Natural History of Chronic Hepatitis C

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Much controversy surrounds the issue of the natural history of hepatitis C virus (HCV) infection. Many authorities view the disease as inexorably progressive with a high probability of advancing over time to cirrhosis and occasionally hepatocellular carcinoma (HCC) and, therefore, likely to be responsible for causing death. Others regard chronic hepatitis C as having a variable outcome, the majority of infected persons not dying from the disease, but more likely from the comorbid conditions that so often accompany infection by this agent, or from more common medical conditions. Disagreements probably derive from the manner of conduct of the study and the populations studied. Efforts to determine natural history are handicapped by the primary characteristics of the disease, namely that its onset rarely is recognized and its course is prolonged exceedingly. Thus, different outcomes have come from retrospective rather than from prospective studies, but both have concluded that at least 20% of chronically infected adults develop cirrhosis within 20 years. More recent studies that used a retrospective/prospective approach, focusing largely on young infected individuals, have produced different results. Among these young people, particularly young women, spontaneous resolution of the viral infection is more common than previously thought and cirrhosis has been identified in 5% or fewer of them. The major failing for all groups studied, young and old, is that natural history studies have rarely exceeded the first 2 decades, so that outcome beyond this time is not known, other than through modeling. Several host-related and extraneous factors probably affect the natural history. (HEPATOLOGY 2002;36:S35-S46.)

An issue of much concern for any disease, particularly if it has a strong component of chronicity, is to be able to define its natural history. Knowledge of the long-term outcome of the disease is profoundly important for the both the patient and the physician. The patient needs the information for future planning purposes as well as to provide help in evaluating the treatment options; the physician needs the information to be able to inform the patient of the consequences as well as to assess the need for treatment, its urgency, and its stringency. Clearly, the more serious the expected outcome, the more willing is the physician to recommend treatment, even if it is only moderately effective and even if associated with potentially serious side effects.

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; CI, confidence interval.

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0270-9139/02/3605-1005$35.00/0

doi:10.1053/jhep.2002.36806

Requirements for Determining Natural History

Certain items of information must either be known or must be acquired to accurately determine natural history.[1] This includes the ability to identify onset of the disease, to have an indicator that marks the existence of the chronic disease if it is not otherwise recognized, to be able to track the full course of the disease, to have the disease unmodified either by treatment or by comorbid conditions, and to be able to identify and record associated endpoint morbidity and mortality events. Unfortunately, certain characteristics of hepatitis C virus (HCV) infection create difficulties in fulfilling many of these requirements.[2]

Impediments to Determining the Natural History of Hepatitis C

The majority of persons who develop acute hepatitis C are unaware of this fact, so that disease onset is rarely identified other than through assumption, based on the potential circumstance of exposure. Progression from acute to chronic hepatitis traditionally is defined as persistence of increased levels of the aminotransferases for 6 months or more but more appropriately now by the persistence of HCV in the blood beyond that time period; failure of the virus to clear occurs in 54% to 86% of cases

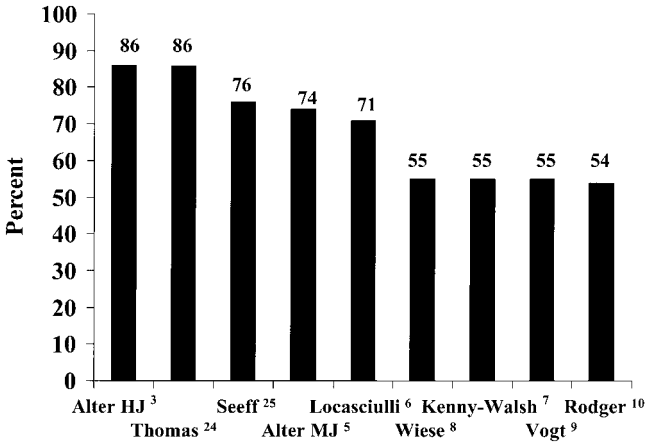

Fig. 1. Rates of persistence of hepatitis C virus infection after acute hepatitis C.[3,5-10,25]

of acute hepatitis C (Fig. 1).[3-10] Transition from acute to chronic hepatitis almost always occurs in the absence of symptoms. Thereafter, the chronic phase that evolves lasts many decades, culminating eventually, in some infected individuals, in the development of overt end-stage liver disease (essentially orchestrated by the development of cirrhosis), or persisting until death ensues from another cause. Evolution to cirrhosis itself also generally occurs without symptoms, and the presence of cirrhosis may remain unrecognized until the liver becomes sufficiently compromised to advance to overt hepatic decompensation. Decompensation may occur soon or, more usually, several years after cirrhosis is recognized. Therefore, virtually a lifetime of follow-up evaluation is required to fully establish the entire spectrum of liver-related consequences (or lack thereof).

Acquiring valid information on the natural history of chronic hepatitis C is made difficult not only by the long duration needed to gather the information but also by the fact that commonly there are accompanying factors that can modify the course, thus creating an unnatural history of hepatitis C. These include the now common use of antiviral treatment, the fact that HCV infection is frequently associated with other similarly transmitted viral infections such as the hepatitis B virus (HBV) and the human immunodeficiency virus (HIV), and the fact that heavy alcoholism is a common accompaniment among some subgroups of infected individuals. Taking all these items into account, it should not be surprising that there has been much difficulty in reaching an agreement on the long-term consequences of chronic HCV infection and that these difficulties have created controversy regarding the true natural history of hepatitis C. Some investigators describe common evolution to end-stage liver disease or hepatocellular carcinoma (HCC)[11-15]; others perceive these outcomes to be less frequent.[16-19] It is probable that both of these views are valid, the variance accounted for by differences in the disease stage and the types of populations studied.

