prominent clinical factor valuable in identifying patients at risk of major ulcer bleeding (1).

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Azathioprine and Prognosis in Primary Biliary Cirrhosis

Dear Sir:

Our paper "Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis: final results of an international trial," which was published in GASTROENTEROLOGY (1), was commented on by Dr. Joseph Roll (2) in the editorial "A new treatment for primary biliary cirrhosis?"

We think Dr. Roll describes the therapeutic situation in primary biliary cirrhosis (PBC) in a very balanced way. In addition, Dr. Roll demonstrates the potential use of our prognostic index for optimal timing of liver transplantation in patients with PBC. We have only a few comments.

We do not think the result of this trial needs to be controversial. Azathioprine has been tested in only one other trial including only 45 patients (3). The two trials (1,3) have given rather similar results with respect to the magnitude of the therapeutic effect, but the small number of patients in the early trial (3) explains why the trend toward a beneficial effect of azathioprine did not reach statistical significance. Even substantial beneficial effects of azathioprine could not be excluded by that trial. Unfortunately, many clinicians incorrectly took its negative result as a proof of the ineffectiveness of azathioprine, and attention was focused on penicillamine instead. Regrettably, the effect of penicillamine turned out to be disappointingly small and its side effects frequent, as demonstrated by the numerous trials that have been performed until now.

In the analysis of our trial we adjusted for imbalance in prognostic variables between the treatment groups. After the adjustment the beneficial effect of azathioprine was statistically significant. Dr. Roll asks the question: Is it possible that unknown prognostic variables may be unequally distributed between the studied groups and thus bias the results? Theoretically, yes, it is, and that is why randomization is and always will be indispensable in clinical trials. Statistical adjustment for imbalance can never be a substitute for randomization. But will statistical adjustment for imbalance in the known prognostic variables affect the random distribution (as a result of the randomization) of unidentified prognostic variables between the groups in such a way that estimation of the treatment's effect will be biased anyway? No, we do not think so. If an unknown prognostic variable is correlated with the known variables being corrected for, that variable will also to some degree (depending on the strength of the correlations) be corrected for automatically, and that is what we want. If an unknown prognostic variable is not correlated with any of the known ones, then adjustment for these will not affect the influence of that variable. In that case, we have to rely on the randomization being successful. Thus, adjustment for imbalance in prognostic variables can only improve our possibilities of making an unbiased comparison between the treatments; it cannot make them worse. Therefore, it is well worthwhile searching for more prognostic variables.

However, we would emphasize that the result of this trial could only be seriously affected by an imbalance in an unknown variable of very high prognostic value not being correlated with the variables included in our Cox regression model (1). That this should be the case is very unlikely.

We should like to point out that the therapeutic gain of azathioprine in an average patient [prognostic index (PI) = 3.00] is about 20 months. In patients with lower indices (better prognosis) the gain in terms of added survival time may be higher, even though the survival time without treatment is long. However, the PI is less precise for extreme (very high or very low) values of the PI, because such patients were relatively few in our study [Figure 3 in (1)]. Therefore, we support the view of Dr. Roll that asymptomatic patients should not be treated, especially in view of the cost and potential side effects (although fewer than for penicillamine) of long-term treatment with azathioprine. However, asymptomatic patients should be offered regular control and therapy if they develop symptoms.

Like Dr. Roll, we think that our PI may be used for optimal timing of liver transplantation. In a retrospective study of 29 patients with PBC, the actual survival after transplantation was significantly longer than the estimated survival (using PI) without transplantation, in spite of an increased mortality soon after the operation [Neuberger J, Altman DG, Christensen E, Tygstrup N, Williams R. Use of a prognostic index in liver transplantation for primary biliary cirrhosis. Transplantation (provisionally accepted for publication)]. However, the PI presented (1) has been developed using the baseline data at the admission to the trial. It is possible to make a PI of more general validity using time-dependent variables (4,5). The development of such a time-dependent PI, by which prognosis can be updated using the most recent information, is under way for PBC.

