**Background & Aims:** Portal hypertension can complicate primary biliary cirrhosis, but studies evaluating the direct measurement of the portohepatic gradient (PHG) are rare. The aim of the study was to determine the prevalence and prognostic value of portal hypertension in patients treated with ursodeoxycholic acid. **Methods:** A total of 132 patients from a local “PBC clinic” were enrolled in this cohort study. The PHG and biochemical values were measured at inclusion and every 2 years. Factors associated with survival were analyzed. **Results:** Mean PHG at inclusion was 7.2 ± 5.8 mm Hg. It was higher than normal (6 mm Hg) in 46 patients (34.9%) and higher than 12 mm Hg (variceal bleeding risk limit) in 26 patients (19.7%). There was a difference between the 3 subgroups in the probability of survival free of liver transplantation (P < .0003). After 2 years of treatment, a decreased or stable PHG (hazard ratio, 4.64; 95% confidence interval, 2.01–10.72) and normalization of aspartate aminotransferase (AST) level (hazard ratio, 2.89; 95% confidence interval, 1.03–8.05) were predictive of better survival on multivariate analysis. “Responders” (stable or improved PHG and normalized AST level at 2 years) have a 15-year survival similar to that of a control Quebec female population. **Conclusions:** Significant portal hypertension is a common complication of primary biliary cirrhosis. Changes in the PHG and normalized AST level after 2 years of ursodeoxycholic acid treatment can be used to identify a subgroup of responders with survival comparable to that of a control population.

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease that progresses slowly over time to become true cirrhosis. In addition, changes found in sinusoids (deposition of collagen within the space of Disse and the development of a new basement membrane underlying the sinusoidal endothelial cells) will result in an increased resistance to blood flowing through the liver and consequently an increase in portal venous pressure. Portal hypertension is usually defined by a pressure gradient greater than 6 mm Hg between the portal vein and a hepatic vein in a free position (the portohepatic gradient [PHG]).

Progression of portal hypertension leads to esophageal and gastric varices that, when large, may bleed. However, portal hypertension can be present in the absence of varices. Its presence can then only be ascertained by determination of the PHG. Because of the presinusoidal component of the gradient in PBC, this requires direct access to the portal vein. Indeed, in the early stages of the disease, the major site of resistance within the portal bed is mainly located at the presinusoidal level. Thus, a gradient can exist between the portal vein pressure and the sinusoidal pressure (usually determined by wedged hepatic vein pressure), and the hepatic vein pressure gradient (difference between the wedged hepatic vein pressure and the free hepatic vein pressure) may underestimate the actual PHG. Although well recognized, the exact physiopathology of this phenomenon is still not completely elucidated. Nodular regenerative hyperplasia, a rare condition, as well as lymphoid aggregates in the portal tracts (such as granulomas) can be contributing factors. Thrombosis of terminal portal venules and contracture of the sinusoidal endothelial cells and/or stellate cells can also be incriminated but are found in other types of cirrhosis independently of the site of portal hypertension.

**Abbreviations used in this paper:** AP, alkaline phosphatase; GGT, \( \gamma \)-glutamyl transpeptidase; PBC, primary biliary cirrhosis; PHG, portohepatic gradient.
There is a paucity of studies on portal hypertension in patients with PBC and, in most of them, portal hypertension was not directly measured.  

Currently, ursodeoxycholic acid (UDCA), as first proposed by Poupan et al in 1987, is the only drug approved for the treatment of patients with PBC and is widely used all over the world. Several randomized clinical trials have been reported showing sustained improvement in biochemical parameters, in particular bilirubin, serum transaminase, alkaline phosphatase (AP), and γ-glutamyl transpeptidase (GGT) levels. A combined analysis of 3 of the major published randomized trials showed that the 4-year transplant-free survival was significantly improved in patients treated with UDCA. However, in a meta-analysis involving 8 of the 11 published randomized trials, Goulis et al did not find a difference between UDCA and placebo in the incidence of death and/or liver transplantation. The effects of UDCA on the development and/or progression of portal hypertension in patients with PBC have not been well assessed in most reported studies and were contradictory in the 2 studies specifically addressing this complication.

The present study was undertaken to evaluate the prevalence and prognostic value of portal hypertension in a large cohort of patients with PBC. A total of 132 patients with PBC were included and followed up for up to 17 years, with measurement of the PHG at the time of referral to our clinic and then, whenever possible, every second year. In addition, the long-term effects of UDCA treatment on the progression of portal hypertension were evaluated and compared with the biochemical effects to determine if long-term “responders” and “nonresponders” could be identified.

