Recovery, Persistence, and Sequelae in Hepatitis C Virus Infection: A Perspective on Long-Term Outcome

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ABSTRACT *Hepatitis C has emerged in recent years as the most common basis for liver disease in the United States, having infected an estimated 3.9 million people in this country and an estimated 170 million worldwide. Currently, it is the predominant reason for undergoing liver transplantation. The disease it causes is characterized by silent onset in most infected individuals, a high rate of viral persistence, and the potential for development of ever-worsening chronic liver disease, ranging from chronic hepatitis to cirrhosis and occasionally to hepatocellular carcinoma. Such progression, when it occurs, is also most commonly a silent process that may take 20–40, and occasionally even more, years to reach its end point. Because of these characteristics, it has been exceedingly difficult to accurately assess the natural history. Efforts to accomplish this have consisted of retrospective, prospective, and cohort studies. The most concerning data have derived from the retrospective study approach, generally performed at tertiary referral centers. Because these centers commonly attract persons with existing chronic liver disease, they have tended to describe a high rate of progression to cirrhosis and cancer. This "referral bias" is avoided in the prospective and cohort study approach, and data derived from these studies indicate a lower rate of progression and a correspondingly higher rate of either recovery or minimal liver disease. In this review, we briefly describe potential mechanisms of viral persistence; present detailed information on outcomes that have derived from retrospective, prospective, and cohort studies, involving both adults and children; examine the data regarding progression of fibrosis and of progression to hepatocellular carcinoma; consider cofactors that might enhance liver disease progression; and report the emerging data that suggest that spontaneous viral clearance may be higher than is currently believed. We conclude with the view that severe, life-threatening, progressive liver disease clearly occurs in a sizable minority (perhaps 30%) of chronically infected persons but speculate that fibrosis progression is neither linear or inevitable and hence that most hepatitis C virus carriers will have either a stable nonprogressive course or such indolent pro-*

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gression that they will die from an unrelated disease before the severe sequelae of hepatitis C become manifest or will have a sustained "curative" response to therapy. Although this view provides reasonable hope to the hepatitis C virus-infected individual, it does not deny the enormous burden this infection presents as the result of its high prevalence and global distribution. The sheer magnitude of the infected population will result in a large number with severe life-threatening liver disease even if the proportion of infected individuals that develop progressive disease is relatively small.

KEY WORDS: HCV, chronic hepatitis, fibrosis, cirrhosis

As the chronic consequences of hepatitis C virus (HCV) infection receive increased attention from patient advocate groups, public health advisories, and the lay press and as patient concern escalates, it is important to reexamine the natural history of this infection and to place disease outcomes in proper perspective. This is not an easy task because the disease process is indolent and outcomes may not be known for many decades. Thus, studies with 10-year or even 20-year follow-up that provide definitive outcome assessments for most diseases may not be adequate to fully assess the chronic sequelae of HCV infection. At present, there are considerable data regarding 20-year outcomes in HCV infection, but with few exceptions, extrapolations are required beyond that point. In addition to the slow evolution of disease, a balanced perspective must take into account variables such as the age at onset and cofactors, particularly alcohol. Further, one must examine both the disease burden for the infected individual and the disease burden for society. Based on currently available data, it would appear that the societal burden is considerable because of the high prevalence of the infection, but for most HCV-infected individuals, the infection has both low morbidity and low mortality. The problem is that we cannot predict the 20–30% of individuals who will sustain more dire outcomes.

In this review, we examine the evidence that HCV infection has serious and sometimes mortal consequences and, paradoxically, the evidence that this infection can be largely silent and compatible with uncompromised longevity. Specifically, we attempt to provide the framework within which the clinician can address the most common concerns of the HCV-infected individual, namely, "What is the likelihood that I will die of this disease?" "How sick will I become?" "Can I be cured?"

The clinician cannot provide definitive answers to these questions for the individual patient, but by presenting balanced data from natural history studies and treatment options, the physician can render a perspective that can reduce patient anxiety and offer realistic hope that the hepatitis will not progress rapidly, may not progress at all, may be compatible with a normal lifespan, and may respond to therapy.

HISTORICAL PERSPECTIVE

When first recognized, non-A, non-B hepatitis was regarded as a relatively mild illness that generally lacked the typical clinical manifestations of hepatitis A or B.[1] Speculation abounded as to whether non-A, non-B was a distinct viral illness or a nonspecific transaminitis related to postoperative events. The issue was resolved when non-A, non-B hepatitis was linked to needlestick injuries in health workers and, particularly, when human inocula were shown to transmit non-A, non-B hepatitis to chimpanzees.[2–5] Nonetheless, it required an additional 15 years before this nebulous transmissible agent was identified as HCV.[6]

The initial equanimity about the condition gave way to concern when it became apparent that about 50% of those infected had persistence of raised serum enzyme values even though most continued to have no symptoms.[7] Subsequently, liver biopsies established that the chronic asymptomatic hepatitis was accompanied by moderate to marked fibrosis or cirrhosis in about 20% of cases. Concern escalated when sporadic reports began to appear linking hepatocellular carcinoma (HCC) to previous episodes of non-A, non-B hepatitis.[8] The association between non-A, non-B/HCV and both cirrhosis and HCC was then confirmed in multiple studies.[9–12]

Later, epidemiologic studies of anti-HCV positive blood donors[13] and patients with community-acquired hepatitis C[14] revealed that 75–85% of HCV-infected individuals failed to resolve their infection, and population surveys determined that the prevalence of HCV infection in the United States was close to 2.0%, suggesting that almost 4 million people were chronically infected in the United States alone.[15]

Increasingly, the accrued evidence indicates that HCV infection, despite its generally mild clinical presentation, is a problem of considerable magnitude leading to persistent infection and chronic hepatitis in most and to cirrhosis and end-stage liver disease in some. Further, hepatitis C has now become the most frequent reason for hepatologic consultation and the single leading indication for hepatic transplantation, accounting

for 30% of such procedures in the United States.[16] Thus, from obscure beginnings as a mild infection of unknown etiology, hepatitis C has ascended to international eminence as a leading cause of major liver disease. Nonetheless, the proportion of infected patients who reach these well-publicized deleterious outcomes remains poorly defined, and recent data suggest that such dire outcomes are less frequent than commonly feared.

MECHANISMS OF VIRAL PERSISTENCE AND THE PATHOGENESIS OF CHRONIC HEPATITIS

Although viral persistence is a fundamental prerequisite of chronic hepatitis, the mechanisms of viral persistence and liver injury may be distinct. It appears that the primary determinant of persistence is the quasispecies nature of the virus. HCV, like other RNA viruses, exists as a family of closely related but immunologically distinct variants that have been termed the quasispecies. More than 20 strains of HCV have been cloned from a single patient at a single point in time, and this is an underestimate of the total number of variants actually present. Thus, even if the host mounts a neutralizing immune response to the predominant HCV strain, any of the other variants already present could escape the immune attack and replicate to become the new predominant strain. By inoculating chimpanzees with mixtures of known infectious inocula and human sera obtained at various time points after the onset of infection, it has been shown that humans develop neutralizing antibodies to HCV but that these antibodies are highly strain specific and incapable of preventing the emergence of viral variants that can maintain the infection.[17]

Similar conclusions have been reached using in vitro systems that measure the uptake or binding of HCV to cultured cells.[18,19] Recently, Farci et al.[20] measured both the number of strain variants (complexity) and the number and breadth of nonsynonymous nucleic acid substitutions (diversity) that occur during the first 16 weeks of HCV infection and showed that the extent of viral diversity predicts whether HCV infection will resolve or become chronic. It appears that in most HCV-infected patients, the development of antibody exerts immune pressure that drives the quasispecies and leads to an increasingly complex population that can elude the immune attack and result in viral persistence.

