

LIVER, PANCREAS, AND BILIARY TRACT

Long-term Survival in Patients With Hereditary Hemochromatosis

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See editorial on page 1304.

Background & Aims: The course of hereditary hemochromatosis may depend on the degree of iron overload and the time of therapeutic intervention. This analysis evaluates the impact of early diagnosis and iron removal on survival and complications in hereditary hemochromatosis. **Methods:** A cohort of 251 patients with hemochromatosis was followed up for 14.1 ± 6.8 years. **Results:** Survival was reduced in the total group of patients when compared with a matched normal population. Survival in noncirrhotic and nondiabetic patients and in patients diagnosed between 1982 and 1991 was identical with rates expected. Survival was reduced in patients with severe iron overload vs. those with less severe overload. The percentage of early diagnoses increased threefold between 1947 and 1969 to that between 1970 and 1981; there was only a further 20%–25% increase in the last decade. Deaths caused by liver cancer, cardiomyopathy, liver cirrhosis, and diabetes mellitus were increased as compared with expected rates. Liver cancers were associated with cirrhosis and amount of mobilizable iron but not with hepatitis B or C markers. **Conclusions:** Prognosis of hemochromatosis and most of its complications, including liver cancer, depend on the amount and duration of iron excess. Early diagnosis and therapy largely prevent the adverse consequences of iron overload.

In 1983, we completed a long-term study suggesting that patients with hereditary hemochromatosis have a normal life expectancy provided that they are diagnosed in an early stage without liver cirrhosis and diabetes mellitus and that they are treated by repeated phlebotomies until all the excessive iron is removed.¹ Two recently reported studies in smaller cohorts of patients with hereditary hemochromatosis further substantiated the value of early diagnosis and prophylactic treatment.^{2,3} Liver cancer was one of the most frequent causes of death in

patients with hemochromatosis in previous studies, including our own experience.^{1–3} Recently, it has been reported that cancer may even develop in noncirrhotic livers of effectively treated patients with hemochromatosis.^{4,5} Other reports suggest that chronic viral infection (hepatitis B and C virus) may contribute to the high risk of liver cancer in hemochromatosis.^{3,6,7}

In recent years, most attention has been paid to an earlier diagnosis to prevent irreversible tissue damage. It is unclear, however, to what extent these efforts were successful. The present long-term follow-up study of a large cohort of patients with hemochromatosis focuses on the impact of early diagnosis and treatment on survival. In addition, the analysis evaluates various factors that might influence outcome and causes of death, in particular, death from liver cancer. The results also give further information about the question of which complications of hemochromatosis can be prevented or reversed by phlebotomy and which cannot.

Materials and Methods

Between 1947 and 1991, 251 patients with clinical, biochemical, and histological evidence of hereditary hemochromatosis were identified in the Departments of Medicine of the two hospitals participating in the study (University of Düsseldorf, $n = 159$; Bad Kissingen, $n = 92$). Most patients (about 80%) were cared for by the referring physician and were seen once a year at one of the medical centers. From 1979 on, both the diagnostic workup and the therapeutic procedure were performed according to a prospective protocol that included liver biopsy with quantification of liver iron, repeated phlebotomies (500 mL blood once to twice weekly), and another biopsy performed after serum ferritin levels had become normal for confirmation of iron depletion. After iron depletion, all patients received 4–12 phlebotomies per year for the rest of his or her life to prevent reaccumulation of iron. Although there was no prospective protocol for diagnosis and treatment

until 1979, the latter schedule was performed for all patients throughout the study. Diagnosis of hemochromatosis was suggested by the patient's clinical features and by biochemical tests, which included tests of liver function and measurement of serum iron, transferrin saturation, and serum ferritin (after 1976). Deferoxamine tests were performed in only a minority of patients. HLA typing was performed only for the purpose of family screening. The only difference in the diagnostic workup between the two hospitals participating in the study was in the method used to perform the liver biopsy. In particular in the last decade, most patients in the University Hospital in Düsseldorf had biopsies performed under ultrasound guidance, whereas in the Heinz Kalk-Klinik, the majority of patients had a biopsy performed during a laparoscopy.

In the group of patients who did not have cirrhosis at the time of entry ($n = 109$), 41 patients (37.6%) were asymptomatic: 17 (41.5%) were identified by family screening, 15 (36.6%) by elevated serum aminotransferase levels, and 9 (21.9%) by elevated serum iron or ferritin concentrations on routine serum chemistry panels. Of the 109 noncirrhotic patients, 68 (62.4%) had symptoms: 8 patients (11.7%) presented to rheumatologic clinics with arthralgia, 5 had symptoms due to diabetes mellitus (7.4%), and 5 had the triad of diabetes mellitus, (noncirrhotic) liver disease, and skin pigmentation (7.4%). Two of 13 women without cirrhosis presented with amenorrhea, and 3 of 96 noncirrhotic men presented with loss of libido and impotence. The remaining 34 noncirrhotic patients (50%) presented with a variety of nonspecific symptoms, including weakness, lethargy, and abdominal discomfort.

On the other hand, only 7 of the 142 cirrhotic patients (4.9%) were diagnosed without preceding symptoms: 3 were identified through family screening, 2 because of elevated serum aminotransferase levels, and 2 because of elevated serum iron levels of ferritin. Almost all of the 142 cirrhotic patients ($n = 135$; 95.1%) were identified because they presented with symptoms: 16 subjects presented with chronic liver disease (11.9%); 18 with diabetes mellitus (13.3%); 21 with both the latter complications (15.6%); 38 with the triad of diabetes mellitus, cirrhosis, and hyperpigmentation (28.2%); 9 (8%) with impotence; 8 (5.9%) with cardiac complications; and 5 (3.7%) with arthralgia. The remaining 20 cirrhotic patients (14.8%) presented with a variety of nonspecific symptoms.

The diagnosis was confirmed by liver biopsy with histochemical quantification of iron in all patients. Starting in 1984, liver iron concentration was in addition quantified by atomic absorption spectrometry. The quantitative measurements of liver iron concentration were slightly different in the participating centers, and there were also some patients in whom the initial biopsy had been performed at a third place. In recent years, a considerable part of the measurements of liver iron concentration was performed using liver wet weights as reference. For comparison with values calculated for dry weight and with the corresponding data in the literature, the data calculated using wet weights were transferred to data for dry weights by using the assumption that 1 mg wet wt refers to 0.25 mg dry wt. The presence of cirrhosis was established according to generally accepted criteria as described else-

where.⁸⁻¹⁰ In 185 patients, the histological features of the liver could be reevaluated by a follow-up biopsy after iron depletion; in 47 patients, autopsy data allowed confirmation of the initial distinction between cirrhotic and noncirrhotic patients. In many patients, the results of additional follow-up biopsies were available (three biopsies in 71 patients and four or more biopsies in 35 patients). The degree of fibrosis was graded using a score that has widely been used in other recent studies for patients with hemochromatosis^{11,12}: stage 0 includes only septal fibrosis (also termed prefibrotic or nonfibrotic stage), stage 1 includes nonextensive portal fibrosis without bridging septa, stage 2 includes portal fibrosis with bridging septa, and stage 3 includes annular fibrosis with vascular disorganization and cirrhosis. Because laparoscopy was routinely performed for reevaluation of patients in only one of the two centers (Heinz-Kalk Klinik), the present study does not specifically deal with the question of reversal of cirrhosis but only evaluates the histological changes of the fibrotic stages.