**Patients and Methods**

**Patients**

Between June 1987 and March 2000, 212 patients were referred to Hôpital Saint-Luc for diagnosis and/or treatment of PBC. A total of 132 consecutive patients, who gave informed consent, were entered in the present long-term study. Only one eligible patient did not agree to participate in the study. The local human research committee approved the study protocol. The diagnosis of PBC was established according to the following criteria: a chronic cholestatic liver disease of at least 6 months’ duration, positive antimitochondrial antibodies, absence of biliary obstruction by ultrasonography or cholangiography, and a liver biopsy specimen compatible with or diagnostic of PBC. None of the patients were treated with UDCA before inclusion in the study. Patients with a previous history of ascites, bleeding varices, and portosystemic encephalopathy, or in end-stage liver disease, whether candidates or not for liver transplantation, were excluded from this study either because the PHG measurement was not justified or because UDCA treatment was not considered. Those with coexistent liver diseases were excluded. Age and sex of the patients are given in Table 1. Patients were treated with UDCA at a dosage of 13–15 mg/kg body wt per day (divided into a morning and an evening dose) after baseline evaluation and were usually prescribed vitamin D (50,000 U/wk) and vitamin A (20,000 U twice a week) during their long-term follow-up. None of the patients were given cholestyramine, and a few received rifampin for persistent pruritus. The first 30 patients were enrolled in the French controlled trial and were randomized to receive UDCA (15 patients) or an identical placebo (15 patients) for a 2-year period. All patients were then treated with UDCA for the rest of the follow-up study. The other 102 patients received UDCA for the entire study.

Patients were followed up at a specific PBC outpatient clinic, and follow-up data were collected at 3-month intervals during the first year, 6-month intervals for the second year, and yearly thereafter. During each visit, a clinical assessment of symptoms (pruritus, jaundice, edema, and ascites) was performed and fasting blood samples were taken for complete blood cell count and determination of serum levels of bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), AP, GGT, prothrombin time, albumin, and cholesterol (Table 1). Serum immunoglobulins as well as antimitochondrial, antinuclear, and anti–smooth muscle antibodies were assessed at study entry and yearly.

Initial liver biopsies were performed in most cases at Hôpital Saint-Luc at the time of inclusion or within 6 months before study entry. All biopsy specimens were staged (I–C) according to the Ludwig criteria, except in 5 cases in which the specimens were considered inadequate or were not available for local review. No follow-up biopsy specimens were obtained, except for the first 30 patients included in the French study and reported elsewhere.

The end point used in the different assessments of probability of survival was survival free of liver transplantation. Liver transplantation was performed in patients

### Table 1. Baseline Characteristics of the Patients With PBC Included in the Prospective Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value, Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at inclusion (y)</td>
<td>50.28 ± 10.71 (30–78)</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>118/14</td>
</tr>
<tr>
<td>Length of follow-up (y)</td>
<td>8.64 ± 4 (0.5–17)</td>
</tr>
<tr>
<td>Mayo score</td>
<td>3.82 ± 1.04 (1.71–7.89)</td>
</tr>
<tr>
<td>Ludwig stage 1/2/3/4</td>
<td>7/18/32/70</td>
</tr>
<tr>
<td>AST level (IU/L)</td>
<td>93 ± 52 (27–331)</td>
</tr>
<tr>
<td>ALT level (IU/L)</td>
<td>101 ± 77 (20–546)</td>
</tr>
<tr>
<td>GGT level (IU/L)</td>
<td>601 ± 505 (34–3158)</td>
</tr>
<tr>
<td>AP level (IU/L)</td>
<td>488 ± 302 (100–1743)</td>
</tr>
<tr>
<td>Bilirubin level (μmol/L)</td>
<td>17 ± 12 (2–62)</td>
</tr>
<tr>
<td>Albumin level (g/L)</td>
<td>39 ± 4 (22–52)</td>
</tr>
<tr>
<td>Platelet count (/mm³)</td>
<td>245 ± 85 (39–543)</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>10 ± 2 (7–14)</td>
</tr>
</tbody>
</table>

NOTE. All values are expressed as mean ± SD (range).
younger than 65 years of age when the Child–Pugh score was greater than 8/15 or serum bilirubin level was greater than 100 μmol/L, according to the American Association for the Study of Liver Diseases Practice Guidelines. A local multidisciplinary committee beforehand accepted the candidacy of all patients for transplantation.