The importance of antibody in driving viral diversity is further illustrated in patients with agammaglobulinemia, in whom it has been shown that in the absence of antibody the viral population remains homogeneous (see Farci and Purcell in this issue). Despite the correlation between viral diversity early in HCV infection and the subsequent development of chronic hepatitis,[20] it is clear that humoral immune pressure and escape variants are not the only mechanisms determining persistent infection. Bukh et al.[20a] showed in the chimpanzee model that two animals, although infected with the identical full-length monotypic infectious clone, nonetheless had diverse outcomes, with one recovering and the other developing chronic infection. Other speculative mechanisms for viral persistence include the potential that HCV has mechanisms to decrease the effectiveness of antiviral cytokines, to increase the resistance of infected cells to cytotoxic T lymphocyte (CTL)-mediated killing, to infect immunologically privileged sites, or to induce immunologic tolerance.[21]

The net result of this host–virus interplay is that despite the development of antibodies to proteins expressed along the entire HCV genome, most patients are unable to eradicate the virus and manifest persistent infection usually with evidence of chronic liver disease. Further, the immune responses are so highly strain specific that even patients or animals that recover from HCV are susceptible to reinfection.[17,22]

Studies of cell-mediated immunity to HCV are just beginning to emerge, and the role of cell-mediated immunity in viral clearance and liver cell damage is still inconclusive but probably fundamentally important. Of interest, studies of intrahepatic CTL responses in chimpanzees have shown that viral variants can escape the CTL response just as they escape the humoral antibody response.[23] The influence of cell-mediated immunity on viral persistence will be comprehensively reviewed by Rehermann in the next issue of *Seminars.*

The mechanisms of cell death in HCV infection are not fully elucidated. Clearly, liver cell damage is not solely due to viral cytopathic effects because very high titers of virus within the liver and in serum are compatible with minor cell damage. Similarly, it is not clear that cytotoxic T cells are responsible because the worst degrees of liver disease are often observed in patients who are immunodeficient, particularly patients coinfected with human immunodeficiency virus (HIV).[24] Liver cell damage is probably a complex interplay of direct viral injury, cell mediated cytotoxicity, cytokine effects, apoptotic events, and other intracellular events that have not been elucidated.

HEPATITIS C OUTCOME BASED ON PATIENTS REFERED FOR CHRONIC LIVER DISEASE

As might be expected, the most severe outcomes of HCV infection have been observed in retrospective studies that assess persons with already established

chronic hepatitis and attempt to define the rate of development of adverse sequelae by tracing the chronic disease back in time to the moment of acute onset (Table 1).

Kiyosawa et al.[9] conducted a retrospective evaluation of 231 patients with chronic non-A, non-B hepatitis (96 with chronic hepatitis, 81 with cirrhosis, and 54 with HCC) of whom approximately 90% were HCV related and 30–50% had been previously transfused. Serial liver biopsies in some documented the sequential progression from stages of increasingly severe inflammation and fibrosis to cirrhosis and, ultimately, to HCC. When frequent serial biopsies were available, cirrhosis was always found to precede HCC.

Similar data on clinical outcomes of transfusion-associated hepatitis C came from a report by Tong et al.[10] These investigators conducted a retrospective evaluation with short-term follow-up of 131 individuals from a group of 213 patients with chronic hepatitis C referred to their hospital. All 131 selected individuals had received blood transfusion on a single occasion. Initial liver biopsies in 101 patients revealed chronic hepatitis in 21%, chronic active hepatitis in 23%, cirrhosis in 51%, and HCC in 5%. Follow-up over a mean duration of 3.9 years (range, 1–15 years) demonstrated that an additional 7 patients (5%) developed HCC and 20 (15%) died, 8 from complications of cirrhosis, 11 from HCC, and 1 from pneumonia.

Yano et al.[25] examined histologic progression in 70 noncirrhotic patients who had 2–10 liver biopsies (mean, 3.9) obtained over the course of 5–26 years of follow-up. During follow-up, 50% developed cirrhosis, including all patients who had a high histologic grade on a prior biopsy; the rapidity of progression correlated directly with the histologic grade. This important study clearly demonstrates the potentially serious nature of this chronic infection, particularly among Japanese patients. However, again this was a retrospective study of referred cases and had an inherent selection bias. A small number of patients were selected from a large patient base (70/2,000) without specific reasons being offered for their selection.

Niederau et al.,[26] from Germany, conducted a follow-up study of 838 HCV RNA positive patients referred to their tertiary-care center for therapy. The duration of follow-up ranged from 6 to 122 months (median, 50.2 months). At study entry, 141 (16.8%) patients had cirrhosis, mostly classified as Childs' A cirrhosis. A total of 62 patients (3.7%) died during the course of the study, 18 from cirrhosis, 13 from HCC, and 31 from other causes. Mortality was strongly related to the presence of cirrhosis and estimated duration of infection. Importantly, among the 696 patients without cirrhosis, mortality was no greater than that of the general population regardless of duration of infection. All patients who developed HCC either had cirrhosis at entry or developed cirrhosis later.

These studies (Table 1) conducted by referral centers unequivocally demonstrate the severe outcomes that can derive from HCV infection. However, because of referral bias, such studies do not assess the broad spectrum of outcomes that might occur if the entire HCV-infected populations were fully evaluated. Thus, referral-based studies do not determine the proportion of patients who

TABLE 1. Long-term Outcome of HCV Infection According to the Method of Study

Method of Study	*Author (Reference)*	*Country*	*No. Patients*	*Interval from Exposure (mean or range of means, yr)**	*Cirrhosis (%)*	*HCC (%)*	*Liver Death (%)*
Retrospective†	Kiyosawa (9)	Japan	231	10–29	35.1	23.4	NR
	Tong (10)	USA	131	14–28	51.0	10.6	15.3
	Yano (25)	Japan	70	NR	50.0	NR	NR
	Niederau (26)	Germany	838	9–22	16.8	2.0	3.7
	Gordon (62)	USA	215‡	19	55.0	3.7	NR
	Gordon (62)	USA	195§	20	21.0	1.0	NR
Prospective‖	DiBisceglie (27)	USA	65	9.7	12.3	0	3.7
	Koretz (28)	USA	80	16.0	7.0	1.3	1.3
	Mattson (29)	Sweden	61	13.0	8.0	NR	1.6
	Tremolada (30)	Italy	135	7.6	15.6	0.7	3.7
Cohort¶	Seeff (38)	USA	103	20	15**	1.9	2.7
	Seeff (40)	USA	17	45–50	5.9	0.0	5.9
	Kenny-Walsh (43)	Ireland	376	17	2.0	0.0	0.0
	Vogt††(45)	Germany	458	17	0.3	0.0	0.0

*Based on interval from transfusion or initial use of intravenous drugs when that date was known.
†Based on referrals to tertiary care centers for persons with established liver disease.
‡Exposure through transfusion.
§Exposure through intravenous drug use
‖Long-term follow-up of persons studied from the time of acute infection.
¶Recall of patients diagnosed with acute hepatitis in prior prospective transfusion studies followed by renewed prospective follow-up with non-hepatitis controls.
††Study in children.

spontaneously recover from infection, the proportion who have mild disease and do not seek medical attention, or the proportion who die of intercurrent illnesses before their HCV status can be assessed. Thus, by their very design, such selective referral-based studies demonstrate only the more severe outcomes of HCV infection and represent a "worst-case" scenario. It is critically important to know that such severe outcomes occur but equally important to realize that retrospective studies provide incomplete information on the frequency with which progressively severe liver disease occurs in the entire universe of HCV-infected individuals.

