LETTERS TO THE EDITOR

Prediction of severity of acute pancreatitis

SIR,—We read with great interest the article by Fan *et al* (*Gut* 1989; 30: 1591–5) in which they have shown that two factors (serum urea and plasma glucose) were as good as the conventionally used multifactor scoring system of Imrie *et al*¹ and Ranson *et al*² using nine and 11 factors respectively for clinical and biochemical assessment of severity of acute pancreatitis. The major drawbacks of multifactor include (a) use of too many factors, (b) need for a longer duration (48 hours) before assessment of severity can be made, and (c) effect of treatment on various assessment parameters during 48 hours of observation.

Although fascinating, it seems unlikely that the authors' new approach – the use of a discriminant value of the two factors (serum urea >7.4 mmol/l and plasma glucose >11.0 mmol/l) in assessment of severity of pancreatitis – will stand the test of time because of the following reasons. Firstly, the raised serum urea has a very non-specific value as it can be altered because of dehydration, repeated vomitings, poor intake, and other non-pancreatic factors like gastrointestinal bleeding and renal dysfunction. Secondly, the occurrence of upper gastrointestinal bleeding (occurring in 10–20% of patients with acute pancreatitis)³ may significantly affect the serum urea concentration even though it may have no relation to severity of pancreatitis.

Thirdly, the authors' explanation that high serum urea concentration could be a reflection of poor physiologic reserve of major organ system does not seem to have convincing scientific appeal.

Moreover as the plasma glucose intolerance and incidence of diabetes mellitus increase with age and the authors fail to mention whether or not underlying diabetes mellitus was ruled out in their patients with acute pancreatitis, it is possible that a proportion of their patients may have had raised plasma glucose secondary to pre-existing glucose intolerance or diabetes mellitus rather than because of underlying severe pancreatitis.

Finally, we believe that from the standpoint of the clinical management there is no harm in waiting for a day or two to observe the course of acute pancreatitis on conservative treatment even though the course may alter (maybe for the good) the score of the multifactor scoring system, rather than rush to predict the severity of acute pancreatitis at admission.

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Reply

SIR,—We agree that raised serum urea and blood glucose at the time of admission may be influenced by many factors. This inadequacy was reflected by the relatively low predictive value of positive and was fully discussed in the report. However, all the possibilities leading to raised serum urea mentioned by Dr Arora and Acharya were definitely related to a severe attack of acute pancreatitis and I cannot agree that gastrointestinal bleeding is unrelated to severity.¹ Patients with underlying diabetes mellitus were not specifically defined in our report. However, diabetic patients with underlying major organ dysfunction are certainly at high risk of developing systemic complications of acute pancreatitis and deserve to be carefully monitored and aggressively treated at admission.

The policy of waiting for 48 hours to monitor the course of the disease and to collect complete data for grading of severity is not justifiable in modern day medicine. In our previous report,² 13.8% of patients deteriorated within 48 hours. With adequate treatment, fewer patients did so.

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Why do patients with ulcerative colitis relapse?

SIR,—In reply to my letter (*Gut* 1990; 31: 959) Riley *et al* state that of the many studies I quoted 'all are uncontrolled.' This is incorrect and if unchallenged may lead further research workers to discount those criticisms regarding inappropriate methodology which remain valid and thus perpetuate the likelihood of further needless waste of research effort. My 1959 article¹ stated that 98 radiotherapy patients were used as control subjects and interviewed according to the same protocol as the 173 ulcerative colitis patients, while McMahon *et al*² used healthy siblings as controls in their investigation of 23 patients by means of psychometric tests including the Minnesota Multiphasic Personality Inventory and psychiatric interviews. In another investigation of 35 patients entitled 'Psychopathology of ulcerative colitis' Roubicek and Martonova³ used 20 healthy subjects as controls and confirmed the limited value of standard psychiatric tests in these emotionally guarded colitis

subjects by means of sensitive interviewing and the Thematic Apperception Test designed to penetrate emotional defences.

Riley *et al* are right to emphasise the continuing need for 'controlled clinical trials' but if the questions asked are irrelevant to pathogenesis, or the instruments of investigation are too blunt for the purpose asked of them, no amount of control data will help. They may even deceive people into thinking that proper scientific rigour has been applied.

Riley *et al* appear to have listened to commonly recited, but uncorroborated views of others, rather than checked the original sources. Pelser and I⁴ have given examples of how this has often delayed scientific progress for years.

