carcinoma of the prostate was given co-trimoxazole (total dose 13·44 g.) for seven days. The hæmoglobin level fell from 12·0 g. per 100 ml. (M.C.V. 89 fl.) to 8·6 g. per 100 ml. (M.C.V. 96 fl.) during the following 20 days. The marrow was grossly megaloblastic, but he died of acute pulmonary œdema soon after the cause of his anæmia was diagnosed.

Megaloblastic changes may be precipitated rapidly in patients who are on the verge of folic-acid deficiency. This group includes the elderly, pregnant women, and any others whose intake or absorption of folate is inadequate.

I should like to thank Prof. W. M. Davidson and Dr K. G. A. Clark for their encouragement and help.

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NITROFURANTOIN-INDUCED PULMONARY FIBROSIS AND LUPUS SYNDROME

SIR,—During the past ten years several reports on nitrofurantoin-induced acute pulmonary reactions have emerged. The usual symptoms are fever, cough, dyspnœa, and eosinophilia, with an X-ray picture of bilateral interstitial pneumonitis. In 1968 Rosenow et al.[1] described pulmonary fibrosis due to chronic nitrofurantoin medication. We have seen two female patients with impaired lung function associated with liver damage and autoimmune antibodies after long-term nitrofurantoin therapy.

On admission both patients displayed dyspnœa at rest, anorexia, weight loss and fatigue, but no fever or rash. They had been given 100–200 mg. nitrofurantoin daily for 2 years and 1½ years. Lung function was much impaired, mainly due to restriction, and X-rays showed extensive fibrosing alveolitis. Liver damage was demonstrated by raised transaminase levels and by a considerably prolonged half-life of intravenous galactose. Both patients had antinuclear factor (A.N.F.) (titre 1/100) but no L.E. cells. Tissue specific antibodies to thyroid cytoplasm (1/100), glomeruli (1/10) and smooth muscle (1/25) were found by immunofluorescence. There was also an increase of serum IgG, while other immunoglobulins, including IgE, were normal.

After withdrawal of nitrofurantoin both patients started to recover without steroid therapy. 3 months later liver-function tests were near normal. A.N.F. had decreased (titre 1/25) and specific serum antibodies to thyroid cytoplasm, glomeruli, and smooth muscle were absent. The lung function and chest X-rays were improved and the patients had gained both weight and vitality. Nitrofurantoin significantly stimulated lymphocytes from both patients in the lymphocyte-transformation test.[2,3] This fact points to an immune reaction where nitrofurantoin constitutes at least part of the antigen. It is tempting to consider the whole antigen as a conjugate of nitrofurantoin and cell membranes from various tissues. The mechanism behind the symptoms and signs in our patients may then fit with both type II and type IV reactions.[4]

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ENDOTOXÆMIA IN LIVER DISEASE

SIR,—I see that a race has developed between my one-man unit in Newcastle and the M.R.C. Liver Unit (March 30, p. 521) for the privilege of claiming the significance of the role of endotoxæmia in liver disease. On the basis of fewer cases, I can fully confirm what they report concerning renal failure due to endotoxæmia in hepatic failure. To their findings I can add that the cases which I have studied have also shown increased radiofibrinogen catabolism which, in my opinion, is a better way than using fibrinogen degradation products (F.D.P.), which in their series seem peculiarly low, and the serial dilution of protamine sulphate (S.D.P.S.), which itself has come in for heavy criticism. F.D.P. may be low, because in the few cases studied here fibrinolysis was depressed: this carries the added significance that D.I.C. in the presence of fibrinolytic inhibition is likely to result in permanent tissue damage, as, for example, tissue necrosis.[1]

As for the intermediary mechanisms involved, I wish to clarify the following. Firstly, endotoxin is a potent stimulus to the release of renin, and this may be why renal failure occurs so often in conjunction with septicæmia or massive tissue trauma.[2] Secondly, some of the products of intravascular coagulation appear to have vasoconstrictor actions especially in the renal [3] and pulmonary circulations. That endotoxin stimulates coagulation by activation of Hageman factor XII is probably incorrect, for in fact it acts on factor XI,[4] and, although human platelets do not show immune adherence, also by an action on platelets.

There is a broader message which will certainly come up for discussion. This is that my correlated findings of endotoxæmia with radiofibrinogen catabolism studies [5] indicate that portal endotoxæmia and intravascular coagulation are also significant in portal cirrhosis and around the time of operation for obstructive jaundice. In turn these further situations are relevant to the renal failure of liver diseases.

I am sorry that the authors have chosen to quote me on the one point on which there could be some discrepancy—namely, that I noted that cholic acid caused some flocculation of the Limulus lysate.[6] In fact this was an aside comment in a paper describing the relevance of endotoxinæmia to acute renal failure. However, I did not say that it causes gelation. All the same I do interpret strong flocculation with viscidity as a positive result.

This leads to the question of the sensitivity of the Limulus assay, which in the authors' hands is only 5 ng. per ml., although they use the more sensitive chloroform extraction technique. Initially I only used the Reinhold and Fine inhibitor extraction, because I intuitively disliked an agent which can damage proteins. Using either gelation or strong flocculation I am able to detect tenths of a nanogramme. Hence there is my report to the effect that the detection of endotoxæmia in liver disease has much wider application than hepatic necrosis alone, and this is supported by my findings using a platelet N.B.T. test.[7]

It was Gans [8] who drew attention to the possibility of endotoxæmia in liver disease. This is entirely consistent with recent findings on the entry into the portal circulation of bacterial antigens from the gut.[9] Finally, the report of endotoxæmia following portal vein occlusion [10] leads to the suggestion that the high portal venous pressure and the sluggish flow may be the reason why my findings are

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compatible with portal endotoxæmia and intravascular coagulation in cirrhosis.