OUTCOME BASED ON LONG-TERM FOLLOW-UP OF ACUTE HEPATITIS C

The original indication that acute non-A, non-B hepatitis progressed to chronic hepatitis in a large proportion of cases emanated from the long-term follow-up of patients enrolled in prospective studies of transfusion-associated hepatitis.[27–30] These studies, originally designed to investigate the incidence and causes of transfusion-associated hepatitis, were extended when it was observed that many patients still had elevated alanine aminotransferase (ALT) levels at the end of their designed 6-month follow-up (Table 1).

Patients originally enrolled in the NIH prospective transfusion-associated hepatitis studies[31] were reassessed for evidence of chronic liver disease by Di Bisceglie et al.[27]; 65 patients, 53 (82%) of whom had hepatitis C, were evaluated 1–24 years (mean, 9.7 years) after onset of acute non-A, non-B transfusion-associated hepatitis. Forty-five of the 53 (65%) developed chronic hepatitis, of whom 33 consented to liver biopsy. The study described these 33 patients plus 6 others with chronic non-A, non-B transfusion-associated hepatitis who were not enrolled in the original prospective study. When initially biopsied, 4 of 39 (10%) already had cirrhosis. Twenty of the 39 patients were rebiopsied at varying intervals, at which time 4 additional patients had histologic evidence of cirrhosis. Thus, cirrhosis was found in 20% of the 39 patients biopsied, or 12.3% of the total 65 patients assessed; none had HCC. Eleven patients died during follow-up, but only 2 from liver failure. Thus, liver-related death occurred in 2 of 45 (4%) of those with chronic hepatitis.

Koretz et al.[28] followed 80 patients who had developed acute transfusion-associated hepatitis approximately 16 years earlier, 64 (80%) of whom were HCV-infected based on enzyme immunoassay (EIA). Fifty-five of the 80 (69%) had biochemical evidence of chronic hepatitis. Liver biopsies were obtained in only 10 patients and were based on clinical severity; 5 (50%) had cirrhosis. Liver failure after 16 years of follow-up, primarily the development of hypersplenism, developed in 22% of those with chronic hepatitis C. Approximately one third of the cases died during follow-up, but only one (1.3%) from liver disease (HCC).

Mattson et al.[29] reported a 13-year follow-up of 39 of 61 patients who had developed acute transfusion-associated non-A, non-B hepatitis. Serologic and molecular screening of archived blood samples identified acute hepatitis C in 24. Follow-up examination revealed that all 24 were still anti-HCV positive 13 years later and that 16 (66%) continued to have detectable HCV RNA. Most of the patients in follow-up (79%) continued to show abnormal serum enzyme levels whether or not HCV RNA could be detected, whereas 21% seemed to have recovered. Liver biopsies showed the presence of cirrhosis in 8%. One patient (1.6%) died as a consequence of liver disease.

Tremolada et al.[30] reported a follow-up study (mean, 7.6 years) among 135 patients with transfusion-associated non-A, non-B hepatitis, most having undergone cardiac surgery. Almost all cases were a consequence of HCV infection. Chronic hepatitis evolved in 104 (77%). Thirteen percent had splenomegaly and 5%, esophageal varices. Sixty-five patients were biopsied and 21 (32.3%) were found to have cirrhosis. This represents a cirrhosis frequency of 21% among those with chronic hepatitis and 15.6% among all of those diagnosed with acute hepatitis C. Among the 104 with chronic hepatitis, 5 (4.8%) died from liver disease (3, bleeding; 1, liver failure; 1, HCC). Thus, 5 (3.7%) of the original 135 HCV-infected group died as a consequence of liver disease.

Less severe outcomes were noted in the follow-up of community-acquired hepatitis C cases in the Center for Disease Control and Prevention's Sentinel Counties Study.[14] Among 130 identified hepatitis cases, 106 (82%) were diagnosed as hepatitis C, of whom 62% advanced to chronic hepatitis. Liver biopsies were performed in 30 of the 60 individuals with chronic hepatitis; 10 (33%) had "chronic active hepatitis," 1 of whom also had cirrhosis; 13 (43%) had "chronic persistent hepatitis"; and 6 (20%) had chronic lobular hepatitis. Thus, cirrhosis was found in only 1% of the 106 community-acquired hepatitis C cases followed over this relatively short interval. No patient with hepatitis C died over the course of the study.

Thus, these five prospective studies identified that progression from acute to chronic hepatitis C was common, that during the time periods of follow-up (approximately 4–16 years) cirrhosis, when sought, was identified in between 1 and 20% of the cases, that development of HCC was rare, and that liver-related mortality was modest in frequency, ranging from 0 to 3.7%. These prospective studies, which focus on entire populations with an identified episode acute hepatitis C, provide a more balanced portrait of hepatitis C outcomes

than do the retrospective studies that concentrate on patients with already established chronic hepatitis. However, these prospective studies also have their failings in that they were not initially designed to study the chronic sequelae of hepatitis and had no mechanism for systematic liver biopsies. Biopsies thus tended to be performed on those who had the most severe biochemical abnormalities or physical evidence of chronic liver disease, and thus biopsy data are skewed to detect those with more severe liver disease. These studies are also flawed in that the dramatic interplay between hepatitis C and alcoholism was not established at the time the studies were conducted and data on coexistent alcoholism were sparse. Thus, these studies generally underestimate the role of alcohol and attribute all outcomes to the viral infection per se. Although this does not invalidate the outcome data, it confounds the interpretation of the natural history of uncomplicated hepatitis C infection. Finally, these prospective studies do not provide data on long-term clinical outcomes in control patients who did not develop hepatitis and do not extend their follow-up into what may prove to be the critical third and fourth decades of this infection.

OUTCOME BASED ON COHORTS STUDIED LONG AFTER A DEFINED PARENTERAL EXPOSURE

Four studies were designed to investigate the clinical and histologic outcomes of HCV infection in cohorts infected 17–40 years earlier (Table 1). The unique feature of these studies is that the HCV status of the subjects at or near the time of initial exposure was known and that an attempt was made to recall all known positives at least 15 years later. This design allows assessment not only of those who developed chronic infection and severe liver disease, but also those that cleared infection and/or had benign outcomes. In essence, this study design has some characteristics of a prospective study but allows long-term follow-up that rarely can be achieved in prospective studies.