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Effects of albumin infusion in cirrhotic patients

SIR,—Intravenous albumin infusion has been reported as an effective treatment of hyponatraemia in cirrhotic patients with ascites (McCormick *et al*, *Gut* 1990; 31: 204–7). The derangement in renal sodium handling in cirrhosis is well known; however, the mechanisms mediating this abnormality remain incompletely defined.^{1,2} Changes in effective circulatory volume trigger hormonal alterations inducing sodium and water retention. A large proportion of cirrhotic patients with ascites formation show decreased effective plasma volume, activated vasoconstrictor hormone systems, hypoalbuminaemia, and hyponatraemia.^{1,5}

We investigated 15 patients with liver cirrhosis and ascites (5 women, 10 men, aged 52–65 years). Patients were on longterm diuretic treatment and a low sodium diet containing 30 mmol/day of sodium. An intravenous infusion of 20% albumin was given in a dose of 1 g/kg. The diuretic and natriuretic responses as well as the albumin induced changes in vasoactive hormone profile were measured.

Albumin infusion induced nearly a fourfold increase in diuresis and sodium excretion in nine of 15 patients (group A), with the normalisation of serum sodium (Table). Albumin also increased the plasma level of atrial natriuretic factor (ANF) to normal, while decreasing the high plasma renin activity

Urine flow rate (U_v), sodium excretion ($U_{Na}V$), serum concentrations of sodium (Na) and albumin (alb), and plasma concentrations of atrial natriuretic factor (ANF), plasma renin activity (PRA), and vasopressin (AVP) (mean (SEM))

	U_v (ml/min)	$U_{Na}V$ (μ mol/min)	Na (mmol/l)	alb (g/l)	ANF (fmol/ml)	PRA (ng/ml/h)	AVP (pg/ml)
Group A (n=9):							
Control	0.7 (0.2)	40 (6.8)	130 (1.4)	29.1 (1.5)	19.5 (30)	4.4 (1.0)	8.5 (1.5)
Albumin	2.4 (0.2)*	147 (20)*	135 (1.2)*	34.0 (1.2)*	49.5 (6.6)*	1.9 (0.3)†	6.5 (0.8)
Group B (n=6):							
Control	1.2 (0.3)‡	60 (8.0)‡	136 (2.0)‡	34.0 (0.7)‡	36.7 (3.9)‡	0.44 (0.09)§	4.0 (0.5)
Albumin	0.9 (0.2)	73 (11)	136 (1.5)	52.0 (1.2)*	31.0 (2.9)	0.23 (0.05)*	5.9 (1.7)

*p<0.001 v control; †p<0.01 v control; ‡p<0.001 v group A-control; §p<0.01 v group A-control; ||p<0.05 v group A-control.

(PRA) and plasma concentration of arginin vasopressin (AVP) in this group. No responses to albumin infusion were noted in six of 15 patients (group B). These patients had high ANF and low PRA, suggesting a relative volume overload.

It is well known that patients with liver cirrhosis do not represent a homogeneous group.⁵ There are at least two mechanisms leading to sodium and water retention and thus ascites.⁴ Patients with decreased effective intravascular volume have an activated sympathico-adrenal and renin-angiotensin-aldosterone axis, raised vasopressin level, and decreased plasma concentration of ANF (underfilling theory). In contrast, volume overloaded patients have decreased vasoconstrictor and increased vasodilator hormone activity (overflow theory); the renal sodium retention in these cases represents a primary event due probably to intrarenal microcirculatory changes.

The patients presented here show characteristics of both causes of liver cirrhosis. It is of interest, however, that only patients with signs of underfilled effective intravascular volume provided an adequate response to intravenous albumin. Albumin induced centralisation of the circulation results in increased diuresis and sodium excretion and in normalisation of the activated vasoconstrictor and sodium retaining hormone systems. These data may give a better insight into the pathogenesis of sodium and water retention and also into the mechanism of the effect of albumin infusion in liver disease.

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Reproducibility of oesophageal pH monitoring

SIR,—We were interested to see the data which Vandenplas *et al* presented on the reproducibility of oesophageal pH monitoring used for the diagnosis of gastro-oesophageal reflux in children.¹ There are, however, two ways in which our own, similar, study² differs from theirs which we think merit discussion. The first is that Vandenplas *et al* document the child's meal times, position, and behaviour on the first day and exactly mimics this on the second day. In our study we did not impose such limitations with a view to gaining a better understanding of the likely variation in the amount of gastro-oesophageal reflux occurring from day to day. In the normal situation

behaviour varies in a way which may influence the pattern of gastro-oesophageal reflux.

