

Evaluating the efficacy and safety of Danning Pian in the short-term treatment of patients with non-alcoholic fatty liver disease: a multicenter clinical trial

Jian-Gao Fan and Shanghai Multicenter Clinical Cooperative Group of Danning Pian Trial

Shanghai, China

BACKGROUND: Currently, the management of non-alcoholic fatty liver disease (NAFLD) is less than certain. Some choleric might be of potential benefit and deserve further evaluation. This multicenter clinical trial was designed to evaluate the efficacy and safety of Chinese herbal medicine Danning Pian (composed of rhubarb, grant knotweed, dried green orange peel and dried old orange peel) in the short-term treatment of patients with NAFLD.

METHODS: The efficacy and safety of Danning Pian in the short-term treatment of NAFLD were investigated in 232 patients by a multicenter clinical trial during the period of July 1999 to February 2000. The patients consisting of 189 males and 43 females with an average age of 46.1 ± 8.7 years were given 3-5 tablets of Danning Pian orally thrice daily for 3 months in addition to the other comprehensive therapy. The effects of Danning Pian on NAFLD were evaluated by the improvement of clinical symptoms, blood lipids, hepatic enzymes and liver ultrasonographic features. The drug safety was monitored by physical examinations, vital signs, and laboratory tests in addition to the assessment of the adverse events.

RESULTS: All the enrolled patients completed the study except one whose serum ALT level was moderately increased during the therapy with Danning Pian. The effective rate of Danning Pian for the improvement of clinical symptoms, serum ALT levels, blood lipid and fatty liver was 85.8%, 78.2%, 39.6% and 34.0% respectively after the therapy for 3 months. However, the reduction of excessive body weight and waistline did not reach the significant level on the whole after the therapy. The general mild adverse events included diarrhea, skin rash and mild to moderate elevation of serum ALT level. The incidence of adverse reaction was 15.1%.

CONCLUSION: The data of this trial indicate that Danning Pian is effective and safe, generally well-tolerated without severe adverse events, in the treatment of patients with NAFLD over a 3-month period.

(*Hepatobiliary Pancreat Dis Int* 2004; 3: 375-380)

KEY WORDS: Chinese herbal medicine; Danning Pian; fatty liver; non-alcoholic; therapy

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological condition that comprises a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis.^[1-7] Since it was first described in 1980, the prevalence of this disease has been recognized with increasing frequency and is currently estimated affecting 10%-24% of the general population in different countries.^[2,8] Unfortunately, up to the present there is no specific treatment for this condition, although each therapeutic regimen should include a gradual and supervised weight reduction, a balanced diet and exercise as well as a correction of precipitant factors.^[9-14]

Ursodeoxycholic acid (UDCA) is the epimer of chenodeoxycholic acid with biological membrane stabilizing or cytoprotective and immunological effects.^[15] It is reported that UDCA may potentially protect hepatocyte from injury and decrease oxidative stress in patients with NAFLD by decreasing hydrophobic bile acid, a substance increasing cellular damage and oxidative stress in steatotic hepatocytes^[16] and improving insulin sensitivity via a possible mechanism of TNF- α reduction,^[9] which makes UDCA a commonly recommended drug in the treatment of NAFLD.^[17] However, the expensive cost and prolonged administration of this drug has raised economic concerns from some scholars.^[18] It has been demonstrated recently that the similar results produced by UDCA can also be achieved by Danning Pian, a cheap and easily obtained Chinese traditional medicine, in the

Author Affiliations: Department of Gastroenterology, Shanghai First People's Hospital, Shanghai Jiaotong University, Shanghai 200080, China (Fan JG)

Corresponding Author: Jian-Gao Fan, MD, Department of Gastroenterology, Shanghai First People's Hospital, Shanghai 200080, China (Tel: 86-21-63240090; Fax: 86-21-63240825; Email: fanjg@citiz.net)

© 2004, Hepatobiliary Pancreat Dis Int. All rights reserved.

prevention and treatment of chronic cholecystitis.^[19] We presume that Danning Pian comparable to UDCA would be effective in the treatment of NAFLD. The present clinical trial was therefore designed to verify this hypothesis with the efforts in searching a more preferable drug harboring better cost-effectiveness for the treatment of patients with NAFLD.

