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Clinical Pattern and Course of Disease in Primary Biliary Cirrhosis Based on an Analysis of 236 Patients

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A prospective study of the clinical pattern and course of primary biliary cirrhosis based on the data of 236 patients (211 females, 25 males) in an international randomized trial has been performed mainly using life-table technique. The median follow-up period has been 18 mo. After the entry into the study, at which time the median duration of symptoms was 2.1 yr, the estimated 5-yr increase in the cumulative percentage of patients was for pruritus from 75% to 95%, jaundice 59% to 82%, hepatomegaly 54% to 86%, pigmentation 54% to 85%, xanthomas 27% to 50%, GI bleeding 17% to 46%, ascites 7% to 49%, and vertebral collapse 3% to 20%. The frequency of cirrhosis increased from 30% to 82% in 4 yr. The mitochondrial antibody titer showed a high rate of progression with time. In analysis of subgroups, age, histologic stage, and particularly the serum bilirubin level were important prognostic factors. Sex, duration of symptoms, and character of first symptom or sign had no independent prognostic influence. The most important indication of seriously progressive course was rapid development of severe cholestasis independent of the histologic stage.

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Primary biliary cirrhosis (PBC) previously considered uncommon is now diagnosed more frequently,[1–3] partly owing to the wider availability of laboratory screening and the finding of asymptomatic cases.[4–6] Nevertheless, few reports on the natural history of PBC are available. Most of those have been retrospective studies based on small samples[2,7–10] and others have dealt with selected groups of patients.[4–6] Although the typical clinical course of an insidious onset and slow progress, ultimately leading to death from hepatic failure, is well known, the variation in natural history between individual patients is considerable and little is known about factors determining prognosis.

Data from a recent multicentric randomized clinical trial of azathioprine[11] has provided a basis for a more detailed prospective study of the clinical pattern and course in 236 patients with PBC. This report presents the clinical, laboratory, and histologic course of the disease, the influence of some prognostic factors, the causes of death, and the sequence of events preceding death from hepatic failure.

Patients and Methods

Patients were admitted to the trial at the time of diagnosis irrespective of the duration of symptoms or signs. Criteria for entry into the trial were a clinical picture and histologic features diagnostic of or compatible with PBC

and a serum alkaline phosphatase activity greater than twice the upper limit of normal. Each patient had detailed assessment at entry and at 6-mo intervals thereafter. This included an estimate of the degree of incapacitation based on the number of days in the previous 100 spent in each of the following categories: normal health (*a*), reduced well-being (*b*), not able to work but out of bed (*c*), at home in bed (*d*), and in bed in hospital (*e*), calculated as the: Incapacitation index = $(0a + 1b + 2c + 3d + 4e)/4$. Results of hepatic tests, immunoglobulins, and autoantibodies were determined at 6-mo intervals, and liver biopsies were performed at yearly intervals. The histologic assessment included classification into one of the four histologic stages: I. "chronic destructive nonsuppurative cholangitis"; II. "portal inflammation with ductular proliferation"; III. "scarring" (fibrosis); and IV. "cirrhosis" as previously defined.[11] By random allocation 124 patients received azathioprine, 1 mg/kg body weight daily, and 112 received placebo. As the effect of azathioprine on any variable was not significantly better than that of placebo,[11] the treatment and placebo groups have been analyzed together in this report.

Discontinuous variables were statistically analyzed using the r × c Chi-square test, and continuous variables using the Mann-Whitney or Kruskal-Wallis nonparametric tests. Since the patients were followed for different periods of time, the course of the disease was mainly studied by the life-table method which allows for incomplete follow-up.[12] Using the time from entry into the trial to the first occurrence of "abnormal" clinical, laboratory, and histologic features, the cumulative percentage of patients in whom these features appeared with time was estimated. The implementation of this method in the analysis of continuous variables demands the definition of a level separating "occurrence" from "no occurrence." Arbitrarily a value corresponding to the "abnormal" (upper or lower) 15th percentile of the distribution at entry was chosen as the limit beyond which a value constitutes an occurrence. This common level permits a comparison of the tendency of different variables to move toward more abnormal values, and a reasonable number of patients are allowed to cross the limit. The occurrence rate of death after entry into the study (the death rate), and clinical, laboratory, and histologic features in patients without these features at entry was compared in subgroups using the log rank test.[12] The relative rate of occurrence of each abnormal feature after entry in two subgroups was expressed as the *occurrence rate ratio* ("relative risk") calculated as $(O_1/E_1)/(O_2/E_2)$, where O_1 and O_2 are the numbers of patients *observed* to develop a particular abnormal feature, and E_1 and E_2 the numbers *expected* to develop that feature in each of the subgroups during the observation period. (For example an occurrence rate ratio of 2:1 means that the feature considered is twice as likely to occur in the one subgroup than in the other during the observation period.) The calculation of E_1 and E_2 utilizes the temporal pattern of the occurrences and assumes that risk of occurrence is the same in the two groups.[12] Whenever important prognostic variables (such as the serum bilirubin) were unevenly distributed in subgroups, comparisons were made after stratification according to such variables. A 1% level of significance has been used in all statistical tests.