Focus of Concern of Chronic Hepatitis C

The primary item of concern for patients with chronic hepatitis C, as it is for many other forms of chronic liver disease, is the occurrence and slow evolution of fibrosis over many years, culminating in cirrhosis. Although the liver histopathology in persons with chronic hepatitis C shows both inflammation and fibrosis, it is the latter that is the factor of greater concern. Inflammation certainly plays a role in the evolving fibrosis, but its presence has no direct effect on the well-being of the infected person. In contrast, portal hypertension, other features of liver failure, the need for liver transplantation, and progression to HCC rarely occur in the absence of cirrhosis. Thus, the natural history is a reflection of the fibrosis status and its progression.

The question of whether chronic hepatitis C *per se* has a negative impact on the quality of life has been an item of inquiry. By using questionnaire instruments specifically designed for this purpose, some investigators have reported that the quality of life is unquestionably compromised,[20,21] but these surveys have been conducted among persons with full knowledge of, and therefore concern about, the chronic infection. Other reports have been less compelling. One important survey conducted in Australia found little evidence that quality of life among persons who had not yet developed cirrhosis was impaired when the survey was administered to infected persons not yet aware of their hepatitis status, whereas it was significantly reduced in a paired group who were informed that they were infected.[22]

Approaches Used to Study the Natural History of Hepatitis C

The ideal method to define the natural history of hepatitis C would be to identify a large cohort of persons of both sexes and of differing ethnicities who are recognized to have acute hepatitis C, and then to follow up these people prospectively, without treatment, until the entire group have achieved a hepatic endpoint or have died, permitting accurate determination of cause of death. For obvious reasons, as described earlier, this is not a tenable approach. Therefore, alternative strategies have been used that have included retrospective and prospective studies and, more recently, a combination of these 2 approaches, retrospective-prospective cohort studies (Fig. 2).

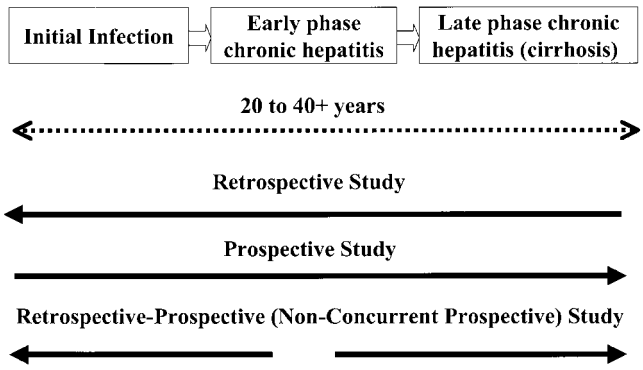

Fig. 2. Strategies used to determine the natural history of hepatitis C.

Retrospective Studies. The first strategies attempted were the retrospective studies, almost all of which were undertaken in academic centers by established investigators, focusing attention on individuals who entered or who were referred to the institution because of their liver disease (Table 1).[11-15] By using this approach, efforts were made to track the liver disease responsible for the referral back to the presumed time of infection, based on the history of first receipt of blood or blood product or of the first use of injection drugs. From this analysis it was possible to draw conclusions on the disease duration and assess the role of many factors on the extent of identified liver disease. Several of these studies were able to trace patients back to the presumed initiation of their infection 20 to 30 years earlier. In a representative group of studies (Table 1),[11-15] cirrhosis was identified to have occurred in 17% to 55% (mean 42%) of the chronically infected persons, HCC in 1% to 23%, and liver-related death in 4% to 15%. Clearly, these data created much consternation. Although they were compelling studies, the results might well have been compromised by the fact that the actual timing of the original acute illness was based on presumption rather than on fact, and that the high rate of identified serious liver disease might have been the result, at least in part, of ascertainment bias because these tertiary care centers were likely to attract patients with overt liver disease of concern but would not be privy to patients with minimal disease not warranting referral.

Prospective Studies. Another group of investigators attempted to address the natural history issue by conducting prospective studies beginning with identified cases of acute transfusion-associated non-A, non-B, or type C hepatitis (Table 1).[16-19] These studies yielded dramatically different outcomes. Again, in a representative group, cirrhosis developed in 7% to 16% (mean, 11%), HCC in 0.7% to 1.3%, and liver-related death in 1.3% to 3.7%. Although the prospective study format represents the preferred approach to studying natural history, the failing of these studies was that their duration of follow-up evaluation was relatively short, ranging between 8 and 16 years, far too short a time to accurately determine outcome. Nevertheless, the data that emerged from them were somewhat more comforting.