The second point which must be discussed relates to the analysis and interpretation of their results. As correctly discussed, the use of correlation coefficients is inappropriate for examining reproducibility and difference analysis should be used. As shown diagrammatically and stated in the text, the differences between the two results increase as the mean result increases – that is, the difference is proportional to the mean. Thus the differences should be analysed after taking logarithms of the results and expressed either as a ratio or a percentage difference and not as absolute values as used here.³ Using this method we showed a 95% chance that a second reflux index would be between 0.27 and 3.7 times the first.

Vandenplas *et al*'s unlogged results for reflux index give a 95% chance of a second study having a result within 8% of the first (as shown in their Fig 3). This would mean that a reflux index of 10% on one study might be followed by a second study with a result anywhere between 2% and 18%. Although none of the children studied had results which changed from normal to abnormal, this potential variation is considerable and does not support the contention that the pH study is 'highly reproducible.' If the logged results had been used the difference would have been a proportion rather than an absolute value and thus less with lower reflux indices and more with higher ones.

The data presented show that considerable differences may occur in two 24 hour oesophageal pH studies in children even when restrictions are placed on their behaviour. Our own study suggests that without such restrictions these differences are even greater. This must be taken into account both clinically and in trials of treatment.

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- 1 Vandenplas Y, Helven R, Goyvaerts H, Sacré L. Reproducibility of continuous 24 hour oesophageal pH monitoring in infants and children. *Gut* 1990; 31: 374–7.
- 2 Hampton F, MacFadyen U, Simpson H. Reproducibility of twenty-four hour oesophageal pH studies in infants. *Arch Dis Child* (in press).
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Reply

SIR,—The comments of Dr Hampton and Dr MacFadyen are very interesting and confirm our opinions. The study by Hampton *et al* is a logical continuation of our study: once pH data had been shown to be reproducible, all factors of possible influence being standardised (our study),¹ a second study was necessary to analyse how much patient related factors influence pH data (Hampton study).² It is logical that data recorded under these study conditions are less reproducible.

The study on the reproducibility shows that if data are clearly within normal ranges there is a good possibility of the results being comparable when recorded a second day. The same is true if data are clearly 'abnormal,' although differences between two consecutive recordings might be higher. Hampton and MacFadyen confirm this in their letter: if the logged results had been used, there would be less difference with lower reflux indexes and more with higher ones. So, the conclusion with unlogged or logged results is exactly the same.

We knew of Bland's book.³ It is our opinion,

however, that it is preferable to compare data in the same way they are presented. Taking logarithms might be mathematically correct, but pH monitoring data for clinical use are not presented as such. Reproducibility also depends on the material that is used: comparability of simultaneous recordings with two identically located antimony electrodes for the same patient ($r=0.90$ for the % time pH <4 reflux index) is statistically inferior to the comparability obtained with two glass electrodes ($r=0.99$ for the reflux index).⁴ Therefore, the results of the reproducibility study of Johnsson and Joelsson⁵ are excellent and comparable to ours: they report a correlation coefficient of 0.87 for two consecutive 24 hour recordings with antimony electrodes.

We stated in the article that we were lucky to have no patient who changed from 'normal' to 'abnormal,' or the other way around. Normal ranges of physiological gastro-oesophageal reflux have been shown to vary 'quite a lot' in large groups of asymptomatic controls.^{6,7} The percentiles for the reflux index in a 'normal' population were shown to vary from 0 to 10% (P5 to P95).⁷

As we stated in a recent review article,⁸ the answer to the simple question of whether data are 'normal' or 'abnormal' is clear cut in only a few cases. There is a considerable overlap between 'normal' and 'pathological.'

The results of our study show that there are only a few problems regarding the interpretation of, for example, a reflux index of <5% or >15%, since the risk that the interpretation of the results of a second day's recording would be different is minimal. There remains a problem for reflux indexes around 10%. The reason for this is the 'all' or 'none' interpretation of pH monitoring data by a computer using a 'cut off' limit. For a software program pH 3.99 is 'abnormal' and pH 4.01 is 'normal.' For the patient, however, there is no difference at all. Therefore, we think that the development of new parameters, such as the 'oscillatory index'⁹ is of great interest. This parameter calculates the percentage of time the pH oscillates around pH 4.00 – that is, between 4.25 and 3.75, and therefore quantifies the all or none consequences of the application of a cut off limit.

Our results show that 24 hour pH monitoring data are 'highly' reproducible.¹ When data are borderline (and this is related more to the use of a cut off limit than to patient or technique related factors) they should be interpreted with care, and the use of percentiles as well as the oscillatory index might be very helpful.

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