Results

Of the 236 patients, 211 were females. The median age was 55 yr (range 24–78), and the median duration of symptoms before entry into the trial was 2.1 yr (range 0–12).

Symptoms and Signs

The first symptom or sign noticed by the patients is shown in Table 1. In 47% it was pruritus, which is probably the most "typical" symptom of PBC. In 19% it was jaundice, GI bleeding, or ascites, each of which indicates fairly advanced liver disease. The latter group had, on the average, a shorter history than the former. In 22% nonspecific symptoms, mainly fatigue and pain in the right upper quadrant of the abdomen, were noted. In 5% symptoms of a possible collagen or autoimmune disorder led to the diagnosis, but 7% had either no symptoms or symptoms unrelated to PBC when the diagnosis was made. Figure 1 shows relative frequency of the symptoms and signs at entry into the trial and the development in the following years. The cumulative percentage of patients in whom pruritus was noticed increased from 75% to 95% in 5 yr. The increase in frequency of jaundice, pigmentation, and hepatome-

Table 1. First Symptom or Sign

Symptom or sign	No. of patients		Median duration before entry (yr)
Pruritus		110	2.7
"Hepatic"		46	1.2
Jaundice	28		
GI-bleeding	14		
Ascites	4		
Unspecific		52	2.0
Fatigue	18		
Abdominal pain	16		
Dyspepsia or nausea	8		
Weight loss	3		
Steatorrhoea or diarrhea	3		
Abdominal mass	2		
Xanthelasmata	1		
Collapse of vertebrae	1		
"Collagen disease"		11	2.1
Arthritis	4		
Sjögren's syndrome	2		
Raynaud's phenomena	2		
Scleroderma	1		
CRST syndrome	1		
Enlarged salivary glands	1		
Other		17	0.0
None	12		
Epistaxis	2		
Fever	1		
Abscess	1		
Diabetes mellitus	1		

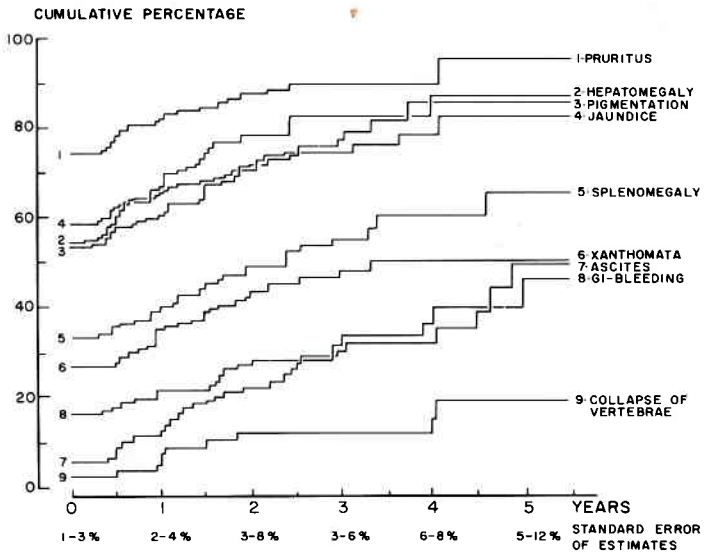

Figure 1. Progression of clinical features with time after entry into the trial.

galy was similar, and after 5 yr the curves reached almost 85%. Splenomegaly lagged behind hepatomegaly, but after 5 yr, approximately 65% had a palpable spleen, 50% had developed cutaneous xanthomas, and 46% had experienced GI bleeding episodes. Ascites increased sevenfold to 49%, but, during the same period, 76% had required a diuretic, implying that the number of patients with tendency for fluid retention was higher. Vertebral collapse was uncommon initially, but after 5 yr 20% had this complication. The number of patients at risk decreases, and the standard error of the curves increases with time.

Of associated diseases, scleroderma was found at the entry into the trial in 11 patients, 1 of whom also had classic rheumatoid arthritis and 1 had the CRST syndrome (calcinosis cutis, Raynaud's phenomenon, sclerodactyly, telangiectasias). During the first 2 yr of observation 4 more patients developed scleroderma. At the time of entry 9 patients had Sjögren's syndrome, associated in 1 patient with the CRST syndrome. Two further patients developed Sjögren's syndrome during the subsequent 2 yr. Seven patients, all with thyroid antibodies, showed signs of myxedema.