Retrospective-Prospective Studies. Even more reassuring are the results of a series of retrospective-prospective cohort studies. These were made possible by the ability to identify reasonably large groups of individuals who, in the past, had developed recognized acute hepatitis C, who could be traced retrospectively, recontacted, and then followed-up prospectively. It is noteworthy that, among 7 representative such studies 6 involved young people (one, young children; 2, young women; 2, young injection drug users; one, young men with community-acquired hepatitis C),[7-10,23,24] and one, middle-aged persons who had developed transfusion-associated hepatitis C (Table 2).[25]

Study Among Young Children. In one study, stored sera from 458 young people who had undergone cardiac surgery during their first 3 years of life were tested for the presence of antibody to hepatitis C (anti-HCV).[9] Sixty-seven (14.6%) of the original samples were found to be positive. The follow-up samples 20 years later revealed that HCV RNA was detectable in 37 (55%) and undetectable in 30 (45%). None had been treated for hepatitis C. Among the viremic individuals, only one had increased alanine aminotransferase (ALT) levels. A liver biopsy examination was performed in 17 of the viremic patients, revealing the presence of fibrosis in 2 and of cirrhosis in only one.

Studies Among Young Women. A low frequency of cirrhosis also was found in 2 studies involving young women who had received HCV-contaminated Rh immunoglobulin (Fig. 3).[7,8] Among a group of 62,667 Irish women who presented for hepatitis C screening during the course of a national inquiry after recognition of use of the contaminated material, 704 were found to be anti-HCV positive, but only 390 (55%) were also HCV-RNA

Table 1. Early Retrospective and Prospective Studies of the Natural History of Hepatitis C

Retrospective studies[11-15]	
Intervals from exposure	9-29 y
Development of cirrhosis	17% to 55% (mean, 42%)
Development of HCC	1% to 23%
Liver-related death	4% to 15%
Prospective studies[16-19]	
Intervals from exposure	8-16 y
Development of cirrhosis	7% to 16% (mean, 11%)
Development of HCC	0.7% to 1.3%
Liver-related death	1.3% to 3.7%

Table 2. Retrospective-Prospective Cohort Studies of the Natural History of Hepatitis C

Study	Group	Exposure Interval (y)	Cirrhosis %		HCC %	Liver Death %
Vogt[9]	Children	17	mean, 2.1%	0.3	0	0
Kenny-Walsh[7]	Young women	17		2.0	0	0
Wiese[8]	Young women	20		0.4	0	0
Seeff[23]	Young men	45-50		5.9	0	0
Thomas[24]	IDU	9-15		1.0	0	2.1
Rodger[10]	Comm acq	25		4.0	0	1.0
Seeff[25]	PTH	23		15.0	1.9	2.8

Abbreviations: IDU, injection drug users; Comm acq, community acquired; PTH, post transfusion hepatitis.

positive.[7] A total of 376 of them were studied further, revealing that 45% had normal ALT values, 47% had values between 40 and 99 IU/mL, and only 8% had values in excess of 100 IU/mL. More importantly, liver biopsy examinations in 363 of them revealed that 49% had no fibrosis, 34% had periportal or portal fibrosis, 15% had bridging fibrosis, and only 2% (7 women) had cirrhosis. Two of these latter 7 women were also heavy alcoholics.

Similar findings were seen in a 20-year follow-up evaluation of East German women who also had received contaminated immunoglobulin (Fig. 3).[8] Among 2,867 women who received the preparation, 1,018 were recalled for further evaluation, 917 of whom had developed increased ALT values within 4 months of receipt of the contaminated product. The remainder (10%) had neither increased ALT values nor detectable HCV markers. Twenty years later, 53% of the group with an original diagnosis of acute hepatitis had normal ALT values, 9% had fluctuating values, and 38% had elevated values. Anti-HCV was still detected in 85% and HCV RNA in 55%. Among 220 women with chronic viremia who underwent liver biopsy examination, 50% had no fibrosis, 47% mild fibrosis, and 3% discrete or marked bridging fibrosis. None had cirrhosis.

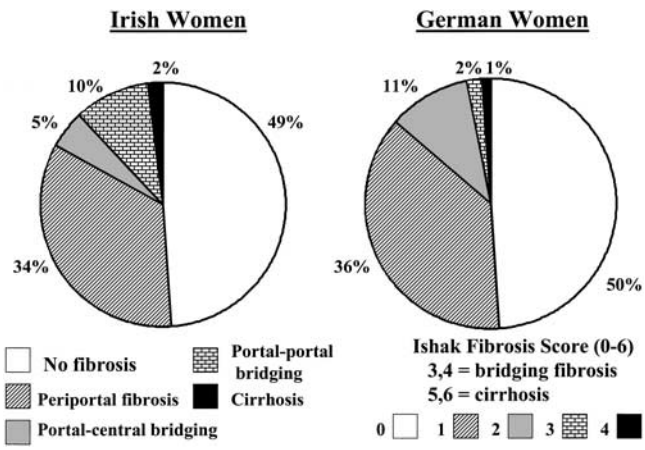

Fig. 3. Liver biopsy results among Irish and German women 17 and 20 years, respectively, after onset of HCV infection from contaminated anti-D immune globulin.[7,8]

Continued follow-up evaluation of these 2 groups of women to determine whether the frequency of cirrhosis will increase with time and whether there will be a significant rate of development of HCC is clearly of profound importance.