Methods

Patients and contributing centers

Two-hundred and thirty-two patients with non-alcoholic fatty liver disease were invited to participate in this clinical trial starting from July 1999 to February 2000 at 10 gastrointestinal centers of Shanghai hospitals including Shanghai First People's Hospital, Zhongshan Hospital, Ruijin Hospital, Changzheng Hospital, Shanghai Sixth Municipal Hospital, Shanghai Ninth Municipal Hospital, Putuo District Central Hospital, Changning District Central Hospital, Zhabei District Central Hospital and Wusong Central Hospital. The patients were composed of 189 men and 43 women, with the mean age of 46.1 ± 8.7 years. Before the trial, informed consent was obtained from each patient and the study protocol was approved by the hospital research ethics committees.

Inclusion criteria

All the patients enrolled in the study should meet the diagnostic criteria for NAFLD issued at the Nanking Meeting October 2002 by Fatty Liver and Alcoholic Liver Disease Study Group of the Chinese Society for Liver Diseases.^[20] The criteria mainly include: 1. chronic hepatic steatosis confirmed by CT and/or B ultrasonography at least twice; 2. presentation at least two of the following manifestations: a) apparent clinical symptoms of liver injury, (b) elevated serum level of alanine aminotransferase (ALT), (c) abnormal plasma lipid (triglyceride >1.9 mmol/L and/or cholesterol >5.2 mmol/L); 3. underlying disease including overweight (body mass index >24 kg/m²) and/or central obesity (waistline for male >90 cm and for female >80 cm); 4. exclusion of alcoholic liver disease (alcohol consumption <40 g per week), drug-induced liver injury and viral hepatitis B and C.

Exclusion criteria

Patients were excluded if they fulfilled any of the following criteria: (1) fecal frequency usually for more than twice daily or presence of a large amount of shapeless stool; (2) treatment data incomplete; (3) treatment with schisandra-like hepatic enzyme-lowering medicine, antihyperlipidemia agents, ursodesoxycholic acids, Hepadif and so on for more than 1 week.

Study design

After enrollment, the patients were treated with 5 tablets of Danning Pian (Shanghai First Traditional Chinese Pharmaceutical Factory, Shanghai Hutchison Pharmaceuticals) orally thrice daily for three months on the basis of healthy lifestyle, balanced diet and physical exercise. The dose was changed to 3 tablets orally thrice daily or 5 tablets orally twice daily if the patient suffered from diarrhea in the course of treatment. Some of the patients were also given orally Yiganling Pian (77 mg, tid), compound vitamin B (2 Tab, tid), vitamin E (20 mg, tid) or others. The efficacy and safety of Danning Pian were evaluated with the corresponding parameters before and 1, 2, 3 months after the drug treatment respectively.

The patient's general conditions including asthenia, anorexia, nausea, abdominal distention, hepatalgia and constipation were recorded and graded as 0-3 scores for each item according to the absence or severity of the symptoms. Meanwhile, body height, weight, and waistline of the patient were also measured.

Fasting blood was collected from the peripheral vein at the observational timepoints and prepared routinely as serum for the determination of biochemical parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transferase (γ -GT), alkaline phosphatase (ALP), total (TB) and direct bilirubin (DB), bile acid, triglyceride (TG), total cholesterol (TC) and blood sugar, which were all assayed by a multifunction-biochemical autoanalyzer.

The findings of liver ultrasonography performed by designated physicians before and after the treatment were classified into normal, mild, moderate and severe abnormal alterations according to the ultrasonographic characteristics.^[14, 21]

Adverse reactions were evaluated by the criteria of the Chinese Good Clinical Practice (GCP).

Assessment of efficacy

The efficacy of Danning Pian was clinically defined as follows:

Prominently effective

1. Obvious improvement of clinical symptoms indicated by a reduction of symptomatic scores for more than 50% after treatment; 2. normalization of elevated serum levels of ALT, TG and/or TC return or a reduction of more than 50% after treatment; 3. fatty liver resolving to a normal appearance or a reduction of severity by two grades after treatment under ultrasonography.