Follow-up data were obtained by sending a questionnaire to the patient and his or her physician. In addition, patients were seen once yearly for a checkup at one of the medical centers. Despite thorough investigations, 2 of the 251 patients (0.8%) were lost to follow-up.

Sixty-nine patients died during the study. The cause of death was established by autopsy in 47 patients; by premortem histological diagnosis in 12 patients with neoplasms; by clinical reports for 2 patients with acute myocardial infarction, 3 patients with bleeding from esophageal varices, 1 patient with a diabetic coma, and 1 patient with a hypoglycemic coma; and by accident reports for 3 patients dying of trauma.

After causes of death in Germany (data from state of Nordrhein Westfalen in 1991) had been determined from published sources,¹³ the number of deaths expected in a normal population matched for age and sex to the patient population was calculated according to person-years of observation in various age (5-year) and sex ranges. A 95% confidence interval was calculated for the number of observed deaths, which was treated as a Poisson variable.¹⁴ Any value for the number of expected deaths that fell outside this 95% confidence interval was considered to be significantly different from the observed number.¹⁴ The mortality ratio was calculated as the ratio of observed to expected deaths.¹⁵

Survival was evaluated with the product-limit estimator method as described by Kaplan and Meier.¹⁶ Follow-up was deliberately censored at 30 years because only 4 patients were followed up for more than 30 years and no death occurred thereafter. The observed survival curve in the 251 patients with hemochromatosis was compared with their expected survival curve, which was calculated by applying the sex- and age-specific death rates for inhabitants of Germany to each patient according to the period when she or he was observed in the study. Expected survival in subgroups of patients was separately calculated by applying the sex- and age-specific death rates for the normal population to each patient according to the time observed in the study. To compare the observed survival in the patients with hemochromatosis and the sub-

groups of these patients with expected survival calculated from statistical data, an interval of 2 SD for the survival rate of the patients was considered to be a 95% confidence interval.¹⁴ Curves for expected survival that were beyond the limit of the confidence interval were considered to be significantly different from curves for survival observed.¹ Curves that were lying within these limits were not considered to be significantly different. In addition, the following subgroups of patients were compared with each other: (1) men vs. women, (2) cirrhotic vs. noncirrhotic patients, (3) diabetic vs. nondiabetic patients, (4) patients without arthropathy vs. those with arthropathy, (5) patients diagnosed between 1947 and 1966 vs. those diagnosed between 1970 and 1981 vs. those diagnosed between 1982 and 1991, and (6) patients who received ≥ 80 phlebotomies to remove the excessive iron vs. those who received < 80 phlebotomies (the latter analysis only included the 185 patients in whom iron removal had been documented by a repeated liver biopsy). Survival in these subgroups was compared by the log-rank test.¹⁷ The effects of clinical variables on survival were further analyzed by a multivariate model using stepwise survival analysis including disease covariates and age at diagnosis. Calculations were performed by using the biomedical data program BMDP.¹⁸ Differences between cirrhotic and noncir-

rhotic patients in the frequency of various features were compared by a two-tailed Z test.¹⁹

Results

Survival Data

Between 1947 and 1991, 251 patients with hemochromatosis were followed up. Their age at the time of entry into the study was 45.7 ± 10.8 years (mean \pm SD) with a range of 18 to 77 years. The mean follow-up period was 14.1 ± 6.8 years (range, 1–33 years); 2 patients were lost to follow-up (0.8%). There were 224 men (89.2%) and 27 women (10.8%). At diagnosis, 120 patients had diabetes mellitus (47.8%) and 131 patients did not (52.2%); 142 patients had liver cirrhosis (56.6%) and 109 did not (43.4%). Cumulative survival was 93% at 5 years, 77% at 10 years, 62% at 15 years, 55% at 20 years, 46% at 25 years, and 20% at 30 years (mean survival, 21.0 years). Survival in the 251 patients was significantly reduced as compared with expected survival in a matched normal population (Figure 1). Life expectancy was reduced in patients with liver cirrhosis as com-

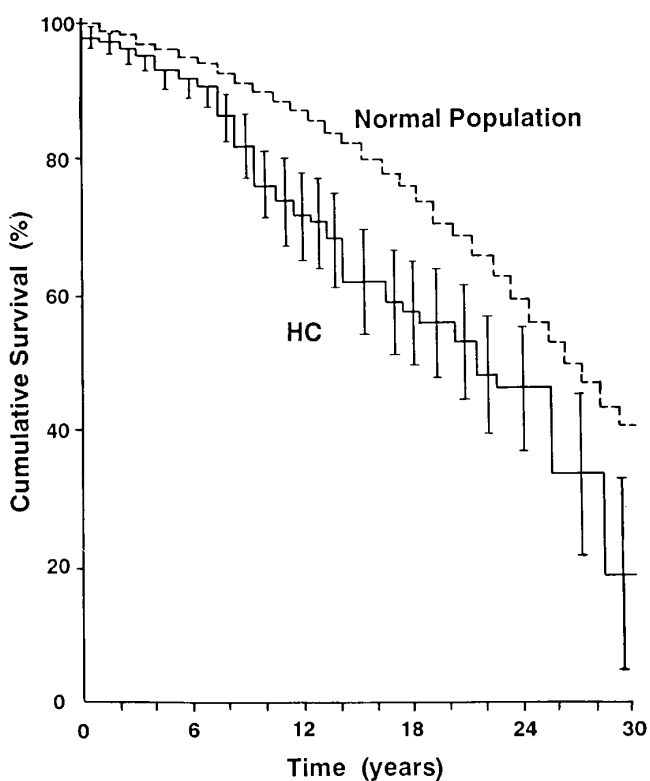


Figure 1. Cumulative survival in 251 patients with hereditary hemochromatosis. A 95% confidence interval was calculated by adding twice the SD from the means (vertical bars). Survival was significantly reduced in patients with hemochromatosis when compared with the expected survival rates for an age- and sex-matched normal population; the expected survival rates were clearly lying outside and above the confidence interval calculated for survival in the patients.

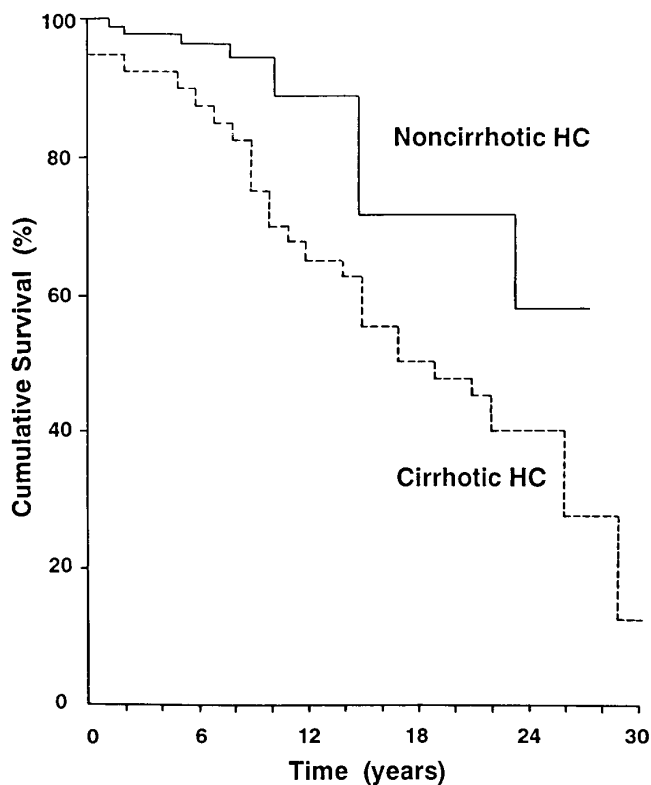


Figure 2. Cumulative survival in 142 cirrhotic and 109 noncirrhotic patients with hemochromatosis. Survival was significantly reduced in the cirrhotic patients when compared with the noncirrhotic patients ($P \leq 0.01$; log-rank test). The mean age and distribution of age were similar in both groups (46.2 ± 11.9 years [\pm SD] [range, 24–75 years] in cirrhotic patients vs. 45.1 ± 11.8 years [range, 18–77 years] in noncirrhotic patients).

