reading frame. Small deletions or insertions may also affect transcription, splicing, or RNA processing. Sequence alterations that resulted in the generation of a stop codon, frameshift, or alteration of conserved splicing sequences were considered by Syngal et al. to be protein truncating and therefore deleterious mutations. When one base is replaced by another in the coding region, such point mutations result in the majority of cases in missense mutations in which base substitution changes the codon to a codon for a different amino acid. The effect of missense mutations on protein function is variable. The investigators therefore attempted to determine the potential pathogenicity of missense alterations by determining the segregation of the alterations with cancers in the kindreds and predicting their effects on gene function. Results of the above analyses were classified as definitive or inconclusive.

A total of 70 families were enrolled, representing 297 colorectal cancer and 364 other cancer diagnoses. Twenty-seven alterations of *hMSH2* and *hMLH1* were found in 24 of 70 families (34.3%). Of these, deleterious mutations could be used with confidence in clinical management of 18 of 70 (25.7%) families. Definitive results were obtained in almost 40% of families fulfilling the Amsterdam criteria for HNPCC and 30% meeting the Bethesda guidelines, but only 16% of families fulfilling the least restrictive criteria harbored clearly deleterious mutations. The most frequent reason for an inconclusive test was the lack of a sequence alteration in *hMLH1* or *hMSH2*. In other cases, identified missense mutations could not be determined with confidence to be functionally deleterious.

Comment. HNPCC is the most common form of familial colorectal cancer associated with germline mutations that has been identified to date. Because HNPCC is an autosomal dominant disorder with high penetrance, frequent screening of affected kindreds in the form of colonoscopy has been suggested (Gastroenterology 1995;108:1405–1411, JAMA 1997;277:915–919). The recognized spectrum of extraintestinal cancers associated with HNPCC is also expanding (Cancer 1996;78:1149–1167, Am J Med Genet 1996;62:353–364). A genetic test that could identify families with HNPCC and at-risk individuals within families is therefore highly desirable. Such testing would no doubt lead to improvement in cancer risk assessment and clinical management of patients and their families. Screening of at-risk individuals with colonoscopy can significantly reduce colorectal cancer rates in families with HNPCC (Gastroenterology 1995;108: 1405–1411). Although groups such as the American Cancer Society (CA Cancer J Clin 1997;47:154–161) have recommended routine genetic testing in those with a family history of HNPCC, potential difficulties involved in routine screening of families with a suggestive history is shown by the recent study of Syngal et al.

Genetic screening for HNPCC is highly desirable, but several potential problems exist in routinely screening families with a history suggestive of HNPCC. Also, the preferred method by which families should be screened has yet to be determined (N Engl J Med 1998;338:1481–1487 and 1998;338:1537–1538). Greater than 90% of colorectal cancers in individuals with HNPCC show microsatellite instability (MSI) as the result of MMR abnormalities. Therefore, some have suggested testing for resultant replication errors in all patients with a history suggesting HNPCC (N Engl J Med 1998;338:1481–1487). Although it is true that the absence of MSI argues strongly against a diagnosis of HNPCC, 15% of sporadic colorectal cancers also show MSI. Furthermore, adequate tumor tissue needs to be available from the proband for such analyses.

Because a high percentage of inactivating germline mutations in MMR genes result in truncated proteins, an in vitro transcription/translation assay method may be used to identify suspected individuals with HNPCC. This approach provided a positive test for alterations in about half of patients who met the Amsterdam criteria for HNPCC (Gastroenterology 1995;109:1368–1374). Such testing, however, will not identify families with missense mutations that result in protein degradation or some functionally inactive proteins.

