Primary sclerosing cholangitis

A Stiehl MD, C Benz MD, P Sauer MD

A Stiehl, C Benz, P Sauer. Primary sclerosing cholangitis. Can J Gastroenterol 2000;14(4):311-315. Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammation and obliteration of intra- and/or extrahepatic bile ducts. The disease is one of the most common cholestatic diseases in adults and is diagnosed with increasing frequency. It is very often associated with ulcerative colitis. Patients with PSC have an increased incidence of bile duct carcinomas, and those with ulcerative colitis also have an increased incidence of colonic carcinomas.

In end-stage disease, liver transplantation is the treatment of choice. Immunosuppressive treatment has little effect. Ursodeoxycholic acid (UDCA), which has been shown to improve liver histology and survival in patients with primary biliary cirrhosis, has a beneficial effect in PSC, provided that patients who develop major duct stenoses are treated endoscopically. The aim is to treat patients as early as possible to prevent progression to the advanced stages of the disease. During treatment with UDCA, stenoses of major ducts may develop, and early endoscopic dilation is highly effective. Because UDCA treatment improves but does not cure cholestatic liver diseases, permanent treatment seems to be necessary. Such prolonged treatment with UDCA may be recommended because, until now, no side effects have been reported. In patients with end-stage disease, UDCA is not effective and liver transplantation is indicated.

Key Words: *Cholestatic liver disease; Primary sclerosing cholangitis; Ursodeoxycholic acid*

Cholangite sclérosante primitive

RÉSUMÉ : La cholangite sclérosante primitive (CSP) est une maladie cholestatique chronique du foie, qui se caractérise par une inflammation fibrosante et l'obstructions des voies biliaires intra- et/ou extrahépatiques. Il s'agit de l'une des maladies cholestatiques les plus courantes chez les adultes, et sa fréquence ne cesse de croître. Elle est très souvent associée à la rectocolite hémorragique. Les patients atteints de CSP ont une incidence accrue du cancer des voies biliaires, et ceux souffrant de rectocolite hémorragique, du cancer du côlon.

Le traitement à privilégier dans les cas de maladie terminale est la transplantation du foie. Le traitement immunosuppresseur ne produit guère d'effets. L'acide ursodésoxycholique (AUDC), qui a déjà montré sa capacité d'améliorer l'histologie du foie et la survie des patients atteints de cirrhose biliaire primitive, s'avère salutaire chez les patients souffrant de CSP, pourvu que les sténoses importantes des voies biliaires soient traitées par endoscopie. Le but est de traiter les patients le plus tôt possible pour prévenir l'évolution de la maladie vers des stades avancés. Toutefois, le traitement à l'AUDC peut entraîner une sténose des principales voies biliaires, mais leur dilatation par endoscopie s'avère une intervention très efficace. Comme le traitement à l'AUDC soulage mais ne guérit pas les maladies cholestatiques du foie, il semble que les patients doivent le suivre indéfiniment. Il peut être prescrit à long terme parce que, jusqu'à maintenant, aucun effet secondaire n'a été signalé. Par contre, l'AUDC est sans effet chez les patients rendus au stade terminal de la maladie, et la transplantation du foie est indiquée.

Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease characterized by progressive fibrosis and obstruction of bile ducts leading to increasing cholestasis and finally to cirrhosis (1-9). In early stages, the patients have elevated levels of serum alkaline phosphatase (AP) and gamma glutamyl transpeptidase (GGT), and serum bilirubin and serum cholesterol levels increase only in later stages. In early stages, the patients may be free of symptoms, and jaundice, pruritus and fatigue appear with progressive disease.