Studies of Young Injection Drug Users. In a community-based cohort study involving 1,667 anti–HCV-positive injection drug users in Baltimore, MD, 919 subjects were assessed during a median follow-up evaluation of 8.8 years, although it was believed that HCV infection had existed for greater than 15 years for 75% of the subjects.[24] Over the course of this time period, approximately 10% spontaneously cleared the virus, the virus persisted in 79%, and the viral status was not resolved in the remainder. Viral clearance was lower in African Americans and in those infected with HIV. End-stage liver disease occurred in 40 persons (4.4% of the cohort), the risk being greater in those over the age of 38 years and those who reported ingestion of more than 260 g of alcohol per week. Thirty-five of the 40 individuals died of liver disease, but these represented less than 10% of the total number of deaths, the remainder being caused by HIV infection (40%), drug overdose (19%), HIV-related opportunistic infections (12%), and miscellaneous causes. Among 210 patients without overt end-stage liver disease who underwent liver biopsy examination, cirrhosis was identified in only 2%. Thus, this study not only showed a surprisingly low rate of development of cirrhosis, but it also pointed to the high rate of competing reasons for mortality among certain infected groups, non–liver-related deaths far exceeding the number of deaths caused by liver disease. This is a theme carried into other risk groups, as is noted later.

A similarly low rate of liver disease progression was found in a long-term follow-up study of persons with acute viral hepatitis, predominantly injection drug users, conducted in Australia.[10] Ninety-five persons admitted to a hospital in Melbourne with acute hepatitis, whose original stored sera tested anti–HCV-positive, were traced approximately 25 years later. At this time, HCV RNA was detected in 51 (54%), indicating that 44 (46%) had spon-

taneously lost the virus. Among the chronically infected group, 35 (69%) had increased ALT values. Cirrhosis was identified in 4 (8%), all among those with increased ALT values. In contrast, among the 44 anti–HCV-positive persons negative for HCV RNA, 38 (86%) had normal ALT values, none of whom had evidence of chronic liver disease, whereas among the 6 with increased ALT values, one had cirrhosis and one had undergone liver transplantation. Thus, a total of 6 (6%) of the original 95 persons with apparent acute hepatitis C had developed cirrhosis or undergone transplantation 25 years after their original infection. There were no cases of HCC.

Study of Young Persons With Community-Acquired HCV Infection. An outbreak of streptococcal infection on a military base in Wyoming between 1948 and 1954 prompted the drawing of blood samples from almost 9,000 persons to test for streptococcal antibodies.[23] The samples were archived in a freezer and were tested almost 50 years later for evidence of HCV infection. The original sera of 17 persons were found to be anti–HCV positive and could be confirmed by recombinant immunoblot assay. Eleven were also positive for HCV RNA. Seven of the 17 had died in the interim, only one from known liver disease. Of the 10 believed to be alive, almost 50 years since the original blood draw, 8 could be traced, 5 of whom had no liver-related illness, 2 had biochemical evidence that suggested cirrhosis but without overt clinical symptoms, and one died in the course of the evaluation with radiologic evidence suggestive of cancer involving the liver, the source of which (liver to lung or lung to liver) could not be determined because neither a liver biopsy procedure nor an autopsy was performed.

Transfusion-Associated Non-A, Non-B/C Hepatitis. Follow-up data from a multicenter study of transfusion recipients yielded different results from those found among the younger individuals described earlier.[25,26] This long-term study involved evaluation of persons originally participating in 3 large-scale transfusion studies (one at the Clinical Center of the National Institutes of Health, one in the Veterans Affairs medical system, and one a national multicenter study supported by the National Heart, Lung and Blood Institute) aimed at determining the incidence of transfusion-associated hepatitis. Cases defined as acute hepatitis (non-A, non-B, or type C) from all 3 original studies were combined for analysis purposes, were matched 2:1 with transfused persons without hepatitis, and then both groups (cases and controls) were followed-up over a period of approximately 25 years for outcome. The average age of these individuals when follow-up evaluation commenced was 49 years, clearly older than the groups just described. Strikingly, all-cause mortality was no different between the cases and controls either at 18 years (44.6% vs. 46.1%) or at 23 years (67.1% vs. 65.0%), but differences, though slight, were found in the frequency of liver-related mortality (Fig. 4). Thus, at 18 years, liver-related mortality was 2.3% among the cases and 1.3% among the controls, increasing to 4.1% by 23 years among the cases and remaining at 1.3% among the controls. Although these data showed a trend to increasing mortality among the cases owing to liver-related deaths (2.8% at 23 years), its frequency was negligible when compared with the overall mortality, suggesting that most deaths were a consequence of the reasons for the original receipt of the blood products rather than from liver disease. Further proof for this view is the evidence that the all-cause mortality rate among both the transfused cases and controls was almost identical but differed significantly from mortality among the general public, matched for age, sex, and race.[27]