Effective

1. Alleviated clinical symptoms manifested by a reduction of symptomatic scores between 20%-50% after treatment; 2. elevated serum levels of ALT, TG and/or TC reduced by 20%-50% after treatment; 3. reduced severity of fatty liver by one grade after treatment under

ultrasonography.

Ineffective

Clinical symptoms, liver test results, blood-lipid parameters, and ultrasonic findings after treatment were not improved or even aggravated.

The following equation was used to calculate the effective rate of the drug: effective rate = [prominently effective cases + effective cases] / total cases × 100%

Statistical analysis

The obtained data were subjected to statistical analysis with EXCEL. Single factor analysis was performed by Student's *t* test for paired data. Statistical significance was defined as a *P* value less than 0.05.

Results

Effects of Danning Pian on the clinical symptoms

Asymptomatic fatty liver was observed in 35 patients with NAFLD, 15% of the total 232 patients investigated. In contrast, various degrees of symptoms such as asthenia, anorexia, nausea, abdominal distention, hepatalgia and constipation were found in the other 197 patients. These symptoms were alleviated or controlled in most of the patients after a 3-month treatment. Prominently effective, effective and ineffective results were observed in 44 patients (22.3%), 125 (63.5%) and 28 (14.2%), respectively with an effective rate of 85.8% (169/197). Constipation was obviously improved after the treatment in 57 patients, but 4, with an ameliorative rate of 92.9%.

Improvement of serum ALT alterations

The levels of serum ALT that were within a normal range and that were elevated but no more than 2 times the upper limit of the normal were observed in 62 and 170 patients respectively before the Danning Pian treatment. After 3-month therapy, this parameter has been significantly improved in patients with an abnormal ALT level before the Danning Pian intervention (62.00 ± 27.41 vs 31.58 ± 15.83 IU/L, $P < 0.001$). The prominently effective, effective and ineffective results were observed in 10 patients (5.8%), 123 (72.4%) and 37 (21.8%) respectively, with an effective rate of 78.2% (133/170). One or more abnormal parameters of AST, GGT, AKP and bile acid in some patients before the treatment were also improved to some extent at the end of the therapy.

Changes of abnormal blood lipid

Serum levels of TG and TC were normal in 97 patients (41.8%) before the Danning Pian therapy. One of the other 135 patients with elevated levels of serum TG and/or TC elevation before the treatment was ex-

cluded from the study because of moderate increase of serum ALT level during the therapy. After 3-month treatment, the prominently effective, effective and ineffective results were noted in 15 patients (11.2%), 38 (28.4%) and 81 (60.4%) respectively among these patients, with an effective rate of 39.6% (53/134). A significant decrease in serum TG levels after the Danning Pian treatment was observed in the 105 patients with elevated serum TG level before the treatment (2.51 ± 0.80 vs 1.58 ± 0.49 mmol/L, $P < 0.05$). In contrast, the increased serum TC levels were not significantly improved after the Danning Pian therapy.

Amelioration of fatty liver alterations

Pathological changes of fatty liver in some patients were alleviated or disappeared after the 3-month Danning Pian therapy, as observed by ultrasonography. Prominently effective, effective and ineffective results were noted in 7 patients (3.3%), 72 (31.0%) and 153 (66.0%) respectively with an effective rate of 34.0% (79/232). The amelioration of fatty liver evidenced by ultrasonography was usually accompanied with the improved parameters of body weight, liver enzyme and blood lipid.

Changes of other parameters

Reduced body weight and waistline was only found in some of the patients treated with Danning Pian for 3 months. In all the investigated patients, however, no significant reduction of body weight and waistline was noted at the beginning and the end of the study, nor were significant changes of fasting blood sugar. Besides, there was no recurrence of cholecystagia and biliary tract infection in patients with biliary tract diseases during the treatment.