The serum marker perinuclear antineutrophil cytoplasmic antibody has been detected in up to 85% of patients with PSC, but the marker is not specific for the disease and may be positive in patients with ulcerative colitis without PSC (10). The frequency of human leukocyte antigens (HLA) -B8 and -DR3 is higher in PSC patients than in controls (60% to 80% versus 20% to 30% in controls). HLA-B8 and HLA-DR3 are found in various autoimmune diseases, and their presence is suggestive of immunological factors involved in

This mini-review was prepared from a presentation made at the World Congress of Gastroenterology, Vienna, Austria, September 6 to 11, 1998
Department of Medicine, University of Heidelberg, Heidelberg, Germany
Correspondence and reprints: Prof Dr A Stiehl, Medizinische Universitätsklinik, Bergheimerstr 58, D-69115 Heidelberg, Germany. Telephone +06221-568707, fax +06221-56587, e-mail adolf_stiehl@med.uni-heidelberg.de
Received for publication March 22, 1999. Accepted March 23, 1999

PSC. There is no reliable serum marker with sufficient sensitivity and specificity to allow the early diagnosis of PSC.

The disease in general is diagnosed by endoscopic retrograde cholangiography, which shows multiple intra- and/or extrahepatic stenoses with prestenotic dilations that give the biliary system its typical appearance (1-9). In some patients, major prestenotic cavities of the bile ducts may develop. Due to the multiple stenoses and prestenotic dilations of the biliary tree, patients tend to have repeated episodes of bacterial cholangitis. Because PSC is a focal disease, the typical fibrosing inflammation around the bile ducts may be missed in a single liver biopsy. Accordingly, liver biopsy allows the histological staging but is of limited value in the detection of the disease.

The prevalence of PSC has been estimated to be five to 10 per 100,000. Approximately 70% to 90% of patients with PSC have inflammatory bowel disease, and 5% to 10% of patients with ulcerative colitis have PSC (11). Of 1500 Swedish patients with ulcerative colitis, 72 had an elevated AP level, and of those, 85% had PSC (12). In this study, the prevalence of PSC in patients with colitis was 5.5 %, and the prevalence of colitis in PSC patients was 90%. As a consequence, an endoscopic retrograde cholangiopancreatography should be performed in all patients with inflammatory bowel disease with an elevated serum AP level; this will allow the majority of patients with PSC to be detected.

BILE DUCT CARCINOMA

An unresolved problem in the treatment of patients with PSC is the development of bile duct carcinomas (3-9). Until now, it has been very difficult to detect cholangiocarcinomas at an early stage. Brush border cytology of dominant strictures is of limited sensitivity (13). The tumour markers carcinoembryonic antigen and carbohydrate antigen 19-9 are neither sensitive nor specific (14). Imaging methods (computed tomography, nuclear magnetic resonance) do not allow the detection of early carcinomas, and the results with positron emission tomography (15) need confirmation in larger trials. When the carcinoma has developed, the prognosis in general is very poor.

In a large multicentre study from Sweden in which 305 PSC patients were followed for a median of 63 months, a bile duct carcinoma was observed in 8% of patients; 44% of these patients were asymptomatic at the time of diagnosis of PSC (12). In 37% of the patients, bile duct carcinoma was diagnosed within one year after detection of PSC; therefore, it seems possible that the patients already had the bile duct carcinoma when the PSC was recognized. This study is the largest series available, and no factors were found that would allow the identification of patients who would later develop a bile duct carcinoma.

The 8% rate of carcinomas in the Swedish multicentre study is similar to the figure reported by several centres (3-9) and is much lower than that observed by others (7,8). Of interest, in the Swedish study, only 8% of patients developed a cholangiocarcinoma, and 30% of patients with end-stage disease who were considered for transplantation had bile duct carcinomas (12). These data explain why the incidences of bile duct carcinoma from transplantation centres are always much higher than the corresponding figures from prospective studies from gastroenterology units. Very high rates of bile duct carcinomas have repeatedly been reported in studies from transplantation centres (16); it appears that they reflect very selected patient groups.

COLONIC CARCINOMA

Colorectal carcinoma occurs more frequently in patients with chronic inflammatory bowel disease than in the normal population. Risk factors are involvement of the whole colon and long duration of the disease. PSC has been shown to be an independent risk factor for the development of colonic carcinoma (17). In a study in which 40 patients with PSC and colitis were matched with 40 patients with the same age, comparable colitis and comparable duration of the disease, the absolute cumulative risk of developing colorectal dysplasia or carcinoma in the patients with PSC was almost five times higher than that in the patients without PSC. The study indicates also that patients with PSC and colitis who develop colonic dysplasia or carcinoma are at a high risk of developing cholangiocarcinoma. It is evident that patients with PSC and colitis need colonoscopic surveillance at short intervals.