Histologic Features

The development of the histologic features from the time of first biopsy is shown in Figures 2 and 3. Within 3 yr the cumulative curves for proliferation and destruction of ductules and for piecemeal necrosis had reached 100%. The number with peripheral cholestasis was higher and increased slightly more rapidly than that of central cholestasis. Permanent destruction of lobular architecture with pattern of cirrhosis increased from 30% at the time of entry to 82% after 4 yr.

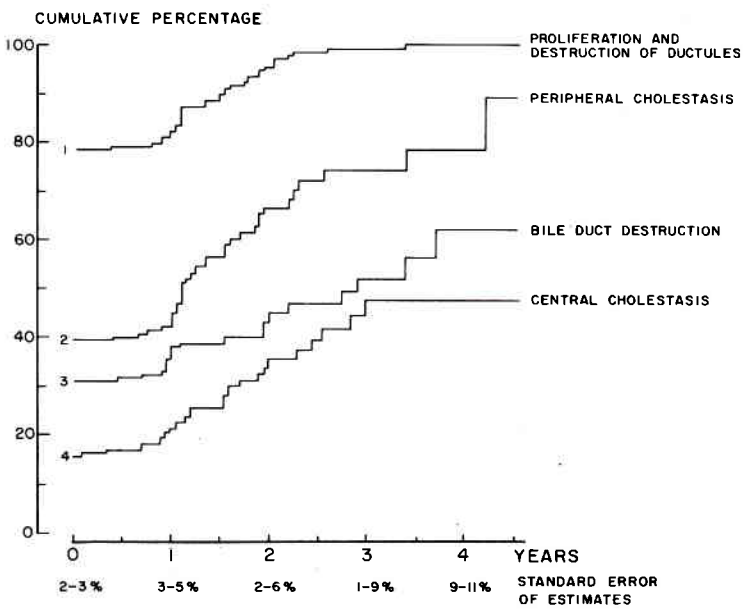

Figure 2. Progression of bile duct and cholestatic changes in the liver with time after entry into the trial.

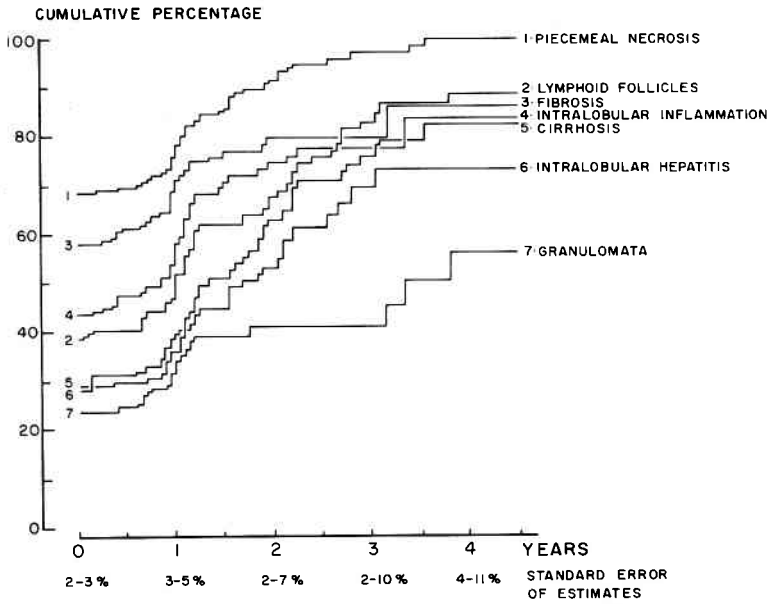

Figure 3. Progression of inflammatory and connective tissue changes in the liver with time after entry into the trial.

Laboratory Findings and Incapacitation Index

Median values for the laboratory tests at entry into the trial and at 6-mo intervals thereafter are shown in Table 2. No consistent (increasing or decreasing) trends with time are apparent.

When analyzed by the life-table method, the curves in Figure 4 and 5 were obtained. They show the cumulative percentage of patients who at one time or another had values *more* abnormal than those stated, which correspond to the upper (for albumin lower) 15th percentile (given in Table 2) of the distribution at entry. The rate of occurrence of such abnormal values is relatively high for albumin and bilirubin as well as for the incapacitation index but low for cholesterol. Activities of alkaline phosphatase and alanineaminotransferase take intermediate positions. The occurrence rate of "abnormally" elevated mitochondrial antibody titers is distinctively higher than those of immunoglobulin G, A, and M. At entry 91% had mitochondrial, 33% smooth muscle, 31% antinuclear, and 26% thyroid antibodies, and these figures did not change significantly with time.