Direct sequencing of exons in *hMSH2* and *hMLH1* is the most straightforward approach to diagnosis, and the approach used by Syngal and colleagues. At least 30% of HNPCC kindreds, however, cannot be shown to have mutations in the genes currently associated with HNPCC. Furthermore, the functional significance of all missense mutations (representing 30% of *hMLH1* mutations) is unclear. Complicating matters, it has recently been shown that methylation of the *hMLH1* promoter may lead to loss of expression of this gene (Cancer Res 1999;59:2024–2033). As the authors correctly point out, "the prevalence of missense mutations, genetic heterogeneity of the syndrome, and the current lack of functional assays presents challenges for the interpretation of genetic test results and counseling of HNPCC families." Construction of mutation profiles (Gastroenterology 1997; 113:1146–1158) and functional assays will help facilitate the development of diagnostic strategies in the future.

While driving on the freeway the other day I passed a sign that read "Paternity problem? Call 1-800-WHOSDAD" advertising a commercial genetics laboratory. The concept of genetic testing has become commonplace to lay individuals and medical professionals alike. With the development of advanced technologies have come expectations that, in some cases, outstrip the reality of what is possible. Genetic testing for HNPCC is possible and clinically important. Pathogenic mutations may be identified in a significant subset of families and lead to improved clinical management. When a significant mutation is identified in a family with a history suggesting HNPCC, direct sequencing or in vitro transcription/translation may be highly reliable in the management of at-risk family members. The limitations of such testing should also be appreciated, because test results must be correctly interpreted and patients given adequate counseling (N Engl J Med 1997;336:823–827). This is an important message from Syngal and colleagues.

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INTRAVENOUS ALBUMIN REDUCES MORTALITY IN PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Gines P, Rodes J (Institut de Malalties Digestives, Hospital Clinic, Institut d'Investigacions Biomediques August Pi-Sunyer, Hospital Vall d'Hebron, and Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Hospital Germans Trias i Pujol, Badalona, Spain; and Hospital Ramon y Cajal, Madrid, Spain). Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403–409.

Spontaneous bacterial peritonitis (SBP) is a common and serious complication in patients with cirrhosis and ascites. Despite prompt and effective antibiotic therapy, SBP continues to be associated with a high mortality rate, about 20%–40% (Hepatology 1988;8:171–175, Am J Gastroenterol 1993;88: 388–392). Factors that have been associated with a poor outcome include a serum albumin level of <2.5 g/dL, serum creatinine level of >2.1 mg/dL, bilirubin level of >8 mg/dL, hepatic encephalopathy, and upper gastrointestinal bleeding (Am J Med 1978;64:592–598, Hepatogastroenterology 1992; 39:520–522, Am J Gastroenterol 1993;88:388–392, Hepatology 1993;17:251–257). Renal impairment, postulated to be caused by a further decrease in effective arterial blood volume as a result of the infection, develops in one third of patients and is the strongest independent predictor of in-hospital mortality (Hepatology 1994;20:1495–1501 and 1998;27:1227–1232). The present study was designed to determine whether plasma volume expansion with albumin could prevent impairment in renal function and reduce mortality in patients with SBP.

A total of 126 patients were randomly assigned to 1 of 2 groups: 63 were assigned to treatment with cefotaxime (1–2 g every 6 hours based on serum creatinine level) and 63 to treatment with cefotaxime plus intravenous albumin (1.5 g/kg within 6 hours of enrollment followed by 1 g/kg on day 3). Inclusion criteria included a polymorphonuclear (PMN) cell count in the ascitic fluid of $>250/mm^3$ in the absence of findings suggestive of secondary peritonitis, age between 18 and 80 years, no antibiotic treatment within 1 week of the diagnosis of SBP, serum creatinine level of ≤ 3 mg/dL, and absence of other infections, shock, gastrointestinal bleeding, ileus, severe encephalopathy, cardiac failure, organic nephropathy (proteinuria, hematuria, or abnormal renal ultrasound findings), and human immunodeficiency virus infection.