pared with those without cirrhosis ($P \leq 0.01$, log-rank test) (Figure 2). In contrast to survival in the total group of patients and in the subgroup of patients with cirrhosis at entry, the survival curve for noncirrhotic patients was not significantly different from that of expected survival (Figure 3). Survival was also reduced in patients with diabetes mellitus as compared with patients without diabetes mellitus ($P \leq 0.002$) (Figure 4). Patients without diabetes at the time of diagnosis had a survival indistinguishable from that expected (Figure 4). The prognosis of hemochromatosis was influenced neither by arthropathy ($P > 0.2$) (Figure 5) nor by sex ($P > 0.2$) (data for sex not shown as a figure). Mean age and distribution by age at the time of diagnosis were similar in each subgroup of patients and could not explain differences in survival (see figure legends). When the effects of clinical variables on survival were analyzed by multivariate stepwise analysis, including disease covariates (diabetes mellitus, liver cirrhosis, arthritis, sex and age at diagnosis), only diabetes mellitus and liver cirrhosis had a significant prognostic value (adjusted relative risks were 4.3 and 2.4 with $P \leq 0.01$ and $P \leq 0.05$, respectively).

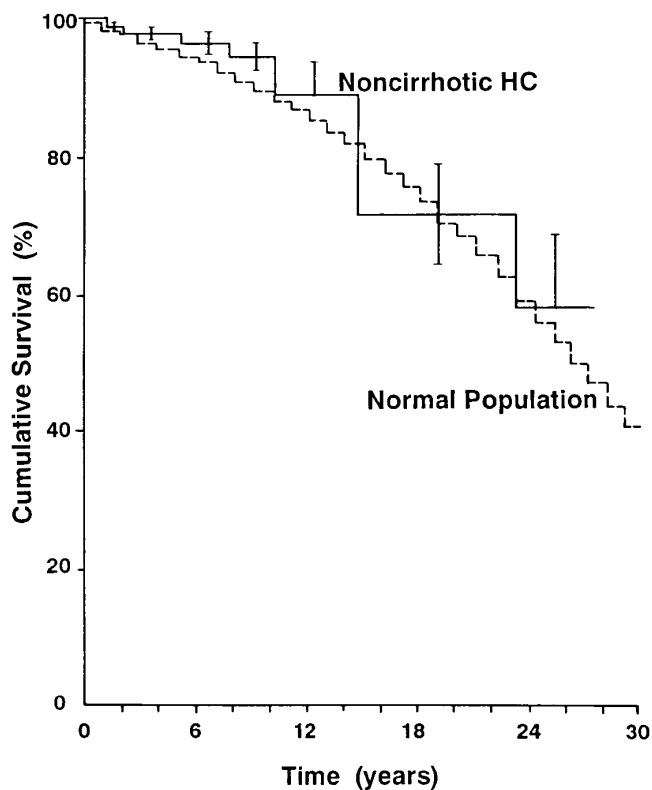


Figure 3. Cumulative survival in 109 noncirrhotic patients with hemochromatosis. A 95% confidence interval was calculated by adding twice the SD from the means (see vertical bars). Survival in patients with noncirrhotic hemochromatosis was reduced when compared with the rate expected; the confidence interval for their survival overlapped the rates expected for an age- and sex-matched normal population.

Iron depletion could be documented by repeated liver biopsy in 185 of 251 patients. These 185 patients received 84.8 ± 4.4 (\pm SD) phlebotomies before iron depletion had been achieved. Thirty-four of the 251 patients died before iron depletion could be achieved. The majority of these early deaths were due to liver cirrhosis and cardiomyopathy. Although the amount of mobilizable iron could not be calculated in patients who died before iron had been depleted, the clinical features in almost all these patients indicated that they had severe iron overload (severity of complications and heavy iron deposition in the liver and heart). In a further 32 patients, mobilizable iron could not be calculated because iron depletion had not been completed by the end of the study. To evaluate the potential effects of phlebotomy treatment, two analyses were performed. (1) Assuming that 500 mL blood contains 250 mg iron, the mean number of phlebotomies (84.8 ± 4.4) in the 185 patients in whom complete iron depletion had been achieved cor-

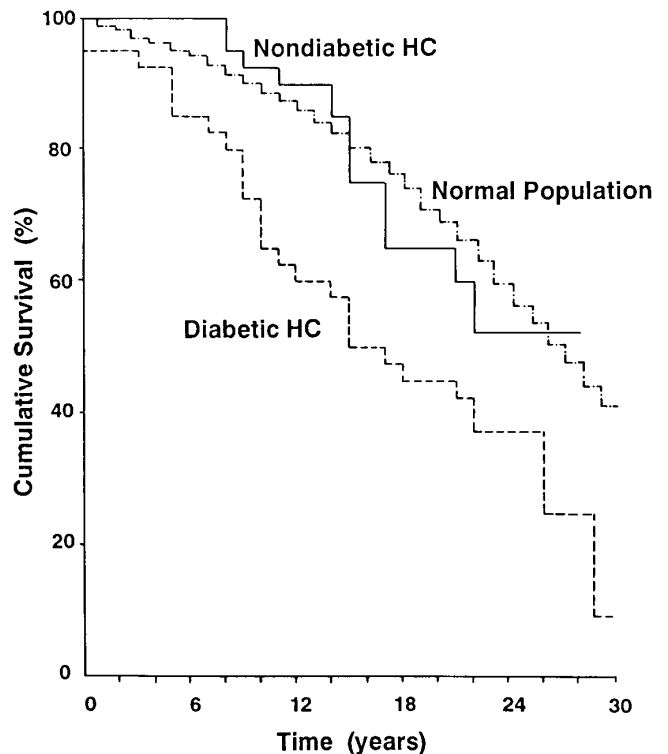


Figure 4. Cumulative survival in 120 diabetic and 131 nondiabetic patients with hemochromatosis. Survival was significantly reduced in diabetic patients when compared with nondiabetic patients ($P \leq 0.01$; log-rank test). The mean age and distribution of age were similar in both groups (46.0 ± 12.1 years [\pm SD] [range, 24–75 years] in diabetic patients vs. 45.4 ± 12.4 years [range, 18–77 years] in nondiabetic patients). Nondiabetic patients had a survival that was similar to that of a sex- and age-matched normal population (broken line), whereas diabetic patients had a reduced survival (expected survival rates lying outside the confidence intervals that are not shown in this figure for illustrative reasons).