Adverse reaction

Thirty-five adverse reactions (15.1%) took place in the 232 patients treated with Danning Pian of Twenty-nine of those reactions manifested with a diarrhea frequency for more than 2 times each day and/or a large amount of watery diarrhea, which could be alleviated by reduced doses. Moreover there were 1 patient with skin rash, 3 with nausea and 2 with elevated ALT level. In the latter 2 patients after treatment for 2 months, one was excluded from the study because of the moderate increase of ALT level.

Discussion

Although the natural history of NAFLD and its subtype forms remains unknown, increasing evidence accumulated in the last few years has indicated that NAFLD is not merely a benign condition but the one with a progressive course towards the end-stage liver disease at least in a

subset of patients. NAFLD is also the most common and often an unrecognized cause of cryptogenic cirrhosis.^[22] Some patients with cirrhotic stage NAFLD may have an accelerated progression towards liver failure and liver cancer, with a similar rate as seen in hepatitis C cirrhosis.^[23,24] Given the facts that obesity, type 2 diabetes mellitus (non-insulin dependent), and hypertriglyceridaemia being the major associated conditions or predisposing factors leading to the development of NAFLD,^[25-34] and the facts that current increasing prevalence of these co-morbidities in the general population, NAFLD seems to be the most prevalent liver disease in the world population, especially in the developed countries.^[35,36]

Nevertheless, there is no specific pharmacologic treatment for NAFLD or its aggressive form—non alcoholic steatohepatitis (NASH). Treatment of patients with NAFLD has typically been focused on the management of associated conditions such as obesity, diabetes mellitus and hyperlipidaemia. NASH associated with obesity may resolve with weight reduction, although the benefits of weight loss have been inconsistent. Appropriate control of glucose and lipid levels is always recommended, but is not always effective in reversing liver condition.^[14] Certain therapeutic modalities such as the long-term use of UDCA that has shown to be of potential benefit for patients with NAFLD are not suitably used in the developing countries because of expensive costs. Therefore, seeking for a more preferable drug harboring better cost-effectiveness for the treatment of patients with NAFLD is urgently necessitated.

Danning Pian is a Chinese patent medicine composed chiefly of rhubarb, giant knotweed, dried green orange peel and dried old orange peel. Clinically this medication has been proved effective in relieving inflammation and promoting bile secretion and litholysis. It is commonly used to treat patients with chronic cholecystitis and cholelithiasis of liver qi stasis type with the similar curative effects of UDCA. Besides, it is also effective in prevention and treatment of certain types of chronic liver disease.^[19] All these suggest that Danning Pian is a suitable candidate for the treatment of NAFLD instead of UDCA.

The present study demonstrated that Danning Pian could effectively ameliorate the clinical symptoms of patients with NAFLD, constipation in particular, on the basis of modifying unhealthy lifestyle. The co-existing chronic cholecystitis and cholelithiasis in these patients were also cured and prevented. The effective rate of Danning Pian for the improvement of elevated serum ALT levels reached as high as 78.2% and the levels of blood lipids, mainly TG, in some patients were significantly decreased after the 3-month therapy. More than one third of the NAFLD patients showed an amelioration of fatty liver alteration at the end of the trial by type B ultrasonography that was employed by a majority of clinical trials to evaluate the therapeutic results.^[20,21]

This finding suggests that Danning Pian is effective in the treatment of patients with NAFLD on the cornerstone of unhealthy lifestyle modification, balanced diet and physical exercise. The therapeutic effects of Danning Pian can be explained by the theory of traditional Chinese medicine as dispersing the liver qi by promoting bile secretion and egestion, resolving heat by catharsis, and lowering blood lipid via discharging diachorema and turbidurine. Scientific research has demonstrated that Danning Pian can relieve inflammation, promote bile egestion and litholysis, resist hepatosteatosis, and scavenge free radicals,^[19] which are protective from fat accumulation in the liver. In a recent animal study, we have found that steatohepatitis with obesity and hyperlipidemia induced by high fat diet in rats was ameliorated to some extent after treatment with Danning Pian (data to be published).

Severe adverse reactions of Danning Pian have not yet been found in clinical practice since its use in the prevention and treatment of biliary tract diseases for more than 10 years.^[19] In the present study, adverse events were noted in 15.1% of the patients, and mostly manifested with a diarrhea frequency for more than 2 times each day and/or a large amount of watery diarrhea, which were mild to or well-tolerated by the majority of patients. The abnormal elevation of liver enzyme in 2 patients during the treatment may be attributable to the non-medicamentous liver lesion induced by other factors.