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SIR,—Dr Wilkinson and others (March 30, p. 521) and Wardle [1] have tried to solve the problem, initially delineated in your columns [2], whether endotoxæmia contributes to the clinical manifestations of hepatic failure. Unfortunately, under the described circumstances the inference drawn from a positive Limulus lysate test may not be correct because false-positive results have been obtained with this test in the presence of thrombin and thromboplastin [3]; therefore this can also be expected to occur in patients with disseminated intravascular clotting, as results of Wardle's study would suggest.

Hence, rather than solving the problem it remains what it has been all along—a very hard nut to crack.

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COMPLICATIONS OF PERCUTANEOUS LIVER BIOPSY

SIR,—Percutaneous liver biopsy is a useful, non-invasive, and relatively safe procedure. There are, however, complications which were reviewed in your columns by Sullivan and Watson.[5] They reported 3 patients with acute pulse and blood-pressure changes within several minutes of the procedure. We should like to report an additional complication.

A 16-year-old girl was readmitted to University Hospitals for re-valuation of liver disease. She had two bouts of hepatitis in 1969 and 1971. After each episode, liver enzymes returned to no[r]. She was again seen in 1973 for fever, vomiting, and ab[d]al pain. Again, she was noted to be icteric and had raised liver enzymes. She also had a urinary-tract infection. An intravenous pyelogram revealed a left radio-opaque renal calculus, which was later removed surgically. However, jaundice and lethargy continued, so she was referred to University Hospitals. Her initial evaluation here included a percutaneous liver biopsy (her second percutaneous and third liver biopsy) which was without complication. The biopsy was difficult to interpret because features of both chronic aggressive hepatitis and biliary cirrhosis were present. She was treated for about one month with high-dose steroids but failed to respond. She was readmitted and a retrograde hepatic ductogram was attempted unsuccessfully. However, she did develop pancreatitis after the procedure and serum-bilirubin rose from 6 to 20 mg. per 100 ml. After recovery from this complication, she was discharged and steroids were tapered off.

She was readmitted for percutaneous transhepatic cholangiography. Laboratory studies revealed S.G.O.T. of 77 I.U. per l., a total bilirubin of 23 mg. per 100 ml., with 11 mg. per 100 ml. direct reacting, a protime of 11·9 sec., a partial thromboplastin time of 34·1 sec., and an alkaline phosphatase of 2115 I.U. per l. She was not on vitamin-K supplementation. She developed a fever for one day, but multiple cultures were negative. Thus, a percutaneous liver biopsy was done for culture and a blood-culture was obtained after the procedure. Shortly after the biopsy, she became restless. 30–45 minutes after the biopsy, the blood-pressure fell from 120/80 to 90/50 mm. Hg, initially without an increase in pulse. Within minutes, her pulse rose to 140–150. Her peripheral cutaneous vascular beds were constricted. An intravenous infusion was started and she was given Plasmanate [7] and then blood, with subsequent increase in blood-pressure and decrease in pulse. The hæmoglobin level rose appropriately to the amount of blood given. *Citrobacter freudii* was cultured from her liver tissue on the first day. She was begun on appropriate antibiotic therapy which resulted in improved clinical and laboratory status.

We suspected an occult infection because our patient's level of jaundice was out of proportion to her liver-function tests and amylases were normal. Therefore, hepatic tissue was obtained for culture before proceeding with the percutaneous transhepatic cholangiogram. Fischer et al.[6] consider fever or cholangitis to be contraindications to transhepatic cholangiography. Initially, we thought our patient had bled from the procedure. However, her physical examination was essentially unchanged except for her shocked appearance. Also her hæmoglobin rose appropriately for the amount of blood she received. Since her hepatic tissue culture grew *Citrobacter freudii*, a gram-negative organism, we postulate that the procedure resulted in the release of endotoxin which caused the hypotension. Her blood-pressure drop with subsequent pulse rise is unlikely to be secondary to heart-block or vagal response, as reported by Falchuk [7]. Le Frock et al.[8] have recorded transient bacteræmia in 14·4% of their patients after percutaneous liver biopsy. They also found the same organism in the hepatic tissue in 5 out of 12 bacteræmia patients. 7 out of 89 (7·8%) patients had organisms recovered from hepatic tissue in their series. One wonders whether bacterial cultures were taken on the liver tissue or from the blood after liver biopsy in the cases reported by Sullivan and Watson [5].

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CUSUMS

SIR,—Dr Freedman (April 20, p. 741) rightly advised cautious interpretation of cusum statistics, because any clinical data may be serially correlated, and the extent of such correlations cannot be estimated. In most clinical situations, there is no information on these and other factors, like the distribution of the variable under study, which would influence the choice of significance boundaries.

The only alternative to what is, admittedly, a somewhat arbitrary choice of significance test is to leave the clinician to make his decision from the cusum chart, using his unaided eyes. Otherwise, there would be no point in using the charts at all. Statistical tests do not make decisions, they only refine our means to take decisions. An unaided decision will be made in the same way as if the investigator had used a V mask, and is subject to the same objections. The error is not the use of the test, but failure to recognise its accepted limitations.

It has been suggested that where a large degree of positive serial correlation exists, this may have the effect of doubling α, but β may remain little affected.[9] The use of a more conservative significance level might then offer some protection against α error.

Cumulative sum techniques can never be regarded as exact statistical methods when applied to biological problems. Nevertheless, we think that their critical application may detect changing trends more efficiently than purely subjective methods.

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