The "concurrent-prospective" approach is illustrated by the collaborative Veterans Administration (VA) study of transfusion-associated hepatitis conducted by Seeff et al.[32] This study assessed long-term mortality after transfusion-associated non-A, non-B hepatitis using data from five separate prospective studies of transfusion-associated hepatitis performed between 1967 and 1980 (two VA studies[33,34]), an NIH study,[31] the national Transfusion-Transmitted Viruses study,[35] and a study conducted at the Walter Reed Army Hospital.[36]

A total of 1,552 of the 6,438 persons who entered the original studies were included in the follow-up study, 568 patients with non-A, non-B hepatitis and 984 matched controls.[32] At initiation of follow-up, an average of 18 years after transfusion, all-cause mortality was 51% in both non-A, non-B hepatitis cases and controls and was related primarily to the cardiac diseases that necessitated the original open-heart surgery. Liver-related mortality occurred in 3.3% of the non-A, non-B cases and in 1.5% of controls ($p = 0.02$). Cirrhosis as the cause of liver death occurred in 1.9% of the non-A, non-B cases and 1.0% of the controls. In the first 18 years of study, death due to HCC occurred in only one patient with non-A, non-B hepatitis (0.2%) and in two control patients (0.2%). Medical records could be examined for alcohol history in 28 of the 34 patients with a liver-related cause of death; among these, 78% of cases and 60% of controls were identified as heavy drinkers. Hence, liver-related mortality was generally low and, when found, strongly correlated with alcohol abuse.

In a follow-up report adding an additional 5 years of evaluation,[37] life-table analysis of all-cause mortality showed an increase among the non-A, non-B hepatitis cases to 69.1% and to 69.4% for the controls ($p = 0.67$). Liver-related death for the entire cohort was 4.0% for the cases and 1.7% for the controls ($p = 0.009$); for cases identified as HCV-related, liver-related death was 2.7% for the cases and 1.5% among their controls ($p = 0.31$) (Table 1). Thus, over the course of 23 years after exposure, most deaths could be ascribed to the underlying disease that initiated transfusion rather than to liver disease; though the proportion who died of liver disease was small, there was a trend toward increasing liver-related death among the non-A, non-B hepatitis cases with increasing time from exposure; the development of HCC was rare; and alcoholism alone or in combination with chronic viral hepatitis appeared to be the primary determinant of liver-related death. The number of deaths in HCV-infected patients in the absence of alcohol was extremely small.

In a separate analysis of this same multicenter cohort, long-term morbidity was assessed by recalling living patients for whom an archived blood sample was available for HCV testing.[38] Of the 146 living patients with a prior episode of transfusion-associated hepatitis, 103 (71%) had detectable HCV markers in a sample obtained during the course of their original hepatitis. An assessment of the 103 HCV-related cases approximately 20 years after disease onset revealed that 74% were still HCV RNA positive, 16% were HCV RNA negative on at least two determinations but had persistent anti-HCV antibody, and 10% had no residual markers of their HCV infection. One half of the viremic patients had biochemical evidence of chronic hepatitis, whereas the other half had normal serum enzymes. By protocol, biopsies were restricted to those with abnormal ALT values. Among these with persistent HCV RNA and ALT elevations, 30% had histologically defined cirrhosis. On the assumption that cirrhosis would occur in no

more than 5% of those with HCV RNA and persistently normal ALT and in less than 1% in those repeatedly HCV RNA negative, an extrapolation to the entire group of HCV-related cases projected that less than 15% of acute hepatitis C cases would develop cirrhosis in 20 years.

Combining the mortality and morbidity data from this large, controlled, ~20-year follow-up study, it appeared that 25% of patients had spontaneously recovered from their HCV infection as evidenced by the loss of HCV RNA and in 10%, the concomitant loss of HCV serologic markers; 75% had persistent infection. Within the full cohort who developed acute hepatitis C, 3.5% subsequently died from liver disease and an additional 15% of living patients had cirrhosis. Thus, severe progressive chronic liver disease occurred in 15–20% of transfusion-related HCV-infected persons. The remaining 55% of the cohort had stable generally asymptomatic chronic hepatitis. The ultimate outcome of those with stable chronic liver disease over the first two decades of infection will determine the true severity of chronic hepatitis C. One can only speculate at present whether the disease will be inexorably progressive over time or whether a significant proportion of patients with chronic hepatitis C will, in the absence of alcohol excess, maintain an indolent nonprogressive infection that will have no impact on mortality and minimal impact on morbidity. It is critical that such cohorts continue in follow-up through the third and fourth decades of their infection.

The high mortality unrelated to liver disease, the inclusion of older patients, and the relatively restricted duration of follow-up in these transfusion studies has detracted from their acceptance as fully valid indicators of the natural history of hepatitis C infection. Some of these concerns could be addressed subsequently when it became possible to test a repository of 10,000 frozen sera that had been drawn from Air Force recruits between 1948 and 1954.[39] Outcome data could be ascertained in 8,568 of these individuals, all of whom were tested for anti-HCV and, when positive, tested by a confirmatory recombinant immunoblot (RIBA) assay and by polymerase chain reaction (PCR) for HCV RNA.[40] Outcome was determined using VA and Medicare files and Social Security and National Death Index tapes. Only 17 of 8,568 (0.2%) were confirmed to be anti-HCV positive in the repository sample; 11 of the 17 (65%) were HCV RNA positive. The average age at initial detection of HCV was 23 years. Over the almost 50-year interval from the first detection of anti-HCV until outcome tracing, mortality in the HCV-positive group (7/17, 41%) was significantly higher than that in the negative group (26%), but only one of the seven deaths was related to chronic liver disease. No HCV-infected patient died of HCC compared with 9 of 8,557 (0.1%) HCC-related deaths in the large population that was HCV negative in the repository sample. Although the sample size was very small, this unique almost 50-year follow-up study of HCV-positive individuals revealed only one death from liver disease and no cases of HCC.

Milder outcomes are also observed in individuals whose HCV infection is detected incidentally during donor screening or other routine evaluation. In an NIH study of anti-HCV-positive blood donors,[41] 15% appeared to have recovered from their HCV infection based on the finding of RIBA-confirmed antibody but repeatedly negative PCR determinations for HCV RNA. Of those with persistent infection, peak ALT level exceeded two times the upper limit of normal in only 16%, and clinical symptoms were minimal. Liver biopsies were initially performed on 60 patients.[42] In 20 donors with persistently normal ALT, the mean histologic activity index (HAI) score was 5.4 and the mean fibrosis score 0.3; the corresponding HAI and fibrosis scores for donors with ALT levels between one and two times the upper limit of normal were 7.7 and 0.6 and for those with ALT levels more than twice normal, 9.0 and 1.2. Only one patient had cirrhosis, that patient being in the high ALT group. The number of biopsies in this population has now been expanded to 94 (Ghany M, Hoofnagle J, Alter HJ, unpublished data). No patients have severe inflammatory changes (HAI 15–18), 13% have stage 3 fibrosis, and 2% have cirrhosis after an average duration of infection of 19 years based on a defined parenteral exposure. Thus, this study of blood donors corroborates the findings in the Seeff study,[38] indicating that at least 15% of HCV-infected individuals spontaneously recover and that less than 15% have severe histologic lesions during the first two decades of infection.

To determine the progression of histologic lesions over time, repeat biopsies were obtained 5 years after the initial biopsy in 47 of 60 patients initially reported. Fibrosis progression over that interval was minimal. The mean fibrosis score increased from 0.5 to 0.9 in 13 donors with normal ALT, remained constant in 19 with ALT levels one to two times the upper limit of normal, and decreased from 1.4 to 0.8 in 15 donors with high ALT levels. Overall, no patients developed severe inflammatory changes or progressed to cirrhosis in the 5-year interval, which brought the average follow-up time since exposure to 24 years.