Measurement of the PHG

Measurement of free portal vein pressure and free hepatic vein pressure was performed using a thin needle (Chiba needle, 22 gauge, 15.2 cm; BD-Canada, Oakville, ON, Canada) through a percutaneous transhepatic approach under fluoroscopic guidance. Upon entering a vascular channel (as secured by blood withdrawal on gentle aspiration), pressure was first recorded with a Statham gauge transducer connected to an electronic manometer, and then 2–5 mL of contrast material was injected to identify the portal vein or hepatic vein localization according to the direction of flow of the contrast (Figure 1). Generally, 2–4 insertions of the needle were needed to enter both a portal vein radicle and a hepatic vein branch. The same criteria as those established by Boyer et al were followed to ensure that valid pressures were recorded. At the time of pressure measurement, all patients were fasting and had received intravenous midazolam (2.5 mg). None of the patients had any complication and moderate pain only occurred, when present, following the accompanying liver biopsy.

The PHG was calculated as the difference between portal vein pressure and hepatic vein pressure on printed recordings. In all patients, the PHG was measured at entry (in most cases at the time of initial liver biopsy during the same procedure). Thereafter, it was measured every second year, at least up to the sixth year. It was not measured after January 2001. The PHG was not evaluated once a complication of the liver disease occurred (decreased platelet count <70,000/mm³, ascites, bleeding varices, hepatoma) or when patients were listed for orthotopic liver transplantation.

Statistical Analysis

Data were analyzed with SPSS 10 software (SPSS Inc, Chicago, IL). Quantitative data were expressed as mean ± SD and were compared with Student t test and with Mann-Whitney test for nonparametric data. Correlations were made using Pearson or Spearman r test. The probability of survival free of transplantation was estimated from survival curves using the Kaplan–Meier method and compared using the log-rank test. Logistic regression analysis was used to estimate predictors for the PHG. To explore the response of the PHG to UDCA and placebo (the first 30 patients included in the controlled trial), one-way repeated-measures analysis of variance was been applied using SAS version 9.1 (with a repeated-measures multiple analysis of variance procedure for UDCA-treated patients and a GLM procedure for patients receiving placebo). The Cox proportional hazards regression model was used to find the factors associated with survival. Two-tailed significance was defined as P < .05 in each analysis.

Results

Patient Characteristics

Demographic, laboratory, and pathologic characteristics at entry into the study are shown in Table 1 and were comparable to those reported in most PBC controlled trials. According to Grambsch et al, 119 patients had a low risk Mayo score (mean, 3.6; range, 1.71–5.30) and only 10 patients had an intermediate- to high-risk Mayo risk score (mean, 6.0; range, 5.55–7.89).

PHG at Inclusion

The mean PHG at inclusion was 7.2 ± 5.8 mm Hg (Figure 2). It was greater than 6 mm Hg (the upper limit of normal) in 46 patients (34.9%) and greater than 12 mm Hg (the lower limit for the risk of bleeding from esophageal varices) in 26 patients (19.7%). The PHG correlated significantly with the Mayo risk score ($r^2 = 0.262; P < .001$) and the liver biopsy stage ($r_s = 0.414; P < .001$) (Figure 3), but there was a large scatter of the data. There were also weak significant correlations with albumin level ($r^2 = 0.219; P < .001$), bilirubin level ($r^2 = 0.163; P < .001$), and platelet count ($r^2 = 0.196; P < .001$). Significant correlations were also found with AST level and prothrombin time, but with very low correlation coeffi-
cients ($r^2 = 0.040$ and 0.062, respectively), while no correlation was found with ALT, AP, and GGT levels or with Child–Pugh and Model for End-Stage Liver Disease scores.

**Predictors of PHG Severity**

To predict the PHG indirectly, we performed a multivariate analysis including Mayo risk score, liver biopsy stage, and platelet count, which were significantly correlated with PHG values using a multiple logistic regression. Bilirubin and albumin levels have been excluded from the analysis because they are part of the Mayo risk score. AST level and prothrombin time were excluded because of their weak correlation coefficients. The 3 criteria regression model has an $r^2$ of only 0.387 ($P < .001$).

### Effects of UDCA on PHG

As specified previously, the first 30 patients were part of the French controlled trial and were randomized to receive either UDCA (group A, 15 patients) or a placebo (group B, 15 patients) for a 2-year period. At the end of this first period (2 years), a second measurement of PHG was performed (14 from group A and 13 from group B). Thereafter, all patients were treated with UDCA for the next 4 years; the PHG was measured at 4 years (n = 12 in group A and B) and at 6 years (n = 10 in group A and n = 9 in group B). After the initial measurement, the PHG could not be measured in 4 patients from both groups for various reasons.