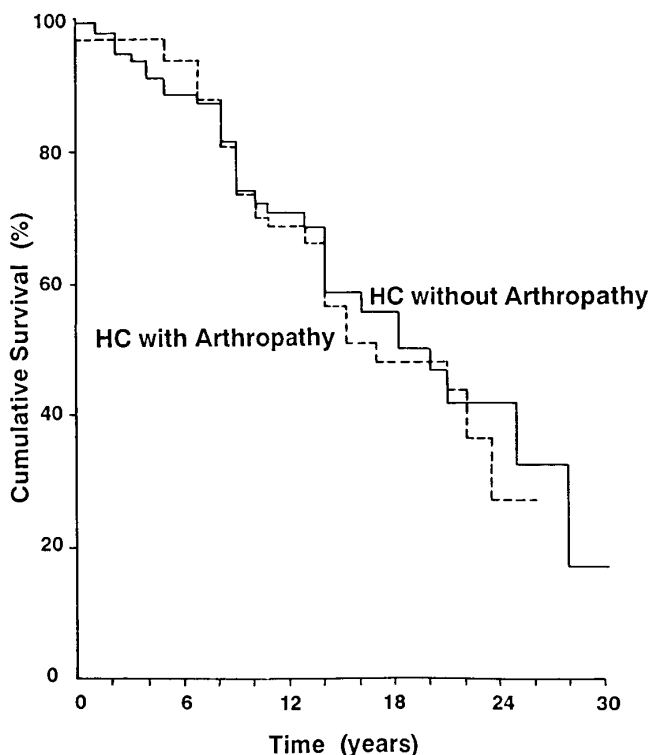


Figure 5. Cumulative survival in 111 hemochromatotic patients with arthropathy vs. 140 patients without arthropathy. Survival was virtually identical for patients with and without arthropathy ($P > 0.2$; log-rank test).

responds to 21.2 ± 1.1 g of mobilizable iron. Iron depletion had been achieved in 35 of the 69 patients who died; mobilizable iron was 29.1 ± 2.6 g in the patients who died and thus significantly higher when compared

Table 1. Total Amount of Iron Removed by Phlebotomies in 185 Patients With Biopsy-Documented Iron Removal and in Various Subgroups of Patients

All patients (n = 185)	Amount of iron (g)	P value
Subgroups		
Liver cirrhosis present	25.7 ± 1.7	≤ 0.001
Liver cirrhosis absent	14.8 ± 1.5	
Diabetes mellitus present	26.3 ± 1.7	≤ 0.001
Diabetes mellitus absent	16.5 ± 1.5	
Arthropathy present	21.4 ± 1.7	> 0.2
Arthropathy absent	20.9 ± 1.8	
Outcome		
Survived (n = 150)	19.4 ± 1.7	≤ 0.01
Died (n = 35)	29.1 ± 2.6	
Causes of death		
Liver cancer (n = 15)	32.9 ± 2.9	≤ 0.05
Other causes (n = 20)	26.1 ± 2.7	

NOTE. The amount of iron removed was calculated from the liters of blood withdrawn by repeated phlebotomies with the assumption that 1 L of blood contains approximately 500 mg iron (each phlebotomy of 500 mL blood refers to 250 mg iron). Data are shown as grams of iron in terms of mean values \pm SE for patients in whom iron depletion could be documented by repeated liver biopsy.

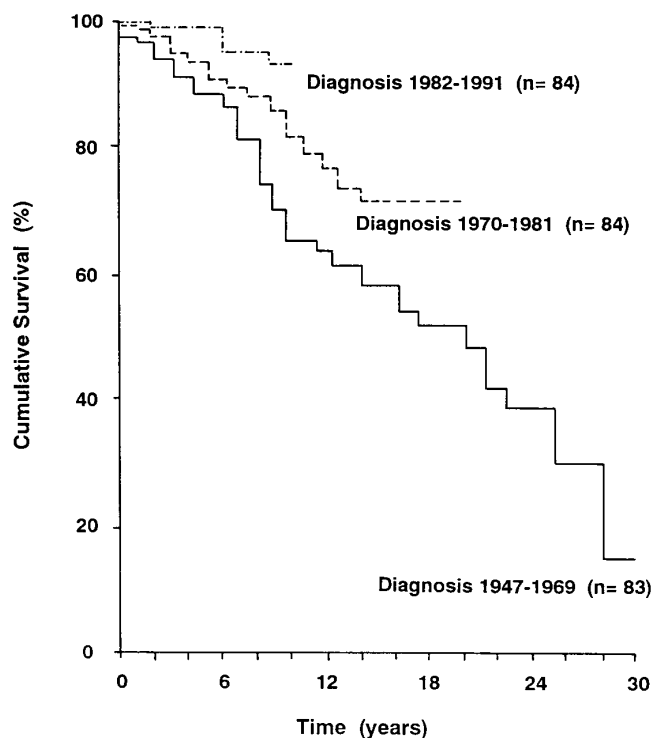


Figure 6. Cumulative survival in three subgroups of patients who were diagnosed in three different time periods: patients diagnosed between 1947 and 1969 (n = 83) had a reduced survival as compared with patients diagnosed between 1970 and 1981 (n = 84), and patients diagnosed between 1982 and 1991 had a better survival than the subgroups diagnosed earlier (log-rank test; $P \leq 0.05$).

with the 19.4 ± 1.7 g iron in the 150 iron-depleted patients who survived the study period ($P \leq 0.01$) (Table 1). (2) The effect of iron removal on survival was analyzed in those 185 patients in whom iron depletion had been achieved. The latter patients were divided into two approximately equal parts according to the number of phlebotomies: 91 patients had received < 80 phlebotomies and 94 patients had received > 80 phlebotomies. Patients with < 80 phlebotomies had a significantly better prognosis when compared with patients who needed > 80 phlebotomies for initial removal of iron ($P \leq 0.002$; log-rank test) (not shown as a figure).

Patients diagnosed between 1947 and 1969 (n = 83) had a reduced survival as compared with patients diagnosed between 1970 and 1981 (n = 84), and patients diagnosed between 1982 and 1991 had a better survival than the latter subgroups (log-rank test; $P \leq 0.05$) (Figure 6). Correspondingly, survival in the subgroup of patients diagnosed between 1982 and 1991 did not significantly differ from the rates expected for that period, whereas survival of patients diagnosed during the two earlier periods was significantly reduced (compare Figures 1 and 6; data not shown in a separate figure). A further analysis of the three subgroups showed that the percent-

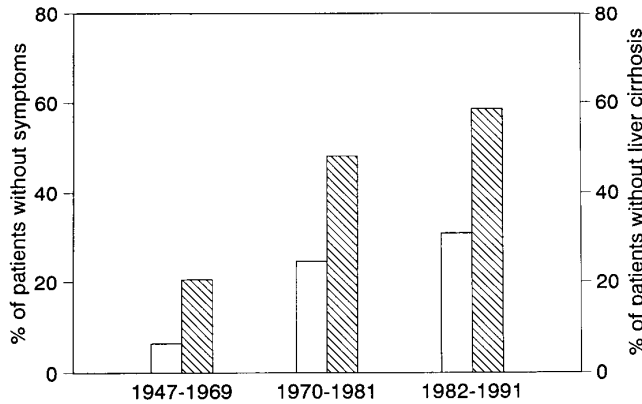


Figure 7. Early diagnoses in 251 patients with hemochromatosis defined as either absence of symptoms or absence of liver cirrhosis at the time of diagnosis. Data are shown as the percentage of asymptomatic and noncirrhotic patients diagnosed in three different time periods as indicated in the figure; see Materials and Methods for further details and number of patients. □, No symptoms; ▨, no cirrhosis.

age of patients without symptoms or cirrhosis at entry significantly increased during the study period (χ^2 test; $P \leq 0.05$) (Figure 7). The percentage of early diagnoses (both in terms of patients without cirrhosis and patients without symptoms) increased more than fourfold between 1947 and 1969 compared with the period between 1970 and 1981, whereas there was only a further 20%–25% increase between 1970 and 1981 compared with the period between 1982 and 1991.