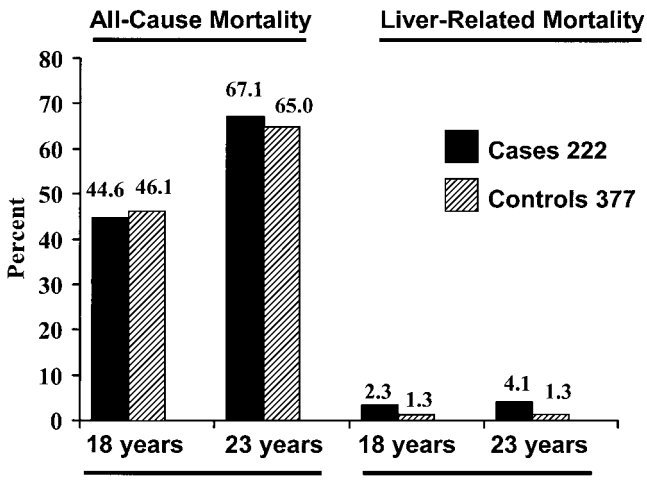

Fig. 4. Transfusion-associated non-A, non-B/C hepatitis mortality approximately 18 and 23 years after transfusion.[25,26]

Of added interest in this study were the data derived from follow-up evaluation of the living cohort. Among 103 persons who had originally developed transfusion-associated hepatitis C and were followed-up over a period of 25 years, 77% remained viremic, 17% were anti–HCV positive but without detectable HCV RNA, and 7% had no detectable evidence (neither anti-HCV nor HCV RNA) of their earlier infection. Fifty percent of the entire group continued to have increased ALT values. Liver biopsy examinations revealed the presence of cirrhosis in 15%, a figure higher than those just described. Possible explanations for the differences may be that this group was older when first infected, that there was a greater volume of viral exposure volume by a unit(s) of transfusion than by that of a small inoculum or needle-stick exposure,[28] or that the underlying illnesses that required

blood transfusion might have added to the pathologic process.

Interpretation of Results of Long-Term Follow-Up Evaluation

As described earlier, the frequency of evolution to cirrhosis differs according to the strategy used to acquire the information. Thus, the mean frequency of development of cirrhosis was 42% for the retrospective studies, 11% for the prospective studies, and 2.1% for the retrospective-prospective cohort studies (excluding the study of transfusion-associated hepatitis C). How does one account for these vast differences? The answer lies in the method of study, the duration of follow-up evaluation, and the population selected for study. Thus, it appears that the retrospective studies concentrated on persons with already well-established and often more serious disease because of the referral base, the prospective studies focused on hepatitis C resulting from transfusions, but the durations of follow-up evaluation were insufficient to provide complete outcome data, whereas the retrospective-prospective studies had the advantage, in general, of studying heterogeneous populations of differing ages and sexes, beginning mostly with identified acute onset, and following-up the cohorts for longer (although not necessarily sufficient) durations of time. The lowest rates of progression appear to be among affected young people, particularly women. This suggests that the liver disease progression is highly variable and appears to be influenced, at least in part, by certain host characteristics, such as age at the time of infection and possibly sex.

A recent effort to examine this issue in detail comes from a survey conducted in Australia of the reported studies of natural history, with the aim of critically evaluating the published data and attempting to determine whether outcomes differ and, if so, to define what the reasons might be (Fig. 5).[29] The investigators undertook a wide search of the literature for all articles relating to the topic published over the past decade and identified a total of 145 published studies. They extracted 57 studies from this group to evaluate, excluding 59 articles in which fewer than 20 cases of HCV infection were reported, and 29 articles that failed to report age or duration of infection.

Examination of these 57 articles revealed that the studies could be divided into 4 groups based on the methods of recruitment. These were: (1) cross-sectional studies involving patients referred to tertiary care centers (liver clinic series, 33 studies); (2) longitudinal posttransfusion hepatitis studies (posttransfusion cohorts, 5 studies); (3) cross-sectional surveys of persons newly diagnosed at blood donor screening (blood donor series, 10 studies); and (4) longitudinal community-based studies (community-based cohorts, 9 studies) (Fig. 5). Careful analysis of the data indicated that, after 20 years of HCV infection, cirrhosis had developed in 24% (95% confidence intervals [CI], 11% to 37%) of the posttransfusion cohort, whose mean age was 42 years at acquisition of infection; in 22% (95% CI, 18% to 26%) of the liver clinic series, with a mean age of 29 years; in 7% (95% CI, 4% to 10%) of the community-based cohort, with a mean age of 26 years; and in 4% (95% CI, 1% to 7%) of the blood donor series, whose mean age was 22 years. Further evaluation identified older age at infection, sex, and heavy alcohol intake as the major factors associated with rapid disease progression. They concluded that progression estimates were much higher in the liver clinic series, which they attributed to selection bias, and suggested that the community-based cohort studies, with a mean frequency of development of cirrhosis of 7%, was the most representative basis for estimating progression in the general population.

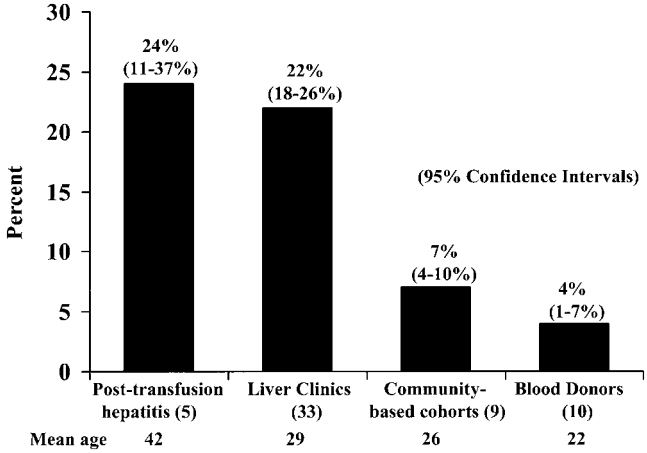

Fig. 5. Rate of progression to cirrhosis approximately 20 years after infection based on mode of study recruitment. A total of 145 studies were evaluated and the 57 that fulfilled the inclusion criteria were analyzed.[29]