Two very important outcome studies were derived from the inadvertent administration of HCV-contaminated Rh immune globulin. Kenny-Walsh et al.[43] recently described clinical outcomes 17 years after HCV infection that resulted from the use of contaminated lots of anti-D immune globulin in Ireland in 1977. Eight batches of HCV-contaminated Rh immune globulin were thought to have been administered. A national inquiry organized tracing of recipients of these contaminated lots. Of 62,667 women who presented for screening, 704 were found to be anti-HCV positive, of whom

390 (55%) were also HCV RNA positive. Extensive evaluation was accomplished for 376 (96%) of those HCV RNA positive persons. Analysis revealed that the mean age at exposure was 28 years, that all genotyped as type 1, that about one third had at least one other hepatitis C risk factor, and that 5% had a history of heavy alcoholism. Serum ALT values were normal in 45%, slightly elevated (40–99 IU/mL) in 47%, and exceeded 100 IU/mL in 8%. The median ALT concentration was 42 IU/mL. Liver biopsies were performed on 363 of the 376 subjects enrolled in the recall evaluation. No inflammation was found in 2%, grade 1–3 inflammation in 41%, grade 4–8 in 52%, and grade 9–18 in 4%. Strikingly, 49% had no fibrosis, 34% showed periportal or portal fibrosis (stage 1), 15% had portal to portal or portal to central bridging (stage 3), and 2%, probable or definite cirrhosis (stage 4). Two of the seven women with cirrhosis were also heavy alcohol drinkers.

These results were quite similar to those of a study in Germany that involved 152 women who also had received HCV-contaminated Rh immune globulin[44]; approximately 15 years after exposure, none of these women had evidence of chronic active hepatitis or cirrhosis. Although the duration of follow-up in these two studies of contaminated Rh immune globulin was only 15–17 years, it is striking that fewer than 2% of HCV infected subjects had cirrhosis and less than 10% had severe inflammation or fibrosis. The relatively benign outcome in these studies may reflect the small size of the viral inoculum, the young age at the time of infection, less rapid progression in females, or simply insufficient duration of follow-up. Nonetheless, these findings substantiate that of the other cohort studies cited above and studies in children cited below, each of which suggest that when the entire HCV-infected population is followed, only a small percentage have severe outcomes during the first two decades of infection. Indeed, in the Air Force study, relatively benign outcomes were observed over five decades of follow-up.

Outcome in Children

Data from studies of infants and children are just beginning to emerge. Hepatitis C infection is not common in children because perinatal spread is uncommon and because needle exposures are generally limited to blood transfusion. The National Health and Nutrition Epidemiologic Survey shows that the prevalence of anti-HCV in children aged 6–11 is only 0.2% and rises to only 0.4% in those aged 12–19.[15] One of the most comprehensive outcome studies in children was conducted by Vogt et al. in Germany,[45] who enrolled 458 children who had cardiac surgery before the implementation of blood donor screening (Table 1). The patients had undergone cardiac surgery a mean of 17 years (range, 12–27 years) earlier at a mean age at first operation of 2.8 years. None had received prior or subsequent transfusions and none had mothers with detectable HCV infection. An age- and sex-matched control group from the general population was also studied. Anti-HCV was detected in 67 (14.6%) patients compared with 3 (0.7%) among the controls. At follow-up evaluation, 37 patients (55%) were HCV RNA positive and 45% appeared to have spontaneously cleared the infection. All but one patient was found to have normal ALT values, and this single patient had severe right-sided congestive heart failure. Of the 17 patients who underwent liver biopsy, only 2 had histologic evidence of portal fibrosis, and both these patients had chronic congestive heart failure that might have accounted for the observed changes. One additional patient had "micronodular" cirrhosis, but this person was co-infected with the hepatitis B virus (HBV), and the relative role of HCV in the pathogenesis of the cirrhosis could not be established.

The study of Vogt et al. is the largest reported outcome study in children and describes a relatively benign course for transfusion-associated hepatitis C over a period of near 20 years. Importantly, they also found that almost one half of the infected children had spontaneously cleared HCV over this interval. The authors concluded that the natural history of chronic hepatitis C in childhood is either more benign or more slowly progressive than in adults.

Losasciulli et al[46] reported serologic and molecular follow-up data on 114 children with childhood leukemia of whom 56 (49%) were HCV RNA positive at the end of chemotherapy. Seventeen year follow-up of the HCV RNA positive cohort revealed that all were asymptomatic, that ALT values were normal in 71%, and that 16 of the 56 (29%) had spontaneously cleared their viremia. No liver biopsy data was reported in this study. A small study by Garcia-Monzon et al.[47] compared the outcome in 24 HCV-infected children and 22 HCV-infected adults. After a mean follow-up of 11 years, the comparative outcomes for children versus adults were as follows: mean viral load 3.6×10^5 versus 5.6×10^5 copies/mL, histologic grade (scale 0–4) 0.6 ± 0.7 versus 3.2 ± 1.1, and histologic stage (scale 0–4) 0.5 ± 0.5 versus 2.6 ± 1.2. Thus, despite similar viral loads, both hepatic inflammation and fibrosis were markedly less in children than adults.

Luban et al.[48] recently provided an interim report of a look-back study of 5,446 pediatric recipients of blood administered between 1982 and 1992. The mean age at transfusion was 1.0 year (range, birth to 10.7 years). The mean age at testing was 11 years (range, 4–17 years). Of 1,753 recipients thus far tested, 36 (2.0%) are confirmed anti-HCV positives compared with 0.3% of an age-matched nontransfused control population. Of the 36 HCV-positive children, all are asymptomatic. The range of ALT was 29–140 IU/L and 80% had at

least one ALT value greater than 1.5 times the upper limit of normal. Thus far, only 7 of the 36 have been biopsied. After a mean interval of 13.6 years since exposure to blood, six patients showed only mild inflammation without fibrosis and one patient had mild inflammation with early bridging fibrosis.

Thus, although data from pediatric follow-up studies are still sparse, the available data consistently show mild outcomes over the first two decades of infection with a high rate of spontaneous recovery (29–45%) as assessed by the loss of HCV RNA. Nonetheless, it is unclear whether hepatitis C is actually milder in children or just more slowly progressive. If the latter, then the long-anticipated lifespan of infected children would allow them to eventually reach the same levels of cirrhosis and HCC as persons infected later in life. It is critical that these childhood cohorts continue to be followed and reported and that additional studies be undertaken among children infected 10 or more years ago.

Fibrosis Progression and Interval to Development of Cirrhosis and HCC

Although retrospective studies do not provide the full spectrum of outcomes, they do provide insight into the interval between the presumed causative exposure and disease development. This is generally achieved by tracing back to a single transfusion episode or to a limited period of intravenous drug use. Both the Kiyosawa study[9] and the Tong study[10] related histologic diagnosis to the date of prior transfusion. In the Kiyosawa study[9] (Fig.1), transfusions had been received a mean of 10, 21.9, and 29 years earlier in patients with chronic hepatitis, cirrhosis, and HCC, respectively. Among the 21 patients with HCC, transfusions had been received as recently as 15 years earlier and as remotely as 60 years earlier. In the Tong study,[10] the mean interval from the date of transfusion to the diagnosis of chronic hepatitis was 13.7 years, to cirrhosis, 20.6 years, and to HCC, 28.3 years (Fig. 1). These two classic studies have led to the useful approximations that the interval to development of histologically recognized chronic hepatitis, cirrhosis, and HCC are 10, 20, and 30 years, respectively.