Analysis of subgroups. DURATION OF HISTORY. Comparison of the data at entry into the trial revealed that patients with long duration of symptoms had higher frequencies of pruritus and cholestyramine treatment but lower frequency of intralobular hepatitis than those with short duration of symptoms ($P < 0.01$). Occurrence rates of abnormal features after the entry did not differ significantly with different duration of symptoms. Thus, the duration of history before diagnosis provides no significant prognostic information.

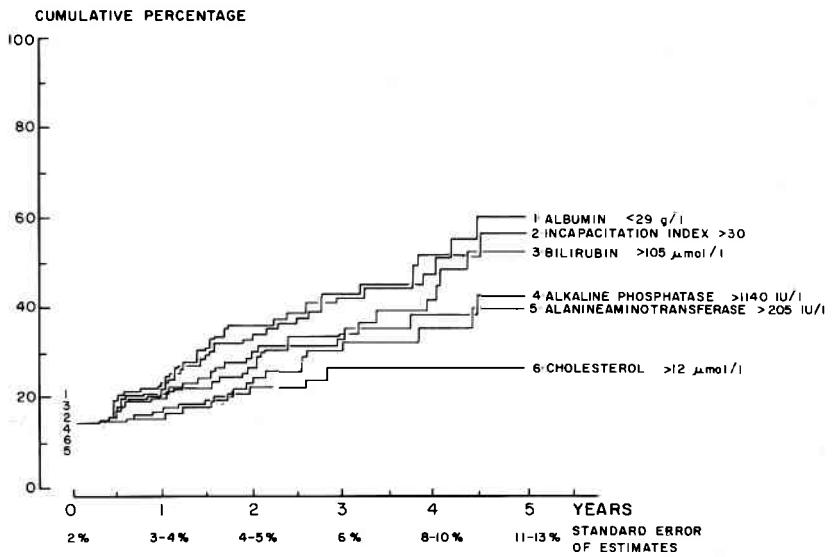

Figure 4. Progression of incapacitation index and liver function tests with time after entry into the trial.

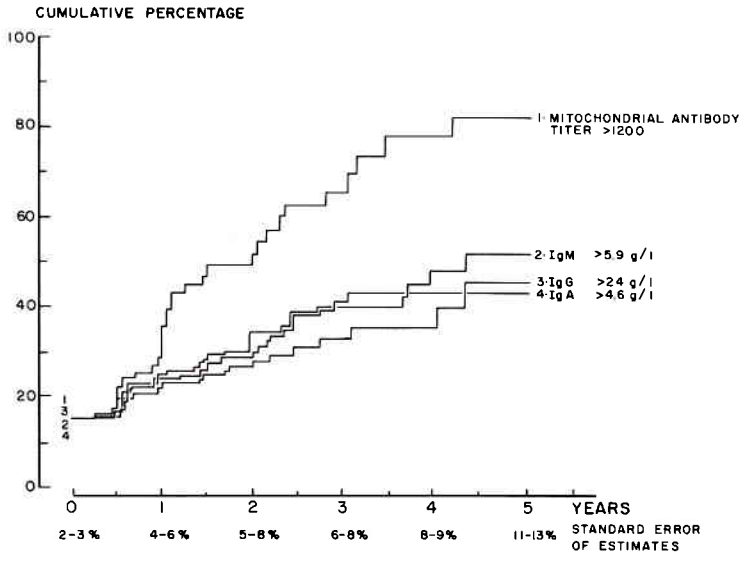

Figure 5. Progression of immunoglobulins and mitochondrial antibody with time after entry into the trial.

AGE AND SEX. At the time of entry, albumin, alanineaminotransferase activity, and the relative frequency of pruritis as the first symptom were lower in older than in younger patients ($P < 0.01$). After entry the occurrence rates of the features in Table 3 provide evidence of an increasingly progressive course of the disease with increasing age. Age-adjustment of the death-rates neutralized this difference.

Subdivision of the patients according to sex did not reveal any significant difference, neither at entry nor during the observation period.

HISTOLOGIC STAGE. At the time of the first biopsy, patients in each of the four histologic stages differed in features (Table 4). Occurrence rates were calculated after stratification according to the bilirubin level at entry, since the bilirubin level appeared to be an important prognostic factor (see below) and correlated with the histologic stage. The death-rate was 2.8 times higher in stage IV ($P < 0.001$) than in other stages, which had similar death rates. Furthermore, the occurrence rate of granulomas decreased markedly from stage I to IV, being 25 times higher in the former than in the latter ($P < 0.000001$). Thus the histologic stage at entry gave some prognostic information independent of the bilirubin level.

