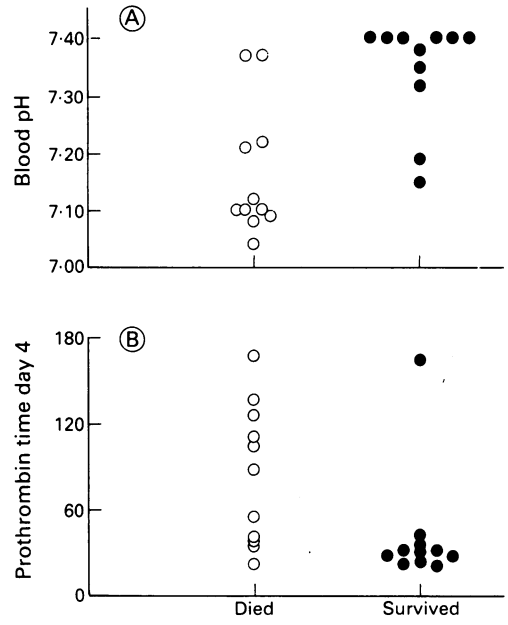

Figure 3: Admission values of blood pH (A) and prothrombin time on day 4 (B) in 22 patients with paracetamol induced fulminant hepatic failure in relation to outcome. There were significant differences between results in the 11 survivors and in the 11 patients who died (p<0·01). Reference ranges are 7·35–7·45 for blood pH and 13–15 seconds for prothrombin time.

The shorter duration of onset of hepatic failure after paracetamol overdose than after non-A non-B viral hepatitis may explain the less pronounced rises in factor VIII concentrations and factor VIII:V ratio we observed at admission in the former group. This may be a result of poor clearance due to suppressed reticuloendothelial function, continued extrahepatic synthesis of factor VIII, or reduced hepatic synthesis of protein C, a potent inhibitor of activated factor VIII.[15] Factor VIII:V ratios have not been used before as a predictor of outcome but their value may derive partly from detecting high factor VIII concentrations released when vascular endothelial cells are damaged. Taken together with low factor V concentrations reflecting decreased hepatic synthetic function, factor VIII:V ratios may give a composite assessment of liver function that is reflected in their power for correctly predicting outcome in 95% of the cases in this series.

Both factor V and factor VIII can be readily measured in any laboratory performing coagulation tests, and a result can be available within five minutes of obtaining a plasma sample. After paracetamol overdose, a plasma factor V concentration of ≤10% of normal should be taken as a poor prognostic sign. In conjunction with a substantial increase in factor VIII (factor VIII/V ratio >30) or severe hepatic coma within two or three days of overdose, factor V levels of ≤10% seem valuable in selecting such patients for transplantation, but this requires confirmation in a large series.

LMMBP was the recipient of a scholarship from Conselho Nacional de Desenvolvimento Cientifico e Technologico-Brazil.

1 Scott DK, Vale JA. Paracetamol poisoning. *Pharmacol Clin J* 1990; **21**: 95–7.
2 Davis M. Protective agents for acetaminophen overdose. *Semin Liver Dis* 1986; **2**: 138–47.

3 Peleman RR, Gavaler JS, van Thiel D, *et al.* Orthotopic liver transplantation for acute and subacute hepatic failure in adults. *Hepatology* 1987; **7**: 484–9.
4 Bismuth H, Samuel D, Gugenhein J, *et al.* Emergency liver transplantation for fulminant hepatitis. *Ann Intern Med* 1987; **107**: 337–41.
5 Ringe B, Pichlmayr R, Lauchart W, *et al.* Indication and results of liver transplantation in acute hepatic failure. *Transplant Proc* 1986; **18**: 86–8.
6 O'Grady JG, Gimson AES, O'Brien CJ, *et al.* Controlled trials of charcoal hemoperfusion and prognostic factor in fulminant hepatic failure. *Gastroenterology* 1988; **94**: 1186–92.
7 Tygstrup N, Ranek L. Assessment of prognosis in fulminant hepatic failure. *Semin Liver Dis* 1986; **2**: 129–37.
8 Gimson AES, O'Grady J, Ede RJ, *et al.* Late onset hepatic failure: clinical, serological and histological features. *Hepatology* 1986; **2**: 228–94.
9 Gimson AES, White YS, Eddleston ALWF, *et al.* Clinical and prognostic differences in fulminant viral hepatitis type A, B and non-A non-B. *Gut* 1983; **24**: 1194–8.
10 O'Grady, Alexander GJM, Hayllar KM, *et al.* Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439–45.
11 Francavilha A, Makowka L, Polimeno L, *et al.* A dog model for acetaminophen induced fulminant hepatic failure. *Gastroenterology* 1989; **96**: 470–8.
12 Bernuau J, Goudean A, Poynard T, *et al.* Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986; **6**: 648–51.
13 Baele G, Matthigs E, Barbier F. Antihaemophilic factor activity, FVIII related antigen and von Willebrand factor in hepatic cirrhosis. *Acta Haematol* 1977; **57**: 290–7.
14 Kelly DA, O'Brien FJ, Hutton RA, *et al.* The effect of liver disease on factors V, VIII and protein C. *Br J Haematol* 1985; **61**: 541–8.
15 Langley PG, Hughes RD, Williams R. Increased factor VIII complex in fulminant hepatic failure. *Thromb Haemost* 1985; **54**: 693–6.
16 Trey C, Davidson C. The management of fulminant hepatic failure. In: Popper H, Schaffner F, eds. *Progress in liver disease*. Vol 3. New York: Grune & Stratton, 1970: 292-8.
17 Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990; **335**: 1572–3.
18 Harrison PM, O'Grady JG, Alexander GJM, *et al.* Serial prothrombin ratios: a prognostic indicator in paracetamol induced fulminant hepatic failure. *BMJ* 1990; **301**: 964–6.
19 Gazzard BG, Henderson JM, Williams R. Factor VII levels as guide to prognosis in fulminant hepatic failure. *Gut* 1976; **17**: 489–91.
20 Langley PG, Williams R. The effect of fulminant hepatic failure on protein C antigen and activity. *Thromb Haemost* 1988; **59**: 316–8.
21 Mosvold J, Abildgaard V, Jenssen H, *et al.* Low antithrombin III in acute hepatic failure at term. *Scand J Haematol* 1982; **29**: 48–50.
22 Bernuau J, Bourliere M, Rueff B, *et al.* Transplantation for fulminant hepatic failure. *Lancet* 1990; i: 407.