Clinical and Laboratory Features

Almost all cirrhotic patients (95.1%) had symptoms at the time of diagnosis, whereas more than one third of noncirrhotic patients did not (Table 2). The two main complications of hemochromatosis, liver cirrhosis and diabetes mellitus, were closely related; at diagnosis, 83.5% of noncirrhotic patients did not have diabetes mellitus, whereas 71.8% of cirrhotic patients did (Table 3). Further clinical and biochemical features of the 251 patients with hemochromatosis as well as those of the subgroups with and without liver

Table 2. Relationship Between the Presence of Liver Cirrhosis and Diabetes Mellitus in 251 Patients With Hemochromatosis at the Time of Diagnosis

	Diabetes (%)		Total
	Present	Absent	
Cirrhosis			
Present	102 (71.8)	40 (28.2)	142 (56.6)
Absent	18 (16.5)	91 (83.5)	109 (43.3)
Total	120 (47.7)	131 (52.2)	251 (100)

NOTE. $\chi^2 = 73.4$; $P < 0.9 \times 10^{-15}$.

Table 3. Relationship Between the Presence of Liver Cirrhosis and Symptoms in 251 Patients With Hemochromatosis at the Time of Diagnosis

	Symptoms (%)		Total
	Present	Absent	
Cirrhosis			
Present	135 (95.1)	7 (4.9)	142 (56.6)
Absent	68 (62.3)	41 (37.6)	109 (43.4)
Total	203 (80.9)	48 (19.1)	251 (100)

NOTE. $\chi^2 = 42.5$; $P < 0.7 \times 10^{-10}$.

cirrhosis are shown in Tables 4 and 5. Among the main symptoms, weakness, lethargy, and loss of libido or potency were slightly more frequent in cirrhotic vs. noncirrhotic patients ($P \leq 0.05$), whereas abdominal pain was markedly more frequent in cirrhotic patients ($P \leq 0.01$) (Table 4). Physical and laboratory signs of liver disease, such as hepatomegaly, splenomegaly, jaundice, ascites, impaired liver function, increase in serum aminotransferase levels, and esophageal varices, were also significantly more frequent in cirrhotic patients (Tables 4 and 5). The occurrence of pigmentation, loss of body hair, and gynecomastia was not significantly different in both groups (Table 4). Plasma iron, transferrin saturation, serum ferritin, grade of liver iron staining, and amount of mobilizable iron were significantly higher in cirrhotic patients (P values given in Tables 1 and 5). Electrocardiographic changes were found in nearly half of cirrhotic patients but in only a small percentage of noncirrhotic patients (Table 4). Only 11% of the 251 patients had a markedly increased alcohol intake (more than 60 g per day). Alcohol consumption was similar in cirrhotic and noncirrhotic patients ($P > 0.2$) (Table 4).

The nonspecific symptoms of weakness, lethargy, and abdominal pain were reduced after the initial removal of iron in the majority of patients (Table 6). Signs of liver disease (e.g., elevation of serum aminotransferase levels and hepatomegaly) decreased in more than 70% of patients, whereas endocrine and arthropathic changes improved in only 19%–30% of patients after iron removal. Insulin dependency could be eliminated by iron removal in none of the patients, although the daily dose of insulin could be reduced in 41% of patients. On the other hand, less advanced changes in glucose metabolism, such as non-insulin-dependent diabetes mellitus and impaired glucose tolerance, could be improved in 37%–40% of patients (Table 6).

Liver Fibrosis, Liver Iron Concentration, and Amount of Mobilizable Iron

The stage of hepatic fibrosis corresponded both with the amount of mobilizable iron and liver iron concentration (Table 7). Also, mobilizable iron was closely

Table 4. Frequency of Clinical Features at the Time of Diagnosis in All Patients With Hemochromatosis and in the Subgroups of Cirrhotic and Noncirrhotic Patients

	Percent of all patients (n = 251)	Percent of patient subgroup		P value by Z test
		Cirrhotic (n = 142)	Noncirrhotic (n = 109)	
Symptoms				
Weakness, lethargy	82 (205)	88 (125)	73 (80)	≤0.05
Abdominal pain	56 (140)	68 (97)	39 (43)	≤0.01
Arthralgia	44 (111)	44 (62)	45 (49)	NS
Loss of potency	36 (81/224)	43 (55/127)	27 (26/97)	≤0.05
Amenorrhea	15 (4/27)	13 (2/15)	17 (2/12)	NS
Dyspnea on exertion	12 (31)	14 (20)	10 (11)	NS
Neurological symptoms ^a	4 (11)	6 (9)	2 (2)	NS
Physical findings				
Hepatomegaly	81 (203)	89 (127)	70 (76)	≤0.01
Pigmentation	72 (181)	75 (106)	69 (75)	NS
Loss of body hair	16 (39)	23 (33)	6 (6)	≤0.05
Splenomegaly	10 (26)	17 (24)	2 (2)	≤0.05
Peripheral edema	9 (23)	13 (18)	5 (5)	≤0.05
Jaundice	8 (19)	13 (18)	1 (1)	≤0.01
Gynecomastia	7 (15/224)	8 (10/127)	5 (5/97)	NS
Ascites	5 (13)	9 (13)	0 (0)	≤0.01
Other findings				
Electrocardiographic changes	35 (88)	46 (65)	21 (23)	≤0.01
Esophageal varices	12 (29)	20 (29)	0 (0)	≤0.001
Ethanol consumption				
<10 g/day	45 (114)	48 (68)	42 (46)	NS
10–60 g/day	44 (111)	42 (59)	48 (52)	NS
>60 g/day	11 (26)	13 (18)	7 (8)	NS

NOTE. Values given as percent of the corresponding subgroup; the raw number of patients is given in parentheses after the percentage value. NS, not significant.

^aDisorientation (n = 3), depression (n = 3), marked lethargy (n = 2), Parkinsonoid symptoms (n = 2), and hearing loss (n = 1).

related to the liver iron concentration in patients in whom quantitative measurements were done ($r = 0.69$; $P \leq 0.01$). The degree of fibrosis, staged from 0 to 3 (see Materials and Methods), was significantly reduced after removal of iron (Table 8). Of the 185 patients in whom complete iron removal was documented by a repeat biopsy, 42 patients showed a decrease of the fibrosis stage and only 2 patients showed progress (χ^2 , 33.19; $P = 0.000009625$) (Table 8).

Changes in Clinical Features and Mobilizable Iron During Different Time Periods

The percentage of asymptomatic patients significantly increased and the amount of mobilizable iron significantly decreased during the three different time periods of follow-up (1947–1969 vs. 1970–1981 vs. 1982–1991) (Figure 7 and Table 9). Corresponding to the increase of patients diagnosed with less severe iron overload, the percentage of patients with liver cirrhosis, diabetes mellitus, electrocardiographic changes, and loss of potency significantly decreased during the study periods (Table 9). In contrast, the percent-

age of patients with arthralgia did not change during the follow-up period (Table 9).