Factors That Might Have an Impact on the Rate of Progression

As is evident from the preceding discussion, the natural history of chronic hepatitis C is highly variable, the differences reported being based partly on the groups studied as well as on the methods used for study. However, there clearly are other factors that also are likely to affect the rate of disease progression. These can be considered according to one of three categories: factors that are viral related, those that are host related, and external factors that may modulate disease progression (Table 3).

Viral-Related Factors. Factors that conceivably could play a role include viral concentration, viral geno-

Table 3. Factors That Could Have an Impact on Progression of Chronic Hepatitis C

Viral Related	Host Related	External
Viral concentration	Age at infection; aging	Alcohol
Viral genotype	Sex	Smoking
Viral quasispecies	Race	Environmental contaminants
	Coinfection	
	HBV	
	HIV	
	Comorbidity	
	Hemochromatosis	
	NASH	
	Schistomiasis	
	Genetic	
	Human leukocyte antigen class II antigens	
	Disease expression	
	Normal enzymes	

Abbreviation: NASH, nonalcoholic steatohepatitis.

type, and viral quasispecies. Viral concentration is an important factor in regard to treatment issues,[30,31] but there is no evidence to indicate that it has any effect on disease progression.[32,33] Similarly, viral genotype has profound treatment implications,[30,31] but most investigators have failed to identify genotype as an indicator of likely progression,[34,35] although there are rare reports that suggest a higher rate of progression among persons infected with genotype 1b.[36] Regarding the role of quasispecies, studies in humans have suggested that quasispecies evolution is associated with progression of acute to chronic hepatitis C,[37] although studies in chimpanzees have not fully supported this finding.[38] However, there is no evidence to indicate that it plays a role in progression once chronic hepatitis has developed.

Host-Related Factors. A number of items within this category appear to have a significant impact on the likelihood of progression of chronic liver disease. These include age at infection or the aging process, sex, race, coinfections, comorbid conditions, genetic factors, and disease expression.

As described earlier[6-9] and by others,[35,39] age appears to be an important determinant of progression. This clearly relates to age at the time of infection, the data suggesting that the younger the age at infection, the lower the rate of progression. What is not known, is suspected, but is thus far unproven, is whether the rate of progression of the chronically infected person increases as the affected person ages. This relates to the continuing uncertainty as to whether evolution of fibrosis plateaus over time, whether it increases at a linear rate, or whether there is an exponential increase in the rate of fibrosis with advancing age (see later). The explanation offered for the potential to increase the rate is the inability of the aging immune system to contain the pathologic process.[35]

Regarding sex, there is moderate evidence to indicate that the rate of progression of liver disease is lower among women than among men.[35,40] There also is emerging evidence to indicate that, paradoxically, the rate of progression to cirrhosis is lower among African Americans who are infected than among infected Caucasians (Table 4).[41-43] The paradox stems from the evidence that African Americans have a higher rate of infection,[44] a higher rate of HCC,[45] and a lower response rate to treatment.[46,47]

An unequivocally important factor in disease progression is coinfection with other viruses that have the same risk factors for transmission as HCV. Coinfection with HCV and HIV is particularly common among persons with hemophilia and injection drug users. Studies in these groups have repeatedly and compellingly shown that coinfection with HIV is associated with more rapid progression of hepatitis C.[48-51] The issue of HCV-HIV coinfection is discussed in detail elsewhere in this issue of HEPATOLOGY.[52] Similarly, coinfection with HBV has an additive effect on the rate of fibrosis progression in persons with hepatitis C.[53,54]

Several comorbid conditions also may have an impact on progression of fibrosis in persons with hepatitis C. Several reports have shown an association between increased hepatic iron stores and more rapid progression of fibrosis[55-57] and a decreased rate of response to interferon treatment in persons with chronic HCV infection.[58-60] However, a randomized, controlled trial of phlebotomy followed by interferon treatment failed to show an increased rate of sustained response in those phlebotomized, but it did show a lowering of serum ALT levels and slight improvement in histology activity index.[61] In view of these relationships, a study was undertaken to determine whether the presence of the hemochromatosis gene, C282Y, in 137 persons with chronic hepatitis C was associated with more advanced liver disease.[62] Ten patients had C282Y mutation, but none were homozygous. Liver disease was found to be more advanced in persons with the mutant allele (heterozygotes); specifically, there was a higher frequency of cirrhosis, even though there were relatively minor increases in hepatic iron stores, suggesting

Table 4. Frequency of Progression to Cirrhosis Among Persons With Chronic Hepatitis C According to Race/Ethnicity

	Percentage With Cirrhosis	
Study	African American (%)	Caucasian (%)
Wiley [41]	22.0	30.0
Fleckenstein [42]	7.4	12.4
Harris [43]	2.2	7.2

that phlebotomy may be a useful therapy in this subgroup.