SURVIVAL

The median length of survival from diagnosis ranges from nine to 12 years (3-9). The survival in asymptomatic patients is longer than that of symptomatic patients (6). At the time of diagnosis, many patients are asymptomatic and later develop fatigue, pruritus and jaundice. There is no correlation between the severity of PSC and that of ulcerative colitis.

Several survival models have been used to predict the outcome in PSC. In a survival model based on data of five referral centres, age, serum bilirubin and hemoglobin levels, hepatic histological stage and splenomegaly adversely affected survival (18). The aim of such survival models, which were evaluated retrospectively, was to predict the optimal time of liver transplantation. For practical purposes, however, the value of these survival models seems of only limited value because of the great variability of the disease in the individual patient.

TREATMENT

Treatment of PSC patients with immunosuppressive, anti-inflammatory or antifibrotic agents has not been successful. Reports on a beneficial effect of methotrexate need confirmation in controlled trials (19). Because repeated episodes of bacterial cholangitis are typical for the disease, immunosuppressive treatment may even be harmful.

The major breakthrough came with the observation that ursodeoxycholic acid (UDCA) has a beneficial effect in patients with primary biliary cirrhosis (PBC) (20-26). Subsequently, patients with various forms of cholestatic liver diseases, including PSC, have been treated with UDCA

TABLE 1
Development of cholangiocarcinomas (CA) in patients with primary sclerosing cholangitis

Author, reference (year)	Follow-up (years)	CA (%)
Aadland et al, 3 (1987) (n=38)	4.7 (mean)	10
Helzberg et al, 4 (1987) (n=42)	4.7 (mean)	5
Lebovics et al, 5 (1987 (n=38)	4.7 (mean)	0
Herrmann et al, 6 (1988) (n=70)	8.3 (mean)	4
Wiesner et al, 7 (1989) (n=174)	6 (mean)	19
Farrant et al, 9 (1991) (n=126)	5.8 (median)	6
Broome et al, 12 (1996) (n=305)	5.2 (median)	8
Stiehl et al, 34 (1997) (n=65)	4.3 (median)	3*

**Patients treated with ursodeoxycholic acid*

(27-30). That stenoses of the major bile ducts cannot be treated with UDCA and need endoscopic treatment presents a problem.

EFFECT OF UDCA ON LABORATORY PARAMETERS

Stimulated by the report of a beneficial effect of UDCA in primary biliary cirrhosis (PBC), in 1987 we started a trial in patients with PSC (27). A double-blind, placebo controlled study was initiated after one year of treatment with UDCA, which demonstrated beneficial effects similar to those seen in patients with PBC and was well tolerated in patients with additional ulcerative colitis. UDCA led to significant improvement of AP, GGT, alanine aminotransferase and aspartate aminotransferase levels. The changes are similar to those seen in three other controlled studies (Table 2) in which serum bilirubin also improved significantly (28-30). Serum cholesterol levels decreased in patients with elevated levels before treatment and were unchanged in the others (27). Changes in immunoglobulin (Ig) A, IgM, and IgG were not significant. Following UDCA, biliary secretion of bile acids, phospholipids and cholesterol increased significantly (31).

In a further controlled study using a relatively low dose of UDCA (600 mg/day), no improvement of laboratory parameters was observed (32), indicating that such a low dose is ineffective. Moreover, a recent placebo controlled study from the United Kingdom showed that UDCA doses of 20 mg/kg significantly improved liver histology, whereas in the same centre, a dose 10 mg/kg, which had been used previously, was ineffective. Cholestasis leads to the decreased absorption of UDCA (33), which may account for the fact that high doses of UDCA are needed for the treatment of PSC. The minimal dose of UDCA that should be recommended in PSC is 15 mg /kg; 20 mg/kg may be even more effective.