The rate of fibrosis progression to cirrhosis was evaluated in a large multicenter histologic analysis conducted by Poynard et al.[49] A total of 2,235 patients were recruited from three large population-based studies performed in France. Fibrosis progression was determined as a ratio between the fibrosis stage (scale of 0–4 METAVIR units) and the estimated duration of infection in years. The METAVIR scoring system incorporated fibrosis staging and activity grading using carefully defined parameters. Most data were derived from single biopsies, although 70 patients had paired biopsy samples. The median rate of fibrosis progression was

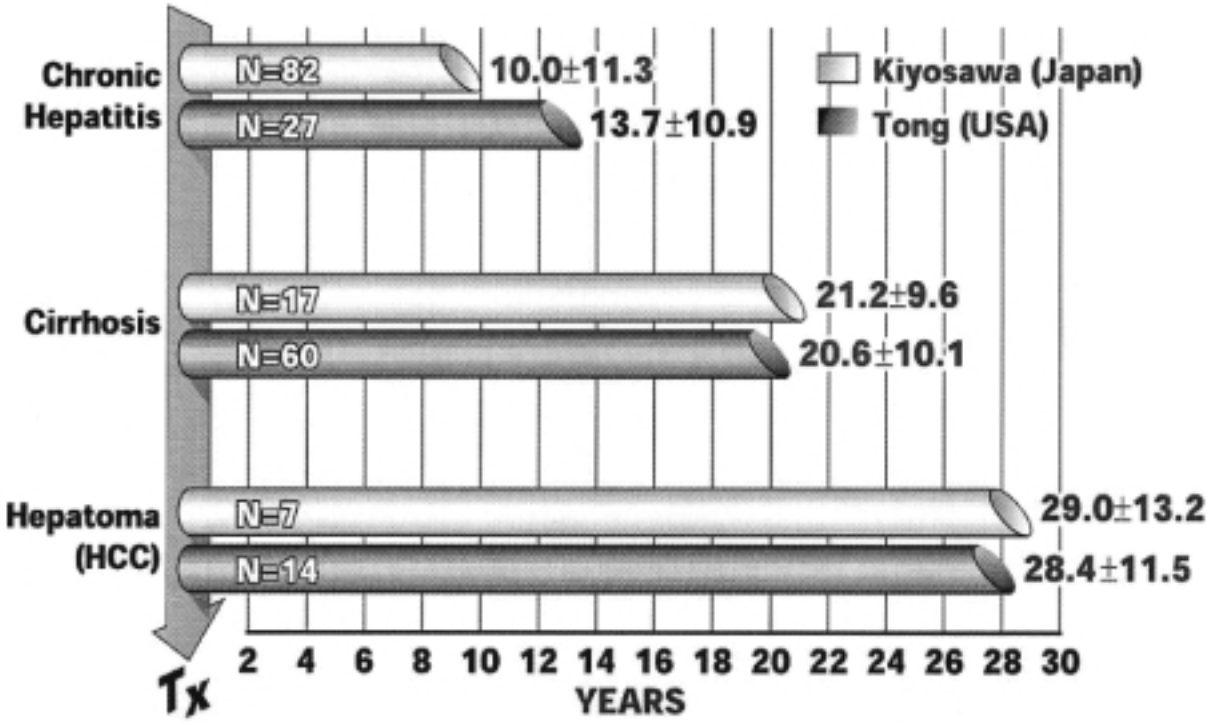

FIG. 1. The time course of HCV-related disease in two retrospective studies[9,10] that performed liver biopsies on referred patients with a past history of blood transfusion. The indicated duration of disease was based on the interval from the time of transfusion to the time of liver biopsy.

0.133 units/year. Thus, if fibrosis progression were linear, it would require 7.5 years to progress from one fibrosis stage to another and a median of 30 years to progress from no fibrosis to cirrhosis. By incorporating other variables in fibrosis progression, Poynard et al. estimated that the development of cirrhosis would range from a median of 13 years among men who were infected over the age of 40 and drank more than 50 g of alcohol/day to a median of 42 years for women infected under the age of 40 who did not drink. Because the rate of fibrosis progression was not normally distributed, they considered it likely that there are three separate populations with regard to outcome: rapid fibrosers, intermediate fibrosers, and slow fibrosers. These data prompted their view that about one third of HCV-infected persons will advance to cirrhosis in less than 20 years and that another one third would either never develop cirrhosis or would do so over a span of at least 50 years. These estimates are very consistent with the progression intervals defined by Tong et al.[10] and Kiyosawa et al.[9] and also with the observations of the previously cited prospective studies of transfusion-associated hepatitis.[27–30]

Outcome After the Development of Cirrhosis

An important and somewhat unexpected observation was that of the long duration of survival even after the development of cirrhosis. Fattovich et al.[50] conducted a retrospective follow-up study of 384 patients with compensated HCV-related cirrhosis to assess morbidity and mortality (Table 2). Fifty-one patients (13.3%) died during follow-up, 17 from HCC, 16 from liver failure, 6 from bleeding, and 15 from causes unrelated to cirrhosis. Thus, 9% died from liver-related causes 9–124 months (mean, 50 months) after study entry. Survival probability was 96% at 3 years, 91% at 5 years, and 79% at 10 years unless decompensation ensued, in which case survival fell to 50% at year 5. The annual mortality rate was 1.9% during the first 5 years. Multivariate analysis identified elevated bilirubin, physical evidence of cirrhosis and portal hypertension, older age, and low platelet count as independent risk factors for survival. Treatment with interferon was not identified to be an independent prognostic factor for survival.

HCC developed in 29 (8%) patients over periods of 7–134 months (mean, 48 months), the cumulative probability of its occurrence being 4% at 3 years after recognition of cirrhosis, 7% at 5 years, and 14% at 10 years. The calculated yearly incidence of HCC development was 1.4%. Among the remaining 355 patients, 65 (18%) developed evidence of decompensation at a mean interval of 37 months. Overall, most patients with documented cirrhosis in the Fattovich study survived for more than 10 years without evidence of hepatic decompensation or HCC.

A similar analysis was undertaken by Serfaty et al.[51] (Table 2). Among 668 patients with HCV infection referred to a tertiary care institution in Paris, 103 (15.4%) had cirrhosis. These patients were followed for a median period of 40 months (range, 6–72 months). Fifty-nine of the 103 were treated with interferon-α, six of whom developed normal ALT and three, a sustained virologic response. Twenty-six (25%) of the 103 patients with cirrhosis developed hepatic complications, consisting of HCC in 11 patients and hepatic decompensation without HCC in 15. HCC developed in 3% after 2 years and 11.5% after 4 years for a calculated annual incidence of 3.3%. The cumulative probability of decompensation without HCC at 2 and 4 years was 15% and 20%, respectively. Sixteen percent of patients died in follow-up, all but one from hepatic causes (liver failure, HCC, bleeding), and three patients underwent transplantation. The annual incidence of death or transplantation was 5.5%, and conversely, the cumulative probabilities of survival were 96% at 2 years and 84% at 4 years. In contrast to the Fattovich study,[50] interferon therapy was shown to reduce the risk of hepatic decompensation and HCC in patients with established cirrhosis.