On inclusion, PHG values were slightly but not significantly higher in patients from group A than in patients from group B (8.3 ± 5.0 and 7.0 ± 3.9 mm Hg, respectively). At 2 years, the PHG increased slightly but not significantly in group A (to 10.1 ± 4.2 mm Hg) whereas the PHG increased significantly in group B (to 9.7 ± 5.0 mm Hg; $P < .05$). At 4 years, the PHG values decreased slightly in group A (7.5 ± 2.8 mm Hg) and remained stable in group B (11.1 ± 2.8 mm Hg), but the difference between the 2 groups did not reach the level of significance ($P = .08$). Most interestingly, in group B, PHG values returned toward preinclusion values by the end of the 6 years of follow-up (ie, by the end of the fourth year.

---

**Figure 2.** Individual values of the PHG recorded in the 132 patients with PBC on inclusion in the prospective study. Portal hypertension is defined by a gradient >6 mm Hg; 12 mm Hg is the threshold value for the risk of variceal bleeding.

**Figure 3.** Correlation between the PHG and the Mayo score (left panel) and the Ludwig biopsy stage (right panel).
of UDCA treatment (Figure 4 and see Supplementary Figures 1 and 2 online at www.gastrojournal.org).

To explore directly the effects of UDCA and placebo on the PHG, one-way repeated-measures analysis of variance was applied to the 2 groups. In patients from group A, PHG values did not change significantly all along the 6 years of UDCA treatment (P = not significant). By contrast, in patients from group B, there was a significant change in PHG values when measured on inclusion and then at 2, 4, and 6 years (P < .05).

**Long-Term Follow-Up Data**

The mean follow-up period was 8.64 ± 4 years (range, 0.5–17 years), and data were censored on December 31, 2004. There were a total of 13 liver transplantations and 23 deaths, while only 7 patients were lost to follow-up. Death was due to liver failure (n = 4), hematoma (n = 4), and bleeding varices (n = 2), whereas it was not related to the liver disease in 13 patients. During follow-up, 13 patients were admitted for bleeding varices and were not further evaluated with PHG measurement.

The importance of portal hypertension on the overall survival of patients with PBC was evaluated by separating patients in 3 groups according to their initial PHG: (1) patients with no portal hypertension (PHG ≤6.0 mm Hg; n = 86), (2) patients with moderate portal hypertension (PHG 6.0–12.0 mm Hg; n = 20), and (3) patients with severe portal hypertension (PHG >12.0 mm Hg; n = 26).

There was a significant difference between the 3 subgroups in the probability of survival free of liver transplantation (P < .0003) (Figure 5), while a significant difference was also found between the 2 extreme subgroups (P < .0001).

The Cox proportional hazards regression model was used to assess whether any parameters recorded on inclusion could be associated with survival. Several biochemical parameters (including AST, ALT, AP, GGT, and albumin levels and platelet count), liver biopsy stage, PHG, and Mayo score were included in the analysis. Bilirubin level and prothrombin time were excluded because they were part of the Mayo score. Only the Mayo score was significantly associated with survival, with a hazard ratio of 2.22 (95% confidence interval, 1.63–3.02; P < .00001).

**Long-Term Responders and Nonresponders to UDCA Treatment**

Data obtained in the first 30 patients included in the French controlled trial were highly suggestive of a positive effect of UDCA treatment on the progression of portal hypertension after 2 years of treatment.

We therefore analyzed whether PHG changes measured at the end of the second year of treatment could have a prognostic value in the long-term survival of treated patients. Of the 132 patients included in the prospective study, 101 patients had at least 2 measurements of the PHG while treated with UDCA during long-term follow-up. Patients were separated into 2 groups according to PHG changes at the end of the second year. In the first group of 81 patients (80.2%), PHG remained stable or improved over time (mean change, −0.6 ± 2.1 mm Hg). PHG was ≤6 mm Hg in 52 of these patients, and it was already >6 mm Hg in the 29 other patients. Conversely, in the second group of 20 patients (19.8%), PHG worsened during long-term follow-up (PHG increase >20%; mean increase, 7.4 ± 4.4 mm Hg). PHG was already >6 mm Hg in 11 of these patients, while it was ≤6 mm Hg in the 9 other patients. A highly significant difference was found between the 2 groups of patients in their probability of survival free of liver transplantation. We used a 20% cut-off value by analogy with studies evaluating the efficacy of drug therapy for portal hypertension.23 When the PHG changes observed at 2 years were included in the Cox proportional hazards regression model reported previously, both Mayo score and PHG changes were significantly associated with survival, with hazard ratios of 2.74 (95% confidence interval, 1.71–4.39; P < .0001) and 1.63 (95% confidence interval, 2.24–11.74; P < .0001), respectively.