EFFECT OF UDCA ON SYMPTOMS

Patients with PSC in part suffer from pruritus and fatigue (1-9). During treatment with UDCA, both symptoms improved in some patients, but the effect was not significant compared with placebo (27).

TABLE 2
Ursodeoxycholic acid (UDCA) in primary sclerosing cholangitis: Results of placebo controlled studies with UDCA doses greater than 10 mg/kg

Author, reference (year)	AP, GGT, ALT or AST	Bilirubin	Histology
Stiehl et al, 27 (1994) (n=20)	Improved	Unchanged	Favourable*
Beuers et al, 28 (1992) (n=14)	Improved	Improved	Favourable
Lindor, 29 (1997) (n=105)	Improved	Improved	Unchanged
Mitchell et al, 30 (1997) (n=24)	Improved	Improved	Favourable

**Favourable effect compared with pretreatment histology. AP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; GGT gamma glutamyl transpeptidase*

TABLE 3
Endoscopic treatment of patients with primary sclerosing cholangitis with dominant stenoses of major bile ducts

Author, reference (year)	Stent	Dilation
Johnson et al, 36 (1987) (n=35)	11	24
Lee et al, 41 (1995) (n=53)	22	31
van Milligen et al, 41 (1996) (n=25)	21	0
Stiehl et al, 34 (1997) (n=23)	5	91

EFFECT OF UDCA ON LIVER HISTOLOGY

In three of four studies in which changes in liver histology were evaluated after UDCA treatment, cellular infiltrates in the portal triads decreased significantly, whereas all other changes were not significant (27,28,30). In one study, no effect of UDCA treatment on liver histology was observed (29). UDCA most efficiently improved liver histology in a very recent study in which a very high dose of UDCA (20 mg/kg) was administered. It is unclear whether a decrease of the inflammation around the bile ducts in PSC affects the development of bile duct carcinomas in this disease. In the placebo group of one controlled study, three of 53 patients developed a bile duct carcinoma, and in the group treated with UDCA, none of 52 patients developed bile duct carcinoma (29). The tendency in this study in which the patients were treated for two to five years is of interest. Longer lasting trials are necessary to answer the question of whether UDCA can reduce the incidence of cholangiocarcinomas definitely.

STENOSES OF MAJOR BILE DUCTS DURING UDCA

In a prospective trial on the effect of UDCA on bile duct disease in which repeat cholangiographies were performed (34) during treatment with UDCA, 10 of 65 patients treated for up to eight years (mean 45 months) developed progressive stenosis of major bile ducts. Endoscopic dilation of these stenosis is highly effective (Table 3) (34-42). Repeat cholangiography in patients with narrowing of major bile ducts

seems essential to detect stenoses of major bile ducts early (34). It is evident that mechanical obstruction of major bile ducts cannot be treated by UDCA effectively and that endoscopic measures are essential if conservative treatment is to be effective.

EFFECT OF UDCA ON SURVIVAL

In a controlled two-year study (29) in which endoscopic treatment of major duct stenoses did not play a role, UDCA treatment did not improve survival without liver transplantation. This is in contrast to findings of a prospective, nonrandomized study, in which 65 patients were treated with UDCA and whenever necessary by additional endoscopic dilations from May 1987 to December 1995 (34). The actuarial Kaplan Meier estimate of survival after treatment with UDCA and dilation of major duct stenoses improved significantly compared with the predicted survival (P=0.001) (34).

Liver transplantation significantly improves survival compared with the predicted survival. According to the European Transplant Registry of 1995, of 675 patients who underwent transplantations for end-stage PSC, 72% were alive after five years. In centres where early transplantation is recommended, the survival rate in patients with PSC and colitis has been reported to be approximately 80% after five years and 70% after eight years (43). In view of the fact that the incidence of bile duct carcinomas is much lower than the lethality after transplantation, we do not think that it is justified to recommend prophylactic liver transplantation in precirrhotic stages of the disease to prevent the development of bile duct carcinomas. In a study that is currently being conducted at our institution, all patients with stages 1 to 2 liver disease treated with UDCA and, whenever necessary, by endoscopic means are alive at 12 years without liver transplantation. Therefore, it seems very questionable whether the recommendation of early transplantation is justified.