BILIRUBIN. Grouping according to the level of serum bilirubin at entry showed significant differences (Table 5). The bilirubin level was related significantly to the frequencies of peripheral and central cholestasis. The median bilirubin level in patients with central cholestasis was 125 μmol/liter.

After entry the occurrence rates of the features in Table 6 indicate an increasingly progressive course of the disease the higher the serum bilirubin level at entry. This emphasizes its significant prognostic value, independent of the histologic state.

FIRST SYMPTOM OR SIGN. Data at entry were to some extent related to the first symptom or sign described in Table 1. Comparison of cases starting with "hepatic" features and pruritus, respectively, showed that the former had a higher age (median 58 vs. 52 yr), shorter duration of history (1.2 vs. 2.7 yr), higher serum bilirubin (63.5 vs. 33.9 μmol/liter), and more cirrhosis (52% vs. 27%). Cases starting with "collagen disease" or "other" features (Table 1) had comparatively low bilirubin (median 16.9 μmol/liter), alanineaminotransferase (68 IU/liter), alkaline phosphatase (350 IU/liter), cholesterol (6.3 mmol/liter), low frequency of pruritis (36%), cirrhosis (14%), and high frequency of bile duct destruction (58%) and of granulomas (48%) ($P < 0.01$). Occurrence rates of abnormal features after entry in the groups defined in Table 1 were not significantly different for any variable when stratified according to age, histologic stage, and bilirubin level at entry. Thus the character of the first symptom or sign gave no significant prognostic information independent of those three factors.

DEATH FROM HEPATIC FAILURE. Thirty-six patients who died from heptic failure with or without GI-bleeding had at entry more advanced disease (Table 7), even though the duration of their history was not significantly different from the rest. Occurrence rates for a number of features (Table 8) also indicated more rapid progression of the disease. This was independent of the advanced histologic stage or higher bilirubin level, since the calculations were made after stratification according to these factors.

The cumulative percentage of patients in whom each abnormal feature occurred before death could be calculated, with time of death from hepatic failure as reference point (Figure 6). During the 2 yr be-

Table 2. *Median Values of Laboratory Tests and Incapacitation Index at Six Monthly Intervals*

Variable	"Abnormal" 15th percentile at entry	Months after entry into the trial									
		0	6	12	18	24	30	36	42	48	54
Bilirubin (*μmol/liter*)	105	30.6	25.0	27.0	25.0	33.9	25.5	30.0	27.0	44.0	69.0
Alkaline phosphatase (*IU/liter*)	1140	533	504	472	537	465	462	400	410	505	659
Alanineaminotransferase (*IU/liter*)	205	103	88	86	92	105	102	98	100	114	134
Cholesterol (*mmol/liter*)	12	8.10	7.50	7.70	7.51	7.28	7.47	7.49	8.50	7.24	6.30
Albumin (*g/liter*)	29	34.9	35.5	35.0	35.4	35.7	35.2	35.0	34.6	36.0	33.0
Immunoglobulin G (*g/liter*)	24	14.1	14.9	14.7	16.3	14.6	15.5	16.0	16.4	13.3	14.5
Immunoglobulin A (*g/liter*)	4.6	2.72	2.60	2.76	2.97	2.39	2.76	3.00	1.71	1.55	3.27
Immunoglobulin M (*g/liter*)	5.9	3.30	2.55	2.70	2.69	2.95	2.62	2.73	2.99	2.60	3.49
Mitochondrial antibody titer	1200	320	320	480	320	320	160	320	180	480	480
Incapacitation index	30	0	0	0	0	0	0	0	0	0	1.5
Number of patients		236	157	127	103	86	67	53	32	26	14

fore death the frequency of hepatomegaly and jaundice increased from about 65% to nearly 100%, GI-bleeding from 20% to 58%, and ascites from 15% to nearly 100%. Histologically the development of peripheral cholestasis preceded cirrhosis which preceded central cholestasis.