As expected, in the present study, significant decreases were also found in serum levels of AST, ALT, AP, and GGT 2 years after initiating UDCA therapy (P < .0001). However, serum bilirubin level, albumin level, and the Mayo score were not modified (P = not significant). We
therefore tested the hypothesis that, in addition to PHG changes observed in the 101 patients with PBC, improvement induced by UDCA in biochemical parameters could be used to better select responders from nonresponders. Kaplan–Meier survival curves were computed for patients separated into 2 groups according to changes observed in their biochemical parameters 2 years after UDCA treatment. The analysis included patients with and without normalized values or a decrease of \( \geq 40\% \) from the initial values for AST, ALT, AP, and GGT. No significant difference could be found in the probability of survival between all paired groups of patients, except for the 48 patients who had normalized AST levels after 2 years of UDCA treatment compared with the 53 who did not have normalized AST levels \( (P < .001) \).

The Cox proportional hazards regression model was used to find if any changes observed after 2 years of UDCA treatment were associated with survival and could be used as predictors of long-term survival; only changes observed in the PHG (hazard ratio, 4.64; 95% confidence interval, 2.01–10.72) and normalization of AST level (hazard ratio, 2.89; 95% confidence interval, 1.03–8.05) were selected as factors with a high predictability of survival. Therefore, we identified patients with stable or improved PHG and normalized AST level at 2 years as responders and patients who did not meet these 2 criteria as nonresponders. The 15-year survival was significantly different in the 42 responders compared with the 59 nonresponders \( (P < .001) \) (Figure 6). In addition, the 15-year survival of responders was similar to that of the Quebec female population, matched for age and observed during the same period of follow-up.

When considering the initial values obtained in responders and nonresponders, significant differences were found for AST, ALT, GGT, and bilirubin level as well as Mayo score \( (P < .001) \), AP level \( (P < .02) \), and Ludwig biopsy stage \( (P < .004) \), while no difference was found for platelet count, suggesting that responders had better liver function at the introduction of UDCA therapy. Although statistically significant, the difference between the 2 groups was of a small magnitude with a large overlap and could not be used to differentiate responders from nonresponders on an individual basis.

**Discussion**

The present study reports, for the first time, the real incidence and severity of portal hypertension in a large series of unselected patients with PBC referred to a tertiary hospital for the diagnosis and treatment of their uncomplicated liver disease. Portal hypertension (PHG \( > 6.0 \text{ mm Hg} \)) was present in about 35% of the 132...
The severity of portal hypertension could not be predicted by other noninvasive parameters. Indeed, while significant correlations could be found between the PHG and several biologic and pathologic parameters, these correlations were weak and not clinically useful, even when combining different parameters in a multivariate regression analysis. On the other hand, the determination of the PHG, on first evaluation of the disease, was significantly correlated with long-term survival (Figure 5). However, using a Cox proportional hazards regression model including several biochemical and pathologic parameters, the PHG and the Mayo score recorded on inclusion in the study, only the initial Mayo score was significantly associated with survival.

The natural history of the progression of portal hypertension was also rarely reported in patients with PBC and relies mainly on 2 studies from the Mayo Clinic. In 1989, Gores et al. reported that, over a 7-year period, esophageal varices developed in 31% of their patients with PBC and that 40% of those patients experienced variceal bleeding within 4 years of development. More recently, Lindor et al. found that esophageal varices were present in 22% of patients with PBC who entered their clinical trial using UDCA and that new varices developed in 25% and 58% of untreated patients (placebo group) at 2 and 4 years, respectively. They also found a significantly decreased risk of developing esophageal varices after 2 and 4 years of UDCA treatment. However, these data were not confirmed by Combes et al., who reported a nonsignificant increase in the development of new varices and in the incidence of bleeding varices after 2 years of UDCA treatment when compared with placebo.