Diuretic treatment or therapeutic paracentesis was not allowed until the infection had resolved, i.e., signs of infection disappeared and the PMN cell count was $\leq 250/mm^3$. Renal impairment during hospitalization was defined as a nonreversible worsening of renal function manifest as a $>50\%$ increase in blood urea nitrogen (BUN) or creatinine levels in patients with preexisting renal insufficiency (i.e., serum creatinine of 1.5–3 mg/dL at baseline) or as $>50\%$ increase in BUN or creatinine to levels >30 and 1.5 mg/dL, respectively, in patients without renal insufficiency at baseline.

Despite no significant differences between the groups in terms of clinical and laboratory data at enrollment and rate of resolution of infection, the incidence of renal impairment was significantly lower among the patients treated with cefotaxime and albumin (6 of 63 or 10%) than among those treated with cefotaxime alone (21 of 63 or 33%; $P = 0.002$). Even more impressive, in-hospital mortality was significantly reduced from 29% (18 of 63) in patients treated with cefotaxime to 10% (6 of 63) in patients treated with cefotaxime and albumin ($P = 0.01$). Although plasma renin activity was similar in the 2 groups at baseline, on days 3, 6, and 9, the level of plasma renin activity was significantly higher in the patients treated with cefotaxime alone than in those treated with cefotaxime and albumin.

The investigators conclude that addition of intravenous albumin to an antibiotic regimen reduces the incidence of renal impairment and death in cirrhotic patients with SBP.

Comment. SBP is defined as bacterial peritonitis that occurs in patients with ascites in the absence of recognized secondary causes such as bowel perforation or intra-abdominal abscess. The diagnosis may be made by finding a PMN cell count in the ascitic fluid of $>250/mm^3$ (sensitivity, 85%; specificity, 93%; diagnostic accuracy, $>90\%$) (Mayo Clin Proc 1995;70:365–370). More than 90% of cases of SBP are monomicrobial, with *Escherichia coli* and *Klebsiella* species accounting for more than half the cases. Gram-positive organisms, primarily streptococcal species, account for 25% of cases. Anaerobic infection is rare and probably represents no more than 5% of cases (Mayo Clin Proc 1995;70:365–370). Cefotaxime, as used in the present study, is a drug of choice for empiric treatment of SBP and produces greater resolution of infection and less nephrotoxicity and superinfection than combination therapy with ampicillin and gentamicin (Hepatology 1985;5:457–462, 1993;17:251–257, and 1995;21: 674–679). Nonetheless, despite adequate antibiotic therapy, about a third of patients succumb to liver failure, nosocomial infection, gastrointestinal bleeding, and/or renal failure (Hepatology 1988;8:171–175, Am J Gastroenterol 1993;88:388–392, Hepatology 1994;20: 1495–1501, Semin Gastrointest Dis 1997;27:264–272, N Engl J Med 1999;341:443–444, Am J Gastroenterol 1999;94:2193–2197).

Albumin comprises 60% of total proteins present in human plasma, is responsible for 70% of the plasma colloid osmotic pressure, and, as a result, plays a critical role in fluid distribution between extracellular compartments (Clin Sci 1998;95:459–465). Because the most sensitive predictor of in-hospital mortality in patients with SBP may be a deterioration in renal function (Hepatology 1994;20:1495–1501), the present study was designed to determine in a randomized manner whether expansion of plasma volume, and hence maintenance of effective renal perfusion, by infusion of intravenous albumin could reduce renal deterioration and mortality in patients with SBP treated with a standard antibiotic regimen. Not only was the incidence of renal impairment significantly lower in the group treated with albumin, but in-hospital mortality was impressively reduced by two-thirds, from 29% to 10%. The causes of in-hospital death were combined liver and renal failure (13 patients in the cefotaxime group and 5 in the cefotaxime plus albumin group), gastrointestinal hemorrhage (2 patients in the cefotaxime and 1 in the cefotaxime plus albumin group), septic shock (2 patients in the cefotaxime group), and liver failure (1 patient in the cefotaxime group). The facts that the bulk of excess deaths could be attributed to renal failure and that both renal failure and mortality were reduced in the group randomized to albumin support the notion that albumin, by maintaining effective plasma volume, can prevent the deterioration in renal perfusion precipitated by infection, i.e., SBP, in cirrhotic patients with ascites.