HCV and HCC

Although the data for a causal relationship between HCV and HCC are not as compelling as for HBV, they

TABLE 2. Outcome in HCV-infected Patients after the Development of Cirrhosis

Author (Reference)	*No. Patients*	*Mean Follow-up (mo)*	*Hepatic Decompensation*	*HCC (%)*	*HCC Annual Rate (%)*	*Liver Death (%)*	*Annual Death Rate (%)*
Fattovich (50)	384	61	18.0	8.0	1.4	9.0*	1.9
Serfaty (51)	103	40	14.5	10.6	3.3	16.0	5.5

*Survival probability 91% at 5 years and 79% at 10 years unless decompensation ensued, in which case survival fell to 50% at 5 years.

nonetheless strongly suggest that HCV plays a major role in the evolution of HCC, usually through the intermediary development of cirrhosis. Although cirrhosis may not be an absolute prerequisite to the evolution of HCC, it has been substantiated that HCC develops in the setting of cirrhosis in at least 90% of cases. Because HCV does not integrate into the host genome, it is commonly speculated that malignant transformation is the byproduct of the numerous mitotic events that accompany compensatory hepatic regeneration in the face of progressive viral and immune-mediated hepatocellular destruction and fibrosis. This is clearly a simplistic explanation of complex extra- and intracellular events, but it provides a common foundation for the development of HCC in a variety of viral and nonviral diseases that affect the liver.

Although an association between HCV and HCC has been recognized throughout the world, the strongest evidence emanates from Japan, where HCC is the leading cause of cancer death in men. The association has been weaker in Western counties, particularly the United States, and has been more difficult to evaluate in areas such as China, Southeast Asia, and sub-Saharan Africa where HBV is highly endemic and is the leading cause of primary liver cell cancer.

One of the earliest clues to the relationship between HCV and HCC came from the study of Kiyosawa et al.,[9] who performed HCV serology on 54 HBsAg-negative patients with HCC; 94% were shown to have antibody to HCV. Most convincing in this study was the fact that serial biopsies were available from 21 patients who developed HCC at varying intervals after an established episode of transfusion-associated non-A, non-B hepatitis. In cases with frequent biopsies, the sequential progression from acute hepatitis to chronic persistent hepatitis to chronic active hepatitis to cirrhosis and then to HCC was well documented. In those with less frequent biopsies, histologic evidence of cirrhosis was documented before the onset of HCC in 18 of 21 (86%). The transfusion event that was the presumed source of HCV infection occurred 17–60 years earlier and most commonly occurred more than 30 years before the diagnosis of HCC.

A study of HCV seroprevalance among 105 HBV-negative HCC cases was undertaken in five districts of Japan[52]; 76% were found anti-HCV positive by first generation assays compared with 1% of donors in these same districts. A history of blood transfusion was found in 40% of the HCV-positive cases compared with only 5% of those with HCC related to HBV or of unknown cause. Hence, both transfusion and HCV infection were strongly associated with the occurrence of HCC in this population.

Also in Japan, Kato et al.[53] estimated the cumulative risk for HCC development in patients with cirrhosis related to HCV, HBV or a presumed non-ABC (cryptogenic) agent. Although the diagnosis of HCC was initially made using imaging techniques, most patients had histologic confirmation of the cancerous lesion. Based on clinical diagnosis, the 5-year and 10-year cumulative incidence of HCC was 25% and 57%, respectively. During follow-up of approximately 4 years, HCC was recognized in 38% of patients in the HBV group, 44% in the HCV group, and only 13% in the cryptogenic group. The cumulative risk for HCC was slightly, but not significantly, higher in HCV-infected patients compared with HBV-infected patients with a yearly incidence of 7–14%.

A recent representative study from Japan is that of Yoshida et al.[54] that focused on the effect of interferon in the prevention of HCC. This was a multicenter retrospective cohort study of 2,890 patients with chronic hepatitis C who had undergone liver biopsy since 1986; 2,400 (83%) were treated with interferon. HCC developed in 89 interferon-treated patients (3.7%) and in 59 of 490 (12%) untreated patients. Among untreated patients, the annual incidence of HCC increased with the degree of liver fibrosis from 0.5% in those with stage 0 or stage 1 fibrosis to 7.9% in those with cirrhosis. The cumulative incidence of HCC in treated patients was significantly ($p < 0.001$) less than that in untreated subjects for those who had stage 2 or 3 fibrosis at the time of enrollment. Overall, the risk of HCC during the follow-up period of 4.3 years was significantly affected by both the initial stage of fibrosis and treatment with interferon. In a multivariate analysis, the adjusted risk ratio for the interferon-treated group was 0.516 ($p < 0.001$) and 0.197 for the subset who had a sustained virologic response to treatment. Thus, this very large study confirms the progression from chronic hepatitis C to HCC, relates progression to the stage of fibrosis, and demonstrates that successful treatment with interferon can block both fibrosis progression and malignant transformation.

Although most studies on the relationship of HCV to HCC have derived from Japan, to various degrees there is confirmation of this association throughout the world. In Italy, Colombo et al.[12] found anti-HCV in 64 of 91 (70%) HBsAg-negative patients with HCC and in 22 of 41 (54%) patients with HCC who were HBsAg positive. Because the prevalence was similar in HBsAg-positive and -negative cases and because all anti-HCV-positive/HBsAg-negative cases were also anti-HBc positive, it was difficult in this study to isolate the impact of HCV in HCC causation. Nonetheless, the authors concluded that HCV was an important factor in the development of HCC and postulated that combined infection with HCV and HBV would be more likely to result in serious outcomes. In contrast, Chen and Chen,[55] who studied HCC in Taiwan, showed that patients coinfected with HCV and HBV were on the average 10 years older than HCC patients infected only with HBV. The authors

interpreted this observation to indicate that HCV did not accelerate the occurrence of HCC among HBV carriers. In another area of high HBV endemicity, Hadzyannis et al.[56] studied 65 cases of HCC in Greece and compared seroprevalance for HBV and HCV with that of age- and sex-matched controls with benign conditions. In a logistic regression model of HCC cases versus controls, the odds ratio for cases being HBsAg positive was 18.8 (CI, 8.2–43.2) and for being anti-HCV positive was 7.7 (CI, 1.7–35.1). In a study of 380 South African blacks with HCC, Kew et al.[57] found anti-HCV in 110 patients (29%) and in only 1 of 110 controls. However, only 27 (7%) had anti-HCV in the absence of markers for current or past HBV infection. Overall, in areas of high HBV prevalence, it appears that HCV plays a causal role in HCC pathogenesis, but the precise impact is difficult to ascertain because of the more predominant and confounding role of HBV.