Discussion

Analysis of trial data at fixed time intervals may mask deteriorating trends since the more severely ill patients may be lost by death, withdrawal, or drop-out. We therefore mainly analyzed our data by the life-table method which allows for incomplete follow-up.[12] However, this method treats all variables, including the continuous ones, as dichotomous variables and utilizes only the time to the *first* occurrence of an abnormal feature and disregards later fluctuations between "normal" and "abnormal." Furthermore, this method assumes that the variables analyzed develop progressively with increasing degree of abnormality in time. Apart from minor short-term fluctuations, this is true for most of the variables recorded, although the rate of progression may vary. However, manifestations which depend on hepatocellular functions (hypercholesterolemia, xanthomas, and increased activities of hepatic enzymes) may regress in late stages when the liver has been sufficiently damaged by the disease. Other manifestations may regress following symptomatic treatment, e.g., pruritus after treatment with cholestyramine and ascites following diuretic therapy. Therefore the curves obtained by the life-table method are *not* estimates of the actual percentage since incidence of the features may be lower for variables regressing in later stages. For such variables only the early progressive phase is analyzed by the method. Since the method is based on the rate of progression from "normal" to "abnormal," variables which show little or no progression with time are not suited for analysis. But since such variables are also not suited as markers of the stage of progression, they are perhaps less interesting. With these limitations the life-table method is an unbiased method which provides a valid statistical test (the log rank test) for comparison of the rate of the first transition of variables from "normal" to "abnormal" (the occurrence rate) in subgroups.[12] As the earliest complete information on all features was obtained by the time of entry into the trial, this date had to be chosen as the common starting point of the analysis instead of the date of the first symptom. The latter is vaguely defined because of the insidious onset of the disease.

The spectrum of initial symptoms agrees with

Table 3. Significant Effects of Age on the Occurrence Rate of Abnormal Features After Entry into the Trial

Variable	Numbers at risk age (yr)			O/E-ratio age (yr)			Occurrence rate ratio age (yr)			P-Value for trend
	<50	50–59	>60	<50	50–59	>60	<50 :	50–59 :	>60	
Clinical										
Collapse of vertebrae	72	89	67	0/5.5	4/6.0	11/3.5	0 :	1 :	4.7	1×10^{-9}
Incapacitation index >30	65	81	57	7/17.5	22/15.8	14/9.7	1 :	2.6 :	4.5	0.0002
GI-bleeding	63	71	62	4/9.2	8/7.7	10/5.1	1 :	2.4 :	4.6	0.005
Treatment with diuretics	62	79	63	9/16.3	16/14.5	15/9.2	1 :	2.0 :	3.0	0.007
Death	73	92	71	10/19.5	125/21.2	20/14.3	1 :	2.3 :	2.7	0.008
Laboratory										
Albumin <29 g/liter	67	76	59	8/18.0	17/14.9	16/8.1	1 :	2.6 :	4.5	0.0002
Immunoglobulin A >4.6 g/liter	67	75	61	8/12.3	8/11.4	15/7.3	1 :	1.1 :	3.2	0.005

published data.[2,3,7–10] That 19% of the patients presented with jaundice, GI-bleeding, or ascites indicates advanced disease already at that time. It is likely that many patients were in late stages that today might be diagnosed earlier if they were subjected to biochemical screening.[4–6] This is also supported by their older age.

In the whole material, abnormal findings tend to develop along parallel lines. The first symptom in the "average patient" is pruritus followed by hepatomegaly, jaundice, and pigmentation. Splenomegaly is less common and is delayed relative to hepatomegaly by approximately 3 yr. In ~50% of the patients, xanthomas, bleeding, and ascites follow within 1 yr, whereas vertebral collapse develops only in about 20%. This sequence of events is practically the same as that described by Ahrens et al. in 17 patients.[2]

Proliferation and destruction of ductules, and piecemeal necrosis (the most frequent histologic abnormalities) correspond in time with pruritus, and fibrosis corresponds with hepatomegaly. Lymphoid follicles and intralobular inflammation develop in parallel with xanthomas, and central cholestasis with ascites and GI-bleeding. These temporal associations are not precise and seem not to reflect causal associations. In view of the longer time span between biopsies than between clinical investigations (about 1 yr vs. 6 mo.), histologic abnormalities may be detected later than clinical abnormalities. Sparse features may be absent in a small biopsy specimen and early lesions (granulomas and bile duct destruction)[13–15] may have subsided before the biopsy was obtained. These factors tend to underestimate the cumulative percentage of such histologic features.

Life-table analysis of the continuous variables revealed a marked tendency of the mitochondrial antibody titer, bilirubin, albumin, and incapacitation index (designating interference with life style) to develop more abnormal values than the selected

Table 4. Variables at Entry Differing Significantly in Patients with Different Histologic Stage

Variable	Histological stage I 14%	II 40%	III 19%	IV 27%	P-Value
Clinical					
GI-bleeding (%)	11	9	10	37	0.0001
Jaundice (%)	39	48	75	77	0.0003
Ascites (%)	4	2	3	19	0.001
Treatment with diuretics (%)	9	9	9	20	0.005
Splenomegaly (%)	23	27	23	57	0.003
Hepatomegaly (%)	41	46	50	72	0.009
Laboratory					
Median bilirubin (*μmol/liter*)	17.0	18.6	39.0	57.6	0.0001
Median IgA (g/liter)	2.1	2.5	3.1	3.0	0.004
Histological					
Bile ducts present in biopsy (%)	100	71	67	54	2×10^{-7}
Bile duct destruction (%)	79	40	12	11	2×10^{-10}
Peripheral cholestasis (%)	7	39	43	62	3×10^{-5}
Granulomas (%)	55	32	17	6	5×10^{-6}
Intralobular inflammation (%)	69	52	31	31	0.002