This is an important study that was meticulously performed by a highly respected group known for their expertise in the management of ascites and use of intravenous albumin. Nonetheless, certain caveats must be considered. First, the study was not blinded and thus bias may have been introduced. Second, patients assigned to cefotaxime alone, at baseline, had more renal failure, more encephalopathy, more prolonged prothrombin times, higher white cell counts, and higher serum bilirubin and lower serum albumin levels than those assigned to cefotaxime plus albumin. Although differences in each of the baseline parameters did not quite reach statistical significance, in aggregate

they suggest that those patients assigned to the antibiotic alone group were sicker and had more advanced liver disease. Third, it is possible that human albumin products contain infectious agents such as parvovirus, which can cause serious disease, including pancytopenia. This nonenveloped DNA virus is relatively prevalent, with up to 1 of 3300 blood donors being viremic, and is relatively heat resistant (Br J Haematol 1999;106:266–269). Indeed, polymerase chain reaction–detectable parvovirus DNA has been reported to be present in 25% of pasteurized batches of albumin from 3 different manufacturers (Br J Haematol 1996;93:714–719). It is not known, however, if this material is clinically infectious. Fourth, albumin is relatively expensive, costing $15 per gram at our hospital and up to $25 per gram elsewhere. The 175 g of albumin used in this study for a 70-kg patient would cost a minimum of $2625. Fifth, an increase in venous return, expansion of central blood volume, and increases in cardiac output and renal blood flow can be achieved inexpensively simply by having the patient lie down (Hepatology 1992;16:341–346 and 1996;23:1141–1147).

How should we treat the next patient with SBP? This study, even taking into account the caveats, strongly supports the use of intravenous albumin in addition to antibiotics. Only 5.6 patients would have to be treated with albumin to prevent 1 death. An alternative, although not specifically addressed in the study, might be to closely monitor renal function and administer intravenous albumin only to those patients with abnormal renal function on presentation or at the first sign of declining renal function during hospitalization.

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Reply. We agree that a double-blind study would have been better to avoid any possible bias in the analysis of the results, but such a design had many technical difficulties. As is the case in most randomized studies, there were some small and nonsignificant differences between both treatment groups in the baseline characteristics of the patients included. However, it should be emphasized that when multivariate analyses were performed, the treatment group (albumin vs. nonalbumin) was the variable associated with the strongest independent predictive value for both renal impairment and mortality. Although Mogyorósi and Schubert are correct in their comment that the supine posture increases venous return and expands the central blood volume, it is likely that the administration of albumin causes a much greater and prolonged plasma volume expansion than a change in posture. Moreover, because most patients were in the supine position, at least during the first few days of therapy, the effect of posture on central blood volume was likely present in patients in both treatment groups. The suggestion that renal function could be closely monitored and albumin administered only to patients developing renal impairment is an attractive one. Unfortunately, however, it is not known whether albumin, besides being effective in the prevention of renal impairment, improves renal function when renal impairment is already established. This would require a specific investigation. Therefore, based on the findings of our study, it is advisable to give albumin to all patients at diagnosis of spontaneous bacterial peritonitis instead of waiting for renal impairment to occur. The possible transmission of viruses by albumin administration remains a concern and would require methodological improvements in the preparation of albumin; however, this concern applies to all clinical situations in which administration of albumin is indicated. The high cost of albumin and its limited availability in some settings is an important problem. Nonetheless, because the beneficial effect on survival of patients with spontaneous bacterial peritonitis was very marked, it is advisable to give albumin whenever possible. Studies should be performed to assess the efficacy of less expensive approaches, such as the administration of artificial plasma expanders.

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