CONCLUSIONS

PSC may be treated conservatively by UDCA with good treatment results and prolongation of survival without liver transplantation only when patients who develop major duct stenoses are recognized early and are additionally treated by endoscopic means. Liver transplantation is indicated for end-stage disease.

REFERENCES

1. Chapman RW, Arborgh BA, Rhodes JM, et al. Primary sclerosing cholangitis – a review of its clinical features, cholangiography and hepatic histology. Gut 1980;21:870-7.
2. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. Gastroenterology 1980;79:200-6.
3. Aadland E, Schrumpf E, Fausa O, et al. Primary sclerosing cholangitis: long-term follow up study. Scand J Gastroenterol 1987;22:655-64.
4. Helzberg JH, Petersen JM, Boyer JL. Improved survival with primary sclerosing cholangitis: a review of clinicopathologic features and comparison of symptomatic and asymptomatic patients. Gastroenterology 1987;92:1869-75.
5. Lebovics E, Palmer M, Woo J, et al. Outcome of primary sclerosing cholangitis. Arch Intern Med 1987;147:729-31.
6. Herrmann R, Dooley J, Sherlock S, McIntyre N. Progression of asymptomatic primary sclerosing cholangitis. J Hepatol 1988;7:S39. (Abst)
7. Wiesner RH, Grambsch PM, Dickson ER, et al. Natural history, prognostic factors, and survival analysis. Hepatology 1989;10:430-6.
8. Lindor KD, Wiesner RH, MacCarthy RL, et al. Advances in primary sclerosing cholangitis. Am J Med 1990;89:73-80.
9. Farrant MJ, Hayllar KM, Wilkinson ML, et al. Natural history and prognostic variables in primary sclerosing cholangitis. Gastroenterology 1991;100:1710-7.
10. Bansi DS, Fleming KA, Chapman RW. Importance of antineutrophil cytoplasmatic antibodies in primary sclerosing cholangitis and ulcerative colitis: prevalence, titre, and IgG classes. Gut 1996;38:384-9.
11. Olsson R, Danielsson A, Järnebrot G, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. Gastroenterology 1991;100:1319-23.
12. Broome U, Olson R, Lööf L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996;38:610-5.
13. Ponsionen CIJ, Vrouenraets SME, van Milligen AWM, et al. Value of brush border cytology for dominant strictures in primary sclerosing cholangitis. Endoscopy 1999;31:305-9.
14. Hultcrantz R, Olsson R, Danielsson A, et al. A three year prospective study on serum tumor markers used for detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. J Hepatol 1999;30:669-73.
15. Keiding S, Rasmussen HH, Gee A, et al. Detection of cholangiocarcinoma in primary sclerosing cholangitis by positron emission tomography. Hepatology 1998;28:700-6.
16. Nashan B, Schlitt HJ, Tusch G, et al. Biliary malignancies in primary sclerosing cholangitis: timing of liver transplantation. Hepatology 1996;23:1105-11.
17. Broome U, Löfberg R, Veress B, Erikson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. Hepatology 1995;22:1404-8.
18. Dickson ER, Murtauch PA, Wiesner RH, et al. Primary sclerosing cholangitis: refinement and validation of survival models. Gastroenterology 1992;103:1893-901.
19. Kaplan MM, Arora S, Pincus SH. Primary sclerosing cholangitis and low-dose oral pulse methotrexate therapy. Clinical and histologic response. Ann Intern Med 1987;106:231-5.
20. Leuschner U, Fischer H, Kurtz W, et al. Ursodeoxycholic acid in primary biliary cirrhosis: results of a controlled double-blind trial. Gastroenterology 1989:97:1268-74.
21. Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter controlled trial of ursodiol for the treatment of primary biliary cirrhosis. N Engl J Med 1991;324:1548-54.
22. Lindor KDL, Dickson ER, Baldus WP, et al. Ursodeoxycholic acid in the treatment of patients with primary biliary cirrhosis. Gastroenterology 1994;106:1284-94.
23. Heathcote EJL, Cauch-Dudeck K, Walker V, et al. The Canadian multi-center double blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994;19:1149-56.
24. Combes B, Carithers RL, Maddrey WC, et al. A randomized, double-blind, placebo controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1995;22:759-66.
25. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. N Engl J Med 1994;330:1342-7.
26. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997;113:884-90.
27. Stiehl A, Walker S, Stiehl L, et al. Effects of ursodeoxycholic acid on liver and bile duct disease in primary sclerosing cholangitis. A 3 year pilot study with a placebo-controlled study period. J Hepatol 1994;20:57-64.
28. Beuers U, Spengler U, Kruis W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo controlled trial. Hepatology 1992;16:707-14.
29. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. N Engl J Med 1997;336:691-5.