Causes of Death

The causes of death in 69 patients are listed in Table 10. Deaths caused by liver cancer (119 times more frequent), cardiomyopathy (14 times more frequent), liver cirrhosis (10 times more frequent), and diabetes mellitus (14 times more frequent) were significantly increased compared with the expected frequency in Germany (Table 10). Rates of other causes of death, including extrahepatic neoplasms, were not significantly different in patients with hemochromatosis compared with rates expected (Table 10). Thirty-four patients died before iron depletion had been achieved. The remaining 35 patients died after iron depletion had been documented by repeated liver biopsy. Nine of 13 patients who presented with ascites, splenomegaly, esophageal varices, and impaired liver function died before iron depletion could be completed. The 35 patients who died after complete removal of iron had a markedly increased amount of mobilizable iron compared with patients who survived (Table 1). The amount of mobilizable iron was

Table 5. Laboratory Findings at Diagnosis in Subgroups of Patients With Hemochromatosis

	All patients (n = 251)	Patient subgroups		P value by Z test
		Cirrhotic (n = 142)	Noncirrhotic (n = 109)	
Iron data				
Plasma iron ($\mu\text{g}/\text{dL}$)	221 \pm 5	231 \pm 7	208 \pm 8	≤ 0.05
Transferrin saturation (%)	90 \pm 1	94 \pm 2	85 \pm 3	≤ 0.05
Serum ferritin (ng/mL) ^a	2817 \pm 201	3383 \pm 258	2079 \pm 276	≤ 0.01
Grade of iron staining ^b	3.39 \pm 0.02	3.62 \pm 0.03	3.08 \pm 0.03	≤ 0.01
	Percent of all patients	Percent of patient subgroups		
Glucose metabolism				
Glucose tolerance test ^c				
Normal (n = 98) ^e	39 (98)	20 (28)	73 (80)	≤ 0.001
Abnormal (n = 33) ^e	13 (33)	13 (18)	14 (15)	NS
Diabetes mellitus (n = 120) ^d				
Non-insulin dependent (n = 51) ^e	48 (120)	72 (102)	17 (18)	≤ 0.001
Insulin dependent (n = 69) ^e	20 (51)	28 (39)	11 (12)	≤ 0.01
	27 (69)	44 (63)	6 (6)	≤ 0.001
Liver function				
Elevated serum aminotransferase levels ^e	60 (150)	68 (96)	49 (54)	≤ 0.05
Abnormal serum albumin or prothrombin time ^e	17 (43)	30 (42)	1 (1)	≤ 0.001

^aData obtained at time of diagnosis only for those patients who were diagnosed after 1976 (n = 129).

^bAccording to the method of Scheuer⁸ (scale of 0–4+).

^cAbnormal glucose tolerance was defined as a plasma glucose increase >200 mg/dL 2 hours after oral intake of 75 g glucose.

^dAccording to World Health Organization criteria, diabetes mellitus was defined as a fasting or postprandial plasma glucose >120 mg/dL and 200 mg/dL, respectively.

^eValues given as percent of the corresponding subgroup; the raw number of patients is given in parentheses after the percentage value.

calculated from the volume of blood withdrawn during initial phlebotomy treatment until iron removal was documented by liver biopsy (500 mL of blood considered to contain 250 mg of iron). In 15 of 19 patients who died from liver cancer, iron depletion had been achieved. In these 15 patients, the mean interval between documentation of iron depletion and development of liver cancer was 9.1 ± 4.5 years (\pm SD) (range, 3–19 years). The latter 15 patients had a markedly increased amount of mobilizable iron compared with patients who survived and with patients who died from other causes (Table 1).

All hepatic malignancies developed in patients with liver cirrhosis. In addition to the 19 patients who died from liver cancer (16 with hepatocellular carcinoma and 3 with carcinoma from intrahepatic bile ducts), there were two additional biopsy-proven cases of hepatocellular carcinoma in patients who were alive at the end of the study. Hepatitis B surface antigen was absent in serum in all 21 patients who died from liver cancer. Hepatitis B core antibodies could be detected in 5 of the 21 patients. Serum could be analyzed for hepatitis C antibodies in 11 of the latter 21 subjects, none of whom had hepatitis C antibodies.

Discussion

The present cohort study followed up 251 patients with hemochromatosis for up to 33 years (mean, 14.1 years). Mean survival was 21.0 years and thus approximately 2 years

longer than in our previous report.¹ Similar to our previous study¹ and two other recent reports,^{2,3} survival in noncirrhotic and nondiabetic patients was significantly better compared with cirrhotic and diabetic patients and was virtually identical with the survival expected for a sex- and age-matched normal population. Prognosis of hemochromatotic patients was influenced neither by sex nor by arthropathy. Thus, the present results further support the value of early diagnosis and prophylactic iron removal in patients with hemochromatosis. Although the survival in the total group of patients with hemochromatosis is still significantly lower as compared with a matched normal population, survival gradually increased during the long-term follow-up of the present cohort study. Indeed, survival in patients with hemochromatosis diagnosed during the last decade of the study (1982–1991) was not significantly different from a matched normal population. However, it has to be kept in mind that patients diagnosed during the last decade could only be followed up for 10 years or less; thus, it remains to be seen whether long-term survival in this subgroup remains normal after 20 or 30 years of follow-up. In addition, several patients were still diagnosed with liver cirrhosis and insulin-dependent diabetes mellitus in the most recent period from 1982 to 1991. Thus, despite the statistically normal life expectancy in patients diagnosed during the most recent decade, there was still a significant morbidity that supports the need to improve the rate of early diagnosis.

Table 6. Changes in Clinical Features During Initial Treatment Period in 183 Patients With Biopsy-Proven Iron Depletion

	Percent at time of diagnosis	Percent after depletion or iron ^a		
		Improved	Unchanged	Worsened
Weakness or lethargy				
Present	80 (146)	55 (77)	40 (59)	6 (9)
Absent	20 (37)	—	86 (32)	14 (5)
Abdominal pain				
Present	56 (102)	68 (70)	29 (30)	1 (2)
Absent	44 (81)	—	98 (79)	2 (2)
Arthralgia				
Present	45 (82)	30 (25)	50 (41)	20 (16)
Absent	55 (101)	—	86 (87)	14 (14)
Elevated aspartate aminotransferase or alanine aminotransferase levels				
Present	81 (148)	73 (108)	25 (37)	2 (3)
Absent	19 (35)	—	94 (33)	6 (2)
Pigmentation				
Present	68 (124)	68 (84)	32 (40)	0 (0)
Absent	32 (59)	—	100 (59)	0 (0)
Loss of potency (163 men)				
Present	40 (65)	19 (12)	69 (45)	12 (8)
Absent	60 (98)	—	86 (84)	14 (14)
Electrocardiographic changes				
Present	35 (64)	34 (22)	61 (39)	5 (3)
Absent	65 (119)	—	98 (117)	2 (2)
Diabetes mellitus (n = 81)	44 (81)	41 (33)	53 (43)	6 (5)
Insulin dependent	25 (46)	41 (19) ^b	50 (23)	10 (4)
Non-insulin dependent	19 (35)	40 (14)	57 (20)	3 (1)
Glucose tolerance (n = 101)	56 (101)	10 (10)	87 (88)	3 (3)
Impaired	15 (27)	37 (10)	56 (15)	7 (2)
Normal	40 (74)	—	99 (73)	1 (1)

NOTE. Sufficient follow-up information could not be obtained from 2 of the 185 patients with biopsy-proven iron depletion. Values given as percent of the corresponding subgroup; the raw number of patients is given in parentheses after the percentage value.