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Cirrhosis and Portal Vein Thrombosis

Dear Sir:

Okuda et al. (1) report that on autopsy, the incidence of portal vein thrombosis among cirrhotic subjects is 0.21%. We have reviewed the reports of 6990 necroscopies performed at the St. Carlo Hospital in Milan from 1966 to 1984. Of 483 patients with cirrhosis without liver cancer, 29 (6%) showed a portal vein thrombosis. The clinical records of 18 cirrhotic subjects with portal vein thrombosis and 243 without thrombosis were reviewed: 11 of the 18 patients with associated thrombosis had undergone an abdominal operation (4 splenectomies) in the past (7 patients in the last month before death), in comparison with 26 (2 splenectomies) of the 243 patients without thrombosis (11 patients in the last month before death; $p < 0.01$).

We wonder if not only the splenectomy but any other abdominal operation may predispose the patient to portal vein thrombosis in an advanced stage of cirrhosis.

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1. Okuda K, Ohnishi K, Kimura K, et al. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. Gastroenterology 1985;89:279–86.

Reply. You are correct in suggesting that abdominal surgery predisposes to portal vein thrombosis (your value of 0.21% should be 0.573%). We have a national study group supported by the Ministry of Health and Welfare of Japan for the study of idiopathic portal hypertension and portal hemodynamic abnormalities. Several years ago, this group, of which I was the chairman, conducted a clinical study of 184 cases of extrahepatic portal vein obstruction verified by operation or by percutaneous transhepatic catheterization. One out of three adult cases had a past history of abdominal surgery, operations for the biliary tract being the most frequent. These results will be published (1) in the second issue of the *Journal of Gastroenterology and Hepatology*, published by the Blackwell Scientific Publications, Australia, a new international hepatogastroenterological journal. I shall also have a review article (2) in the same issue on the problem of differential diagnosis and the relationship between extrahepatic portal vein obstruction and intrahepatic noncirrhotic portal hypertension, which is also called "hepatoportal sclerosis" in the USA, "idiopathic portal hypertension" in Japan, and "noncirrhotic portal fibrosis" in India. The incidence of thrombosis should be greater with autopsy materials compared with patients.

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"Spontaneous" Bacterial Peritonitis: Transfallopian Route of Infection Confirmed

Dear Sir:

Stassen and colleagues (1) recently reported the first case of spontaneous bacterial peritonitis caused by *Neisseria gonorrhoeae* in a patient with Laennec's cirrhosis and cervical gonorrhea. As noted by the authors, transfallopian tube transmission of bacteria has been suggested as a possible route of infection, but little evidence has been reported to support this hypothesis.

We have recently reported a similar case (2) that further confirms the role of the female genital tract as a possible reservoir of bacteria causing spontaneous peritonitis. A 51-yr-old woman was admitted to University Medical Center, Jacksonville, Florida with Laennec's cirrhosis and apparent spontaneous bacterial peritonitis. After initial physical examination, routine laboratory studies including blood cultures, urine culture, and a paracentesis were performed. She was begun on intravenous fluids and oral lactulose for symptoms of hepatic encephalopathy. Penicillin G and gentamicin were initiated intravenously for possible bacterial peritonitis. After 48 h, the antibiotics were changed to oral ampicillin 500 mg q.i.d. when the urine culture showed >100,000 cal/ml of *Acinetobacter anitratus* which was sensitive to ampicillin. Blood and peritoneal fluid cultures were negative, including anaerobic and fungal cultures.

Ten days later, the antibiotics were discontinued but within 24 h, the patient spiked a temperature to 101.5° F. Paracentesis was repeated and showed 9700 white blood cells/mm^3 (100% PMNs). An abdominal roentgenogram revealed the presence of a Lippes Loop intrauterine contraceptive device that had been present for 16 yr. A pelvic sonogram revealed a normal uterus and fallopian tubes without evidence of an abscess.

After removal of the intrauterine device, the Lippes Loop was cultured. After 48 h, the cultures of the intrauterine device and the repeat culture of the peritoneal fluid which had been obtained revealed the same organism, *Klebsiella pneumoniae*, which was resistant to gentamicin but sensitive to cefoxitin and third-generation cephalosporins; however, repeat blood cultures and urine cultures that had been collected at the time of paracentesis were negative. After appropriate antibiotics, the patient responded and had a full recovery.

We believe that these case reports substantiate the transfallopian tube route of infection in some women with apparent spontaneous bacterial peritonitis. After appropriate cultures are obtained, female patients with suspected spontaneous bacterial