Table 5. Features at Entry Differing Significantly in Patients with Different Levels of Bilirubin

Variable	Bilirubin (μmol/liter) <20 (34%)	20–60 (37%)	>60 (29%)	P-Value
Clinical				
Jaundice (%)	26	62	96	2×10^{-10}
Pigmentation (%)	35	57	72	0.00004
Pruritus (%)	61	85	79	0.001
Xanthomas (%)	15	26	41	0.002
Splenomegaly (%)	24	33	52	0.003
Jaundice as the first symptom (%)	8	6	23	0.006
Laboratory				
Median alanineaminotransferase (*IU/liter*)	85	102	141	1×10^{-6}
Median cholesterol (*mmol/liter*)	7.85	7.75	9.80	0.001
Histologic				
Peripheral cholestasis (%)	21	35	76	3×10^{-10}
Central cholestasis (%)	5	9	41	3×10^{-8}
Cirrhosis (%)	15	37	45	0.0002

15th percentile. The lack of consistent progressive trends in the transectional analysis may be explained by bias caused by loss of the more severely ill patients with time.

The influence of azathioprine (given to half of the patients) on the findings was probably negligible since its effect was not significant on any variable as previously reported.[11]

The clinical association with autoimmune disorders, with the frequency of autoantibodies and with the immunoglobulin levels agree with previous reports.[16–25] However, the frequency of Sjögren's syndrome is lower than in other published series,[18,19] possibly because Schirmer's test was not routinely performed in the assessment. The increase in mitochondrial antibody titer during disease progression is not explained. It confirms previous observations in subclinical cases in which the titers were higher in the presence of histochemical or biochemical hepatic abnormalities than in their absence (geometric mean 256 vs. 57, $P = 0.005$).[22]

The duration of symptoms before entry into the trial did not significantly influence prognosis. This may be due to the fact that patients with short histories comprised both those starting with "hepatic" symptoms, which had progressed far, and those starting with "other" symptoms, which had progressed little. However, the first symptom or sign did not provide significant prognostic information which could not be attributed to differences in age, histologic stage, or bilirubin level.

The unfavorable prognostic influence of older age on disease progression may be explained by reduced compensatory mechanisms such as the cell regenerative capacity of the liver.[26,27] The high occurrence rate of hypoalbuminemia and vertebral collapse cannot be attributed entirely to PBC but also to age itself.[28] The high rate of increased levels of serum IgA in the older patients can probably also be explained by age alone.[29]

The histologic stage (stage IV) had a significant prognostic value for survival, thus refuting the re-

Table 6. Significant Effects of the Bilirubin Level at Entry on the Occurrence Rate[a] of Abnormal Features After Entry

Variable	Numbers at risk bilirubin (μmol/liter) <20	20–60	>60	O/F Ratio bilirubin (μmol/liter) <20	20–60	>60	Occurrence rate ratio bilirubin (μmol/liter) <20 : 20–60 : >60	P-Value
Clinical								
Ascites	79	80	61	2/12.6	11/12.5	22/9.9	1 : 5.5 : 14	8×10^{-7}
Death	81	87	68	4/16.3	19/22.5	33/17.2	1 : 3.4 : 7.8	2×10^{-6}
Jaundice	59	33	3	7/15.8	15/7.6	2/0.6	1 : 4.5 : 7.3	9×10^{-5}
Laboratory								
Alkaline phosphatase >1140 IU/liter	72	75	53	6/11.3	7/9.9	13/4.8	1 : 1.3 : 5.1	0.0004
(Bilirubin >105 μmol/liter	81	87	32	2/12.9	17/14.2	13/4.9	1 : 7.9 : 18	2×10^{-6}
Histologic								
Central cholestasis	77	79	40	5/11.8	4/9.7	21/8.5	1 : 1.0 : 6.0	2×10^{-5}

[a] Calculated after stratification according to the histologic stage at entry.