^aData obtained from a 6-month period after the end of the initial phlebotomy period.

^bThe daily insulin dose could be reduced in 19 of the 46 insulin-dependent patients, but insulin dependency could be abolished in none of the patients.

The increase in survival during the three time periods of the study is likely to be explained by a corresponding increase in the percentage of asymptomatic patients and likewise by a corresponding decrease in the severity and duration of iron excess, which was calculated by the amount of mobilizable

iron. The present data also confirm that the amount of mobilizable iron is closely related to the liver iron concentration. Because the reduced frequency of patients with severe iron excess was closely related to a reduced frequency of patients diagnosed with liver cirrhosis, diabetes mellitus, electrocar-

Table 7. Mobilizable Iron and Liver Iron Concentration (at Diagnosis) According to Different Stages of Hepatic Fibrosis

Stage of hepatic fibrosis	Mobilizable iron		Liver iron concentration	
	No. of patients	Mobilizable iron (g)	No. of patients	Liver iron (mg/g dry wt)
0	11	10.1 ± 0.9	7	11.6 ± 1.8
1	32	13.7 ± 1.3	10	13.9 ± 1.1
2	39	17.4 ± 1.5	9	16.9 ± 1.4
3	93	25.7 ± 1.7	15	22.4 ± 2.0
All patients	185	21.1 ± 1.1	41	16.1 ± 1.6

NOTE. The mobilizable iron was calculated from the number of phlebotomies in 185 hemochromatotic patients in whom a repeated liver biopsy revealed complete iron depletion (for details, see Materials and Methods). Quantitative liver iron concentrations were available only for patients diagnosed after 1984 (for details, see Materials and Methods). For definition of the stages of hepatic fibrosis, see Materials and Methods. There was a stepwise significant increase in both the amount of mobilizable iron and the liver iron concentration with progression of the stages of fibrosis found by *t* test results ($P < 0.05$ for all comparisons).

Table 8. Changes in Fibrosis Stage Due to Iron Removal in 185 Patients in Whom a Repeated Liver Biopsy Showed Complete Iron Depletion

Fibrosis stage	At diagnosis (%)	After documentation of iron removal (%)	Improved	Worsened	Unchanged	Total
0	21/185 (11.4)	30/185 (16.2)	0	1	20	21
1	32/185 (17.3)	42/185 (22.7)	10	1	21	32
2	39/185 (21.8)	32/185 (17.3)	20	0	19	39
3	93/185 (50.2)	81/185 (43.8)	12	0	81	93
Total			42	2	141	185

NOTE. $\chi^2 = 33.19$; $P = 0.000009625$.

diographic changes, and loss of potency, iron overload in hereditary hemochromatosis seems to be a gradual process that increasingly leads to complications as the iron excess progresses.

The analysis of cases with early diagnosis shows that the diagnostic progress has slowed down in the last decade when compared with previous decades. Early diagnosis was defined as biopsy-proven hemochromatotic patients without symptoms or cirrhosis. There was a more than fourfold increase in early diagnoses from 1947 to 1969 compared with the period of 1970–1981. This marked improvement is probably explained largely by advances in the understanding of the inheritance of the disease and by introduction of serum ferritin as a noninvasive test for quantitative assessment of iron stores.^{20–22} Although there was some further increase in the percentage of patients with asymptomatic and noncirrhotic disease from 1982 to 1991, this increase was much smaller than during the preceding decades. Several noncirrhotic patients were detected in rheumatology clinics, which routinely determine serum ferritin levels in patients with arthralgia. Most patients without symptoms were diagnosed by screening in families with an already diagnosed hemochromatotic patient. It is certainly important to further support “screening” in subgroups of persons who have symptoms and findings that are often found in hemochromatosis, such as arthralgia or diabetes mellitus.^{23–25} A certain percentage of these patients will be detected without liver cirrhosis. The screening of siblings of a patient with hemochromatosis is mandatory and may yield an even higher percentage

of asymptomatic disease.²⁶ Both of these two “screening” approaches, however, will result only in limited improvement as shown by the present results because they either rely on some symptoms and findings or they require a family case of symptomatic disease. Further improvement in early diagnosis and thus better long-term outcome will only be possible when screening of nonselected subjects is performed in the general population.²⁷ Determinations of serum ferritin and transferrin saturation are as yet the most efficient laboratory values to be used for early diagnosis; both values will indicate the disease with some certainty, however, only in subjects older than a certain age when iron stores have accumulated to a degree that these laboratory values exceed the upper limit of normal.²⁷ Only the identification of the genetic abnormality will allow the exact identification of homozygous patients independent of age. Until the genetic abnormality can be detected by a reliable and easy test, screening programs may consist of measurements of serum ferritin and transferrin saturation levels, for example, when subjects are examined at work, for insurance reasons, or for a checkup by a primary care physician.

The prognosis of untreated hemochromatosis is poor.²⁸ Although the beneficial effect of iron removal has never been proven by controlled trials, the present data and other recent studies^{1–3} strongly suggest that early diagnosis and iron removal markedly improve survival and may offer the patient a normal life expectancy provided that the patient is diagnosed without having liver cirrhosis. There are no data on the natural history of untreated hemochromatosis in noncirrhotic patients; such patients

Table 9. Changes in Clinical Features and Mobilizable Iron During Three Different Time Periods of Follow-up

	1947–1969 (n = 84)	1970–1981 (n = 84)	1982–1991 (n = 83)	Total (n = 251)	χ^2 value	P value
Liver cirrhosis	79.8% (67/84)	48.8% (41/84)	41.0% (34/83)	56.6% (142/251)	28.7	0.59×10^{-6}
Diabetes mellitus	73.8% (62/84)	39.2% (33/84)	30.1% (25/83)	47.8% (120/251)	35.6	0.18×10^{-7}
Electrocardiographic changes	48.8% (41/84)	32.1% (27/84)	24.1% (20/83)	35.1% (88/251)	12.96	0.20×10^{-2}
Arthralgia	39.3% (33/84)	45.2% (38/84)	48.2% (40/83)	44.2% (111/251)	1.34	0.49
Loss of potency	57.3% (43/75)	30.7% (23/75)	20.3% (15/74)	36.2% (81/224)	23.6	0.74×10^{-5}
Diagnosis of asymptomatic patients	4.8% (4/84)	22.6% (19/84)	30.1% (25/83)	19.1% (48/251)	18.4	0.10×10^{-3}
Mobilizable iron (g)	25.5 ± 1.8	20.7 ± 1.7	17.1 ± 1.4	21.2 ± 1.1	t test	≤ 0.01

may differ from those in whom cirrhosis develops, and their "normal life expectancy" may not be a direct result of phlebotomy therapy. Although there is no experimental or epidemiological support for this hypothesis, the issue cannot be definitely settled because of ethical considerations; it is accepted treatment to deplete these patients of their excess iron.