Nonalcoholic steatohepatitis (NASH) is a common disease and may contribute to progression of fibrosis in some patients with both steatohepatitis and hepatitis C.[63] Indeed, obesity itself, defined as a body mass index greater than 30 kg/m^2, has been associated with more advanced degrees of fibrosis in chronic hepatitis C, as has steatosis and diabetes.[64-67] In a recent study, investigators examined the liver biopsy specimens of 170 patients with chronic hepatitis C and concluded that type 2 diabetes mellitus and steatohepatitis were independently associated with advanced fibrosis.[68]

Other pathologic processes affecting the liver also may play a role in enhancing fibrosis progression in persons with chronic hepatitis C. An example is the effect of concomitant infection with schistosomiasis, common in the past in Egypt where the predominant HCV genotype is type 4. To examine this issue, a study was undertaken that involved 126 Egyptian patients divided into 3 categories—chronic hepatitis C alone, chronic schistosomiasis alone (*Schistosomiasis mansoni*), and both chronic hepatitis C and chronic schistosomiasis.[69] Enrolled patients were followed-up prospectively for approximately 62 months. The group with combined infections was found to have more advanced liver disease, higher titers of HCV RNA, a higher incidence of cirrhosis, HCC (not found in the other 2 groups), and a significantly higher mortality rate. An explanation offered for this finding was that the *S. mansoni* infestation might impair the immune response, promoting a high viral load that could adversely affect a liver already damaged by the schistosomal infection.

A role for genetic influences in hepatitis C has been studied in relationship to clearance of the virus[70,71] as well as to disease progression. Interesting, although conflicting, data have been gathered on human leukocyte antigen class I and II antigens. In one study of HCV-infected persons, B54, DRB*0405, and DQB1*0401 was associated with disease progression whereas DRB1*1302, DRB1*1101, and DQB1*0604 was associated with low hepatitis activity and normal serum transaminase levels.[71] Several other groups have studied a variety of alleles, identifying some to be associated with progression and others to be associated with benign chronic liver disease.[72-75] Other host genetic factors that have been linked to progressive liver fibrosis are polymorphisms in the genes of transforming growth factor-β1 and angiotensin II.[76,77]

Finally, the biochemical expression of chronic HCV infection appears to play a role in disease progression, whether as cause or effect. There is now much evidence that persons with HCV infection and normal values of the aminotransferases, whether persistent or intermittent, are more likely to have lesser degrees of histological abnormality than those with abnormal values, although a small proportion may have histological evidence of cirrhosis.[78,79] Furthermore, among the majority without cirrhosis, the rate of progression of fibrosis is slow or entirely absent.[80,81]

External Factors. Three factors can be considered in this category, of which one has a proven relationship to disease progression, namely overt alcoholism, one is suspected but not proved to be related, namely the effect of smoking, and one in which the relationship is purely theoretical, namely the potential role for environmental toxins or contaminants.

Multiple studies of the natural history of hepatitis C have shown that chronic alcoholism plays a major role in increasing the frequency and rate of progression of chronic HCV infection to both cirrhosis and HCC.[82-87] This fact is beyond dispute. What is still uncertain is the amount of alcohol intake below which disease progression does not occur, whether the pattern of drinking (binge vs. consistent) has an important role, whether the effect is determined by the total amount of alcohol imbibed (the ex-alcoholic vs. the current alcoholic), whether the type of alcohol imbibed has a determining role, what effect alcohol has on viral replication, if the negative effect of heavy alcoholism applies equally to infected men and infected women, what the precise pathogenesis is (synergistic vs. additive), and many more questions.[88] The effect of excess alcohol consumption on the person with chronic hepatitis C is discussed elsewhere in this issue of HEPATOLOGY.[89]

There has been recent interest in the possibility that cigarette smoking might play a role in the development of cirrhosis in persons with hepatitis C, prompted by evidence in patients with alcohol-induced cirrhosis that smoking was an independent risk factor in chronic alcoholics and persons with hepatitis B.[90,91] A major problem in attempting to define whether smoking indeed is an independent risk factor is that almost all heavy alcoholics also are persons prone to smoke. Several studies have identified smoking as being associated with the development of HCC in persons with chronic hepatitis.[92,93] In a recent study of 310 patients with chronic hepatitis C hospitalized for a liver biopsy examination, a relationship was sought between the presence of certain demographic (age, sex) and other factors (alcohol, smoking, route of infection) and histological findings.[94] Smoking was found to be highly significantly associated with increased fibrosis in age-adjusted and multivariate analyses. The investigators suggest that cigarette smoke may contain hepatotoxic compounds that may be responsible for the phenomenon. Although interesting, additional carefully designed stud-

ies are needed to confirm the potential role of smoking as a factor in liver disease progression.

The possibility that environmental factors, such as diet or toxic contaminants, could play a role is purely speculative. This consideration springs from the interesting evidence of the differing outcomes between persons in Japan infected with HCV and those in the west, particularly the United States, infected with HCV. Death from liver disease in Japan virtually is always a consequence of the development of HCC, whereas end-stage liver disease, specifically the consequences of cirrhosis, is by far the predominant mode of demise in the west. Although it is conceivable that the reason for the difference, as has been suggested, is that HCV infection entered Japan several decades before it spread in the west, and therefore a similar phenomenon will eventuate in the west, the difference is so vast that this likelihood seems improbable. That it is unlikely to be a consequence of genetic predilection is suggested by the evidence that HCC among first-generation Japanese born in Hawaii is predominantly a consequence of HBV and not HCV infection.[95] Clearly, the absence of supporting evidence for this possibility detracts from its validity but perhaps spurs interest in addressing this prospect.