Although the effects of non-pharmacological measures such as dietary restriction and physical exercise^[37] and the synergistic effects of other lipid-lowering and hepatoprotective medications co-administered in some of the patients on the NAFLD therapy can not be excluded in the present study, we conclude that clinical symptoms, serum parameters and fatty liver alterations in patients with NAFLD can be improved to some extent after the Danning Pian therapy on the basis of the results of this clinical trial. It is therefore recommended that Danning Pian can serve as an important adjuvant for the therapy of NAFLD patients, especially for those associated with biliary tract diseases and constipation. Too short a time period of observation, not a double-blind, placebo-controlled and randomized trial, lack of hepatopathological data to verify the included cases and the therapeutic results are the limitations of the present study. Further studies to assess the efficacy and safety of long-term Danning Pian therapy for patients with NAFLD by prospective, double-blind, placebo-controlled, parallel group, randomized and multicenter clinical trials would be justified.

Acknowledgements

We are grateful to the following physicians who were members of the Shanghai Multicenter Clinical Cooperative Group of Danning

Pian trial; Hou-Yu Liu, MD, Department of Gastroenterology, Zhongshang Hospital; Yao-Zong Yuan, MD, Department of Gastroenterology, Ruijin Hospital; Xiong Cai, MD, Department of Gastroenterology, Changzheng Hospital; Wei-Xiong Chen, MD, Department of Gastroenterology, Sixth Shanghai Municipal Hospital; Hai-Lin Liu, MD, Department of Gastroenterology, Ninth Shanghai Municipal Hospital; Jun-Rong Wang, MD, Department of Gastroenterology, Putuo District Central Hospital; Xiang-Jun Meng, MD, Department of Gastroenterology, Changning District Central Hospital (who works at Xinhua Hospital now); Nai-Yun Bai, MD, Department of Gastroenterology, Zhabei District Central Hospital; and Zhen-Ping Xu, MD, Department of Gastroenterology, Wusong Central Hospital.

Competing interest

The author or one or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.