Table 7. Variables Differing Significantly in Patients Dying or Not Dying from Hepatic Failure During the Observation Period

Variable	Dying (15%)	Not dying (85%)	P-Value
Clinical			
Pigmentation (%)	81	49	0.0005
Ascites (%)	19	5	0.001
Jaundice (%)	83	55	0.002
Treatment with diuretics (%)	31	11	0.003
Laboratory			
Median bilirubin (*μmol/liter*)	71.2	27.0	0.00001
Median albumin (*g/liter*)	31.5	35.1	0.0001
Histologic			
Bile ducts present in the biopsy (%)	39	75	0.0001
Peripheral cholestasis (%)	67	35	0.0007
Cirrhosis (%)	52	26	0.003

cent claim to the contrary.[30] However, the bilirubin level as an indicator of the severity of cholestasis had the greatest prognostic significance. Our observations thus confirm recently published results showing that life-expectancy, to some extent, can be predicted from serum bilirubin levels.[30]

The patients who died from hepatic failure had more advanced disease at entry and deteriorated more rapidly, independent of the more advanced histologic stage and higher bilirubin levels. The main feature in their more progressive course is the pronounced tendency toward severe cholestasis. These patients had fewer bile ducts on biopsy at entry and central cholestasis occurred in them at an increased rate. These findings may be consequences of the bile duct destruction caused by the disease, since a reduction in the number of bile ducts with progression of the disease is well known[13,15] and has been confirmed by our results. However, the possibility that the number of bile ducts was already reduced before the disease started cannot be precluded. Whether the serious course in these patients indicates a special subgroup of patients or just one end of a continuous spectrum has not been established. Genetic abnormalities making the bile ducts more susceptible to pathogenic agents (bacteria, viruses, or drugs?) have been considered,[31–34] but such abnormality has not been clearly defined so far. PBC in twin sisters[32] and the high prevalence of immunologic abnormalities in relatives of patients with PBC,[31,33,34] emphasizes genetic features in the setting of PBC. The association of PBC with autoimmune disorders particularly with Sjögren's syndrome in which certain tissue types are very frequent[35,36] points to the possibility of a specific tissue pattern in PBC. But, so far, an association of PBC with any particular type has not emerged,[37] probably because Sjögren's syndrome may consist of different subgroups. Furthermore, only 6% of all patients with Sjögren's syndrome do, in fact, have liver disease.[38] The many immunologic abnormalities in PBC patients[39–41] and their relatives[31–34] seem to be secondary phenomena presumably elicited in genetically predisposed individuals by hitherto unidentified etiologic agent(s).

Table 8. Occurrence Rates[a] of Abnormal Features After Entry Differing Significantly in Patients Dying or Not Dying from Hepatic Failure During the Observation Period

	Numbers at risk		O/E-ratio		Occurrence rate ratio	
Variable	Dying	Not dying	Dying	Not dying	Dying : Not dying	P-Value
Clinical						
Hepatomegaly	10	98	8/2.6	29/34.4	3.6 : 1	0.00004
Jaundice	6	90	4/1.6	20/22.4	2.8 : 1	0.0007
Ascites	29	191	13/7.2	22/27.8	2.3 : 1	0.008
Incapacitation index >30	26	177	11/5.3	32/37.7	2.4 : 1	0.009
Histologic						
Central cholestasis	25	174	15/8.8	15/21.2	2.4 : 1	0.007

[a] Calculated after stratification according to histologic stage and bilirubin level at entry.

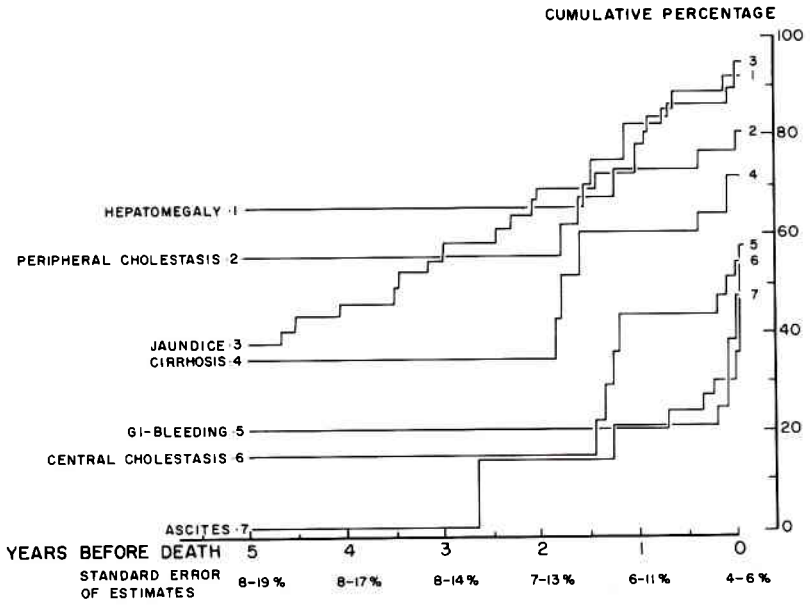

Figure 6. Progression of pertinent features with time before death from hepatic failure.

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