These studies suggested that portal hypertension was a rapidly evolving condition in patients with PBC without UDCA treatment. Unfortunately, no measurement of the PHG was performed. Nowadays such studies are not feasible, because almost all new patients with PBC around the world are treated with UDCA. In the present study, most of the long-term evaluations were performed prospectively while patients were taking UDCA from inclusion in the study, except for the first 30 patients enrolled in the French clinical trial, who were randomly assigned to treatment with UDCA or placebo for the first 2 years.

Data obtained in these patients are of particular importance, because they strongly suggest that UDCA treatment prevents the progression of portal hypertension in most patients with PBC during a 6-year period. By contrast, when patients with PBC were first given placebo, their PHG worsened during these first 2 years; when subsequently treated by UDCA, not only did their PHG not increase further, it even returned to preinclusion values by the fourth year of UDCA treatment. This is the first report suggestive of a direct effect of UDCA on the progression of portal hypertension.

A further analysis of our data showed that changes in the PHG observed while on UDCA treatment for 2 years could be used to identify responders and nonresponders with different long-term survival. Indeed, the patients in whom the PHG remained stable or decreased had a markedly better survival than those with an increased PHG (>20%). Among UDCA-induced changes on biochemical parameters, normalized AST level at 2 years was the only parameter significantly related to better survival. We did not find additional predictive value for any other biochemical changes, namely changes in AP as reported recently by Parés et al. Finally, both changes in PHG and normalization of AST level at 2 years were selected as factors with a very high predictability of survival and used to classify patients as responders and nonresponders to UDCA treatment (Figure 6). In patients considered responders to UDCA, the life expectancy was comparable to that observed for an age-matched population in Quebec. However, the present prognostic model should be viewed with caution due to the relatively small number of end point events during our study (death and/or liver transplantation).

Since the introduction of UDCA in the treatment of patients with PBC, several investigators have tried to identify biochemical parameter changes observed within
the first years of treatment that would be good predictors of the long-term effects of the drug.\textsuperscript{12,15–18} Unfortunately, most studies were not clinically useful, particularly due to the variable definitions of responders and nonresponders (or partial responders) and/or to the absence of survival curves free of liver transplantation. In addition, changes in transaminase levels were not available in all.\textsuperscript{27,28}

The better survival in patients who normalized their AST level seems sound and is in accordance with the work of Coperchot et al.\textsuperscript{29} who reported that initial AST activity was an independent marker of lymphocytic piecemeal necrosis, a factor highly related to development of cirrhosis.

On the other hand, the predictive effect of AST normalization has to be considered by analogy to patients with autoimmune hepatitis, in whom the aim of corticosteroid treatment is to normalize transaminase levels in order to have a good remission and a better prognosis of the liver disease.\textsuperscript{30} UDCA, by decreasing hepatocyte death and by improving cholestasis, may well decrease the inflammatory response, leading to the progression of portal hypertension.

A further analysis of our data also revealed that responders had slightly better liver function on introduction of UDCA therapy than nonresponders. These data confirm the notion that UDCA is more effective in the first stages of PBC\textsuperscript{31,32} and therefore should be initiated early in the course of the disease.

In conclusion, the present study shows that portal hypertension is not a rare complication of PBC and that there are no useful clinical predictors of its severity. Although the evaluation of portal hypertension by measurement of the PHG correlates highly with long-term survival of patients with PBC, the initial Mayo score remains the best predictor of survival. In addition to the well-known effects on biological parameters, UDCA treatment is associated with a stabilization or improvement of portal hypertension, but this effect is not observed in all patients; responders and nonresponders to UDCA can be identified according to changes in PHG and AST levels observed 2 years after UDCA therapy and have significantly different long-term survivals. This notion of responders and nonresponders is new and may well explain the conflicting data found in the literature concerning the effects of UDCA in patients with PBC as reported in various clinical trials.\textsuperscript{16} In addition, the present study clearly shows that the most important information, predicting the response to treatment, was already obtained at the second PHG measurement, performed 2 years following UDCA treatment. Therefore, there should be no need for repeated PHG measurements, because no additional information could be obtained thereafter. In our population, the maximal changes in the PHG, when present, were observed during this initial period, while the PHG remained stable afterward up to 6 years of follow-up. Our findings are of interest when considering the emerging noninvasive methods aimed at evaluating liver fibrosis, particularly elastography, that may prove useful in the indirect assessment of portal hypertension in the near future, thereby avoiding the need for invasive measurement of the PHG.\textsuperscript{33}

**Supplementary Data**

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2008.07.019.

**References**