30. Mitchell SA, Bansi D, Hunt N, et al. High dose ursodeoxycholic acid (UDCA) in primary sclerosing cholangitis (PSC): results after two years of a randomized double-blind, placebo-controlled trial. Gut 1997;40(Suppl 1):TH115. (Abst)
31. Stiehl A, Rudolph G, Sauer P, Theilmann L. Biliary secretion of bile acids and lipids in primary sclerosing cholangitis. Influence of cholestasis and effect of ursodeoxycholic acid treatment. J Hepatol 1995;23:283-9.
32. De Maria N, Colantoni A, Rosenblom E, Van Thiel DH. Ursodeoxycholic acid does not improve the clinical course of primary sclerosing cholangitis over a 2-year period. Hepatogastroenterology 1996;43:1472-79.
33. Sauer P, Rudolph G, Klöters-Plachky P, et al. Influence of cholestasis on the absorption of ursodeoxycholic acid. Dig Dis Sci 1999;44:817-22.
34. Stiehl A, Rudolph G, Sauer P, et al. Efficacy of ursodeoxycholic acid and endoscopic dilation of major duct stenoses in primary sclerosing cholangitis. An 8-year prospective study. J Hepatol 1997;26:560-6.
35. Grijm R, Huibregtse K, Bartelsman J, et al. Therapeutic investigations in primary sclerosing cholangitis. Dig Dis Sci 1986;31:792-8.
36. Johnson GK, Geenen JE, Venu RP, Hogan WJ. Endoscopic treatment of biliary duct strictures in sclerosing cholangitis: Follow up assessment of a new therapeutic approach. Gastrointest Endosc 1987;33:9-12.
37. Huitbregtse K. Therapeutic investigations in primary sclerosing cholangitis. In: Huitbregtse K, ed. Endoscopic biliary and pancreatic drainage. Stuttgart: FRG Georg Thieme, 1988:78-85.
38. Cotton PB, Nickl N. Endoscopic and radiologic approaches to therapy in primary sclerosing cholangitis. Semin Liver Dis 1991;11:40-8.
39. Craig PI, Hatfield RW. Endoscopic therapy in primary sclerosing cholangitis. Eur J Gastroentrol Hepatol 1992;4:284-7.
40. Gaing AA, Geders JM, Cohen SA, Siegel JH. Endoscopic management of primary sclerosing cholangitis: review, and report of an open series. Am J Gastroenterol 1993;88:2000-8.
41. Lee JG, Schutz SM, England RE, Leung JW, Cotton PB. Endoscopic therapy of sclerosing cholangitis. Hepatology 1995;21:661-7.
42. van Milligen AWM, van Bracht J, Rauws EAJ, et al. Endoscopic stent therapy for dominant extrahepatic bile duct strictures in primary sclerosing cholangitis. Gastrointest Endosc 1996;44:293-9.
43. Loftus EV, Aguzilar HI, Sandborn WJ, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis following orthotopic liver transplantation. Hepatology 1998;27:685-90.