The prognosis of cirrhotic patients was also remarkably good. Their life expectancy was at least 5 years longer than that reported in older studies^{29–31} and 10–20 years longer than that reported for other forms of liver cirrhosis, in particular the alcoholic form.^{32–34} The improved survival in cirrhotic patients as compared with patients in older reports is probably due to the fact that some of these patients were identified by "screening methods" and thus at an earlier stage than patients identified because of symptoms. The present survival data are similar to two other recently published series.^{2,3}

The data on the patients' clinical features show that arthralgia was as common in cirrhotic as in noncirrhotic patients, whereas symptoms due to liver disease, diabetes

mellitus, and cardiac or endocrine complications were more common in patients with cirrhosis. This suggests that arthralgia often is an early symptom. This hypothesis is also supported by data showing that the amount of mobilizable iron was similar for patients with and without arthropathy and by data showing that the percentage of patients with arthralgia did not change during the follow-up period, although the rate of noncirrhotic patients markedly increased.

In contrast to arthropathic patients, both cirrhotic and diabetic patients showed a marked increase in mobilizable iron that exceeded that in noncirrhotic and nondiabetic patients by more than 40%, respectively. Plasma iron concentration, transferrin saturation, serum ferritin level, and grade of liver iron staining were also higher in cirrhotic vs. noncirrhotic disease; however, because the values for one group overlapped those for the other, these indexes cannot be used to make any prediction concerning the course of the disease.

The development of the two major complications of hemochromatosis, liver cirrhosis and diabetes mellitus, was appar-

Table 10. Death Rates in 251 Patients With Hemochromatosis Compared With Expected Rates in the Normal Population (Germany) According to Cause of Death

Cause of death	No. of deaths expected	No. of deaths observed	95% Confidence limits for observed deaths	Mortality ratio (observed/expected)
All causes	24.7	69	53.7–86.2	2.79
Neoplasms	8.21	27	17.8–38.1	3.29
of liver	0.16	19	11.4–28.4	118.75
of other sites	8.05	8	3.4–14.4	0.99
Diabetes mellitus	0.29	4	1.1–8.8	13.79
Diseases of the circulatory system	7.41	14	7.6–22.4	1.97
Cardiomyopathy	0.36	5	1.6–10.2	13.9
Myocardial infarction	3.21	4	1.1–8.8	1.27
Others	3.84	5	1.6–10.2	1.40
Diseases of the digestive system	2.50	18	10.7–27.2	7.2
Liver cirrhosis	1.40	14	7.6–22.4	10.00
Others	1.10	4	1.1–8.8	3.64
Trauma	1.15	3	0.6–7.3	2.61
Others	5.14	3	0.6–7.3	0.58

ently closely related. Most patients with cirrhosis at entry also had diabetes mellitus, whereas only a few noncirrhotic patients had it. Cirrhotic patients were symptomatic significantly more often than noncirrhotic patients; the latter relationship was similar for diabetic vs. nondiabetic patients. Patients with diabetes or cirrhosis at diagnosis also had larger iron excess than did patients without these complications. Thus, the presence of both liver cirrhosis and diabetes mellitus were closely associated with the amount of mobilizable iron. Similarly, the stage of hepatic fibrosis was correlated both with the amount of mobilizable iron and with the liver iron concentration. A recent study further supports this relationship by showing that a threshold value of >500 $\mu\text{mol/L}$ iron/g liver is necessary to induce fibrosis.¹¹ In noncirrhotic patients, signs of liver disease often completely disappeared after removal of iron. In cirrhotic patients, iron removal also frequently improved many signs of liver disease. In the total group of patients, nonspecific symptoms and skin pigmentation were reduced in the majority of patients after iron had been removed, whereas symptoms from arthropathy and impotence were improved less frequently. Consequences of liver failure or portal hypertension were infrequent at diagnosis. However, if present, they usually did not respond to iron removal. Patients with less advanced changes in glucose metabolism that may be due to liver disease³⁵ responded well to iron removal and thus probably to improvement in liver disease; iron removal, however, never reversed insulin dependency, potentially because of irreversible destruction of pancreatic β cells by preceding iron excess.³⁶

The degree of fibrosis, staged from 0 to 3 (see Materials and Methods), was reduced after iron removal in 42 of the 185 patients in whom complete iron removal had been documented by repeat biopsy. Reversal of cirrhosis has previously been documented by repeat laparoscopy in a subset of patients treated in one of the medical centers (Heinz Kalk-Klinik).^{37,38} Because laparoscopy was not routinely performed for reevaluation of patients at the other center (University of Düsseldorf), the present study does not specifically deal with the question of reversal of cirrhosis.

There were two major causes of death. Patients who presented with major complications of liver cirrhosis or cardiomyopathy had the worst early prognosis; in this subgroup, many patients died before completion of iron removal. The other major cause of death was cancer of the liver. In addition to the 19 patients who died from liver cancer, the present cohort of patients includes two additional biopsy-proven cases of hepatocellular carcinoma in male patients who were still alive at the end of the observation period. Iron depletion had been documented in 17 of the 21 patients with liver cancer. The mean interval between iron depletion and development

of liver cancer was 9.4 ± 4.8 years in these 21 patients. Thus, the great majority of liver cancers developed in livers that were depleted of iron for many years. As in our previous report, all 21 cases of liver cancer developed in cirrhotic livers.¹ Although there are a few case reports about development of cancer in a noncirrhotic liver in hemochromatosis,^{4,5} the risk is mainly restricted to cirrhotic patients. In addition to the presence of cirrhosis, development of liver cancer may depend on the amount and duration of iron overload because patients who died from liver cancer had significantly greater iron stores than patients who died from other causes. The present analysis does not support recent hypotheses that the hepatitis B or C virus^{3,6,7} plays a role for the increased risk of liver cancer. Cardiac failure due to cardiomyopathy was a relatively infrequent cause of death in our series, although it was significantly more frequent than expected. Similar to our previous analysis¹ and in contrast to an older report in a smaller series of patients,³⁹ the frequency of extrahepatic carcinomas was virtually identical with the rate expected. This suggestion is supported by a short report about an Australian cohort of patients with hemochromatosis that also failed to show an increased risk for extrahepatic malignancies.⁴⁰

The present findings suggest that prognosis and complications of hemochromatosis, probably including the development of liver cancer, depend on the amount of iron excess and on the point at which iron accumulation is interrupted by phlebotomy. Patients who died during the study showed a marked increase in mobilizable iron as compared with surviving patients. Furthermore, survival was markedly reduced in patients who could not be depleted of iron after >80 phlebotomies due to a large iron excess vs. those who could be depleted by <80 phlebotomies. In addition, the present data show that cirrhotic and diabetic patients had a markedly greater iron excess compared with patients who did not have these complications at diagnosis. Correspondingly, prognosis in noncirrhotic patients was markedly better than that in cirrhotic patients and could not be distinguished from that expected for a matched normal population. These data strongly suggest that early diagnosis and removal of excess iron can improve the patient's prognosis to normal life expectancy and largely prevent most complications of iron overload. The present analysis, however, also shows that the increase in rates of early diagnosis has slowed down during recent years, suggesting that further improvement will require screening of nonselected subjects in the general population.²⁵

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- Received May 15, 1995. Accepted November 20, 1995.
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 Supported by the Deutsche Forschungsgemeinschaft (Ni 224/6-1 and 224/6-2 to C.N.).
 Dedicated to Prof. Dr. h. c. Wolfgang Gerok on the occasion of his 70th birthday.