Summary

Once chronic HCV infection is established, it generally, although not invariably, persists for life. The fundamental feature of progression is increasing degrees of fibrosis, culminating in cirrhosis. The rate of progression, however, is slow, usually over decades and, indeed, manifest liver disease is uncommon during the first 2 decades of established chronic hepatitis C. Current data suggest that infection initiated at a young age (perhaps $<$ 40 y) progresses at a slow pace so that, by 20 years after acute infection, cirrhosis will have developed in 2% to 8% of these individuals (Fig. 6). In contrast, infection that begins in persons who are older seems to lead to a higher rate of progression, so that about 20% of these individuals will have progressed to cirrhosis after 20 years. Because of the current paucity of information, the course in the period following the first 2 decades after infection is not known. The questions that desperately need an answer are: will fibrosis progression plateau, will it continue to progress at a linear rate, or will there be an exponential increase in the rate of fibrosis? These questions are particularly relevant for the younger infected person among whom cirrhosis develops less frequently by the 20-year mark. Are they more likely to assume an increased pace of fibrosis progression as they become older and face potential immunologic aging? Poynard et al.[96] have suggested that there are variable rates of fibrosis progression ranging from slow through intermediate to rapid. Features identified in their survey to correlate with the rate of fibrosis progression included age at infection, sex, and alcohol consumption.

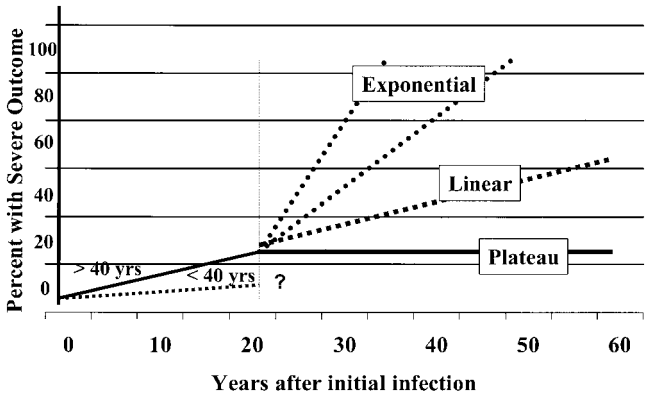

Fig. 6. Projected outcome of chronic hepatitis C. Note that for those first infected as older adults (approximately over the age of 40 y), about 20% developed cirrhosis 20 years after infection. The slope of progression thereafter is not known but theoretically could plateau, progress linearly, or increase exponentially. Among younger infected individuals, cirrhosis developed in 3% to 8% by 20 years after infection. The slope of progression thereafter is unknown.

It is clear, therefore, that the rate of fibrosis progression is highly variable, affected by certain host characteristics, by several external factors, and modified by coinfections and comorbid conditions. Without doubt, a proportion of HCV-infected persons, perhaps 20% or fewer, advance over time to end-stage, potentially lethal, liver disease. However, it is probable that the majority of infected persons will, for a variety of reasons, not suffer the consequences of HCV-related end-stage liver disease. The scientific advances have not yet provided definitive means of determining, for the individual person, what the long-term outcome is likely to be, although an analysis of a wide combination of demographic, biochemical, histological, and extraneous factors can provide helpful information for projecting the natural history. This is the area most desperately in need of future research.

Future Research Needs

Because the course of chronic hepatitis C is markedly protracted, lasting anywhere between 20 and in excess of 40 years, and because treatment now is almost universal, it is extremely unlikely that any meaningful natural history studies can be performed in the future. The only exception to this statement would come from the serendipitous discovery of a large cohort of acutely infected persons from far in the past with archived serum specimens, permitting a retrospective-prospective study approach. Current data provide useful information for the first 20 to 25 years of infection. This information is helpful for infec-

tion that has occurred in middle to late adulthood, but the information is inadequate for persons infected as children or in early adulthood. In general, but not invariably, only a small proportion of this latter group has advanced to cirrhosis at the end of the second decade. Knowledge of the frequency and rate of progression among these individuals who have not developed cirrhosis is unknown but is sorely needed. Investigators who have studied these groups in the past should be encouraged to continue careful follow-up evaluations to collect the needed information.

The most important deficiency in assessing progression of liver disease is the lack of sensitive serum markers of fibrosis. For this reason, evidence for progression during the extended period before development of decompensated cirrhosis needs to come from liver biopsy examination information. Not only is this an uncomfortable and occasionally a dangerous procedure, but also it is subject to errors in sampling and interpretation. Therefore, increased research efforts must go to the development of appropriate markers of fibrosis progression, measures of critical importance for the individual person with chronic HCV infection.

Finally, further research activity should be directed toward a better understanding of the pathogenesis of disease progression and of the many known and unknown factors that contribute to the progression. One example is the issue of age, with respect both to the effect of age at the time of infection and of the process of aging (its effect on liver as well as on the immune system) in the person with already established chronic hepatitis C.

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