References

- 1 Tagle Arrospe M. Non-alcoholic fatty liver. *Rev Gastroenterol Peru* 2003;23:49-57.
- 2 Alba LM, Lindor K. Non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2003;17:977-986.
- 3 Angulo P, Lindor KD. Non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2002;17:S186-S190.
- 4 Gronbaek H, Eivindson MV, Hamilton-Dutoit S, Vilstrup H. Nonalcoholic steatohepatitis—a "new" hepatic disease. *Ugeskr Laeger* 2003;165:1115-1118.
- 5 Mulhall BP, Ong JP, Younossi ZM. Non-alcoholic fatty liver disease: an overview. *J Gastroenterol Hepatol* 2002;17:1136-1143.
- 6 Alvarez-Martinez H, Perez-Campos E. Non-alcoholic steatohepatitis. *Rev Gastroenterol Mex* 2002;67:118-125.
- 7 Linhart HG. Non-alcoholic steatohepatitis. *Schweiz Rundsch Med Prax* 2000;89:963-966.
- 8 de Knecht RJ. Non-alcoholic steatohepatitis: clinical significance and pathogenesis. *Scand J Gastroenterol Suppl* 2001;234:88-92.
- 9 Angulo P. Current best treatment for non-alcoholic fatty liver disease. *Expert Opin Pharmacother* 2003;4:611-623.
- 10 Hookman P, Barkin JS. Current biochemical studies of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) suggest a new therapeutic approach. *Am J Gastroenterol* 2003;98:495-499.
- 11 Sanyal AJ. Treatment of non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2002;17:385-388.
- 12 Oneta CM, Dufour JF. Non-alcoholic fatty liver disease: treatment options based on pathogenic considerations. *Swiss Med Wkly* 2002;132:493-505.
- 13 Angulo P, Lindor KD. Treatment of non-alcoholic steatohepatitis. *Best Pract Res Clin Gastroenterol* 2002;16:797-810.
- 14 Angulo P, Lindor KD. Treatment of nonalcoholic fatty liver: present and emerging therapies. *Semin Liver Dis* 2001;21:81-88.
- 15 Angulo P. Use of ursodeoxycholic acid in patients with liver disease. *Curr Gastroenterol Rep* 2002;4:37-44.
- 16 Kobak GE, Deutsch G, Dahl R, Devereaux MW, Gumprich E, Sokol RJ. Fat-laden hepatocytes are more prone to cellular necrosis than apoptosis when exposed to hydrophobic bile acids. *Gastroenterology Suppl* 2002;122:642.
- 17 Laurin J, Lindor KD, Crippin JS, Gossard A, Gores GJ, Ludwig J, et al. Ursodeoxycholic acid or clofibrate in the treatment of non-alcohol-induced steatohepatitis: a pilot study. *Hepatology* 1996;23:1464-1467.
- 18 Pasha T, Heathcote J, Gabriel S, Cauch-Dudek K, Jorgensen R, Therneau T, et al. Cost-effectiveness of ursodeoxycholic acid therapy in primary biliary cirrhosis. *Hepatology* 1999;29:21-26.
- 19 Zhu PT, Zhang JZ, Wang YS, Gao J. Treatment of chronic biliary tract infection and gallstone diseases with Dan Ning Tab, Hitrechol and UDCA (A comparative clinical trial). *Zhongguo Zhongxiyi Jiehe Waike Zazhi* 1995;4:205-209.
- 20 Fatty Liver and Alcoholic Liver Disease Study Group of Chinese Liver Disease Association. Diagnostic criteria of nonalcoholic fatty liver disease. *Zhonghua Ganzangbing Zazhi* 2003;11:71.
- 21 Shen L, Fan JG, Shao Y, Zeng MD, Wang JR, Luo GH, et al. Prevalence of nonalcoholic fatty liver among administrative officers in Shanghai: an epidemiological survey. *World J Gastroenterol* 2003;9:1106-1110.
- 22 Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 1999;29:664-669.
- 23 Ratziu V, Bonyhay L, Di Martino V, Charlotte F, Cavallaro L, Sayegh-Tainturier MH, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. *Hepatology* 2002;35:1485-1493.
- 24 Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002;123:134-140.
- 25 Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 2001;121:91-100.
- 26 Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999;30:1356-1362.
- 27 Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002;346:1221-1231.
- 28 Angulo P, Lindor KD. Insulin resistance and mitochondrial abnormalities in NASH: a cool look into a burning issue. *Gastroenterology* 2001;120:1281-1285.
- 29 Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, et al. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001;120:1183-1192.
- 30 Cotrim HP, Parana R, Braga E, Lyra L. Nonalcoholic steatohepatitis and hepatocellular carcinoma: natural history? *Am J Gastroenterol* 2000;95:3018-3019.
- 31 Teli MR, James OF, Burt AD, Bennett MK, Day CP. The natural history of nonalcoholic fatty liver: a follow-up study. *Hepatology* 1995;22:1714-1719.
- 32 Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999;116:1413-1419.
- 33 Ratziu V, Bonyhay L, Di Martino V, Charlotte F, Cavallaro L, Sayegh-Tainturier MH, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. *Hepatology* 2002;35:1485-1493.

- 34 Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, et al. Liver fibrosis in overweight patients. *Gastroenterology* 2000;118:1117-1123.
- 35 Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003;37:1202-1219.
- 36 James O, Day C. Non-alcoholic steatohepatitis: another disease of affluence. *Lancet* 1999;353:1634-1636.
- 37 Fan JG, Zhong L, Wang GL, Tian L, Wu W, Li M. Influence of ursodeoxycholic acid on the therapeutic effects of low-calorie diet in obesity and hyperlipidemia rats with steatohepatitis. *Zhonghua Ganzangbing Zazhi* 2002;10:43-45.

Received March 6, 2004

Accepted after revision May 30, 2004

You don't expect me to know what to say about a play when I don't know who the author is, do you? If it's by a good author, it's a good play, naturally. That stands to reason.

— George Bernard Shaw