In contrast to Japan where HCC is a leading cause of cancer death and where most cases appear related to HCV, in the United States, HCC accounts for only 2% of cancer deaths and the role of HCV in cancer causation is less well defined. Yu et al.[58] studied 51 patients with HCC in Los Angeles County; 15 of 51 (29%) patients with HCC had anti-HCV and the relative risk of HCC in those anti-HCV positive was 10.5. Based on combined HCV and HBV markers, it was estimated that of the 51 cases, 9% were related to HCV alone, 20% to HBV alone, and 18% to co-infection with HCV and HBV. Hence, most cases had no identified viral etiology. Di Bisceglie et al.[59] studied HCV prevalence in 99 consecutive cases of HCC and compared that with 98 cases with other malignant tumors. Anti-HCV was found in 13% of HCC patients and in 2% of controls, and the relative risk of HCC for those anti-HCV positive was 7.3. In this same study, 15% of cases were thought related to HBV infection, and the relative risk for HBsAg positive individuals was 17.3. Together, HCV and HBV accounted for only 28% of HCC cases. Thus, in these U.S. studies, HCV-infected patients have a definite increased risk of developing HCC, but the proportion of HCC cases due solely to HCV is low (13–17%). Most cases were unrelated to either HCV or HBV, implicating other viral or nonviral etiologies.

Two other U.S. studies, both involving patients from the Miami area, demonstrated a stronger association with HCC. Hassan et al.[60] retrospectively studied 59 patients with HCC, 90% of whom had biopsy-proven cirrhosis; 53% had anti-HCV by first generation assays and none had other risk factors for HCC. A high proportion (36%) of patients with HCC was negative for both HCV and HBV markers. Liang et al.[61] performed a molecular and serologic analysis of 112 patients with HCC referred to the University of Miami. None of the patients had nonviral risk factors for HCC and 95% had documented cirrhosis. HBsAg was found in 21 (19%) patients. Of the 91 HBsAg negative HCC cases, 29 (32%) had isolated HBV DNA in serum and/or liver and thus probably represent cryptic HBV cases, 42 (46%) were anti-HCV positive, and an additional 8 (9%) were HCV RNA positive in the absence of anti-HCV; 13% had no identified viral marker. Thus, 50 of the 91 HBsAg negative cases (55%) had serologic and/or molecular evidence of HCV infection. In addition, HCV markers were found in 6 of 21 (29%) HBsAg positive cases. HCV RNA was amplified from the liver tissue of seven of nine HBsAg negative cases; three of these patients had no HCV markers in their serum.

This study provides the most compelling evidence that HCV plays a prominent role in HCC pathogenesis in the United States as well as in Japan. Indeed, it has been argued that the differences in the incidence of HCV-related HCC in the United States and Japan is a reflection of time rather than pathogenesis. The average age of Japanese patients with HCC is 10–20 years greater than U.S. patients, raising the possibility that the HCV "endemic" began in Japan 10–20 years earlier than in the United States and that decades from now the United States will experience the same high rates of HCC as now seen in Japan. Alternately, there may be genetic factors or environmental cofactors present in Japan that either accelerate the progression to cirrhosis, providing the backdrop for malignant transformation, or that play a more direct oncogenic role. Only time will resolve this issue.

Cofactors as Determinants of Severity

The outcomes of HCV infection vary so widely from patient to patient that codeterminants of disease progression have long been suspected. Differences in outcome could relate to viral factors (viral load, viral genotype, multiplicity of quasispecies); host factors (age at infection, duration of infection, gender, immune deficiency, genetic susceptibility, co-infection with other viruses such as HBV and HIV, comorbid conditions such as hemochromatosis and iron overload); or external factors (chronic alcoholism, diet, smoking, medicines, established hepatotoxins, or undefined environmental contaminants).

Gordon et al.[62] studied whether the mode of HCV transmission affected long-term outcomes (Table 1). They found that 19–20 years after acquiring hepatitis C, the cumulative risk of developing cirrhosis in 215 patients who had been transfused was 55% compared with 21% among 195 persons who had been exposed through intravenous drug use ($p = 0.001$). The authors concluded that the risk of liver failure was more closely related to the mode of transmission than to other risk factors evaluated, including age and duration of infection.

Of the viral factors, HCV genotypes 1a and 1b appear to be associated with more severe disease and clearly are more resistant to therapy.[63,64] In contrast, there has been no reproducible relationship between viral load and disease outcome.[65] Although a prospective study has shown that the degree of diversity of the viral quasispecies during the first 4 months of HCV infection predicts whether the patient will recover or develop chronic liver disease,[20] there is no apparent relationship between viral diversity and disease outcome once chronic infection is established.

Of host factors, age at the onset of infection appears to be an important determinant of disease progression and severity. As indicated above, infected children seem to have a more benign outcome than infected adults. Also, the mildest outcomes in adults have been observed in those infected under the age of 40, as seen in the study of Air Force recruits[40] and the studies of HCV-contaminated Rh immune globulin[43] described above. Poynard et al.[49] assessed fibrosis progression in relation to nine factors: age at biopsy, estimated duration of infection, sex, age at infection, alcohol consumption, HCV genotype, hepatitis C viremia, cause of infection, and histologic activity grade. Only three factors were independently associated with fibrosis progression: age at infection (older than 40 years), daily alcohol consumption of 50 g or more, and male sex. Niederau et al.[26] also performed a multivariate regression analysis of factors that affected survival in HCV-infected individuals. Older age was a significant independent variable in decreased survival, as was cirrhosis, long disease duration, chronic alcoholism, and intravenous drug abuse. Age, however, is a complex variable to interpret. It is important to distinguish age at the onset of infection from age at the time of diagnosis. Older age at the time of diagnosis may simply reflect duration of infection, and it is clear that for many patients, the longer the duration of infection, the more severe the observed sequelae. In this respect, even though those infected at a younger age appear to do better, they also have a longer anticipated lifespan in which severe outcomes may ultimately emerge. Finally, there is the complex issue of whether there are elements of old age that will accelerate formerly stable disease independent of the duration of infection. Basically, do age-related changes in the host, such as depression of the immune system, accelerate the course of the disease? Unfortunately, it is difficult to design studies that clearly distinguish the influence of disease duration from the influence of age itself.

Hepatitis C progression appears to be more rapid in patients with hypogammaglobulinemia, most of whom have been exposed through contaminated lots of intravenous immunoglobulin. Rates of progression to cirrhosis of 31% and 35% have been observed within 10 years of exposure in two Swedish studies.[66,67] The immunosuppression associated with HIV infection also appears to influence outcome, though the data differ according to the source of infection. In hemophiliacs, who were frequently infected with both HCV and HIV before the viral inactivation of clotting factor concentrates, those coinfected with HIV had more severe histologic changes and higher liver related mortality than those infected with HCV alone.[24,68–70] Although there is a general correlation between low CD4 count, the level of HCV viremia, and disease severity in these studies, the exact mechanism by which HIV adversely influences the outcome of HCV infection is not well elucidated. In intravenous drug abusers co-infected with HIV and HCV, there is a clear inverse relationship between CD4 count and the level of HCV RNA but no consistent relationship between HIV infection and the severity of coexistent hepatitis C.[71]

Genetic factors may also influence the outcome of HCV infection through their effect on the immune response or other susceptibility factors. Although specific human leukocyte antigen alleles, particularly class II DR and DQ loci,[72,73] have been associated with disease progression, there has been no consistent genetic link to the outcome of HCV infection. Active investigations continue in this area, particularly in search of genetic links unrelated to HLA.

Of these potential cofactors, the relationship of alcohol to disease severity is the most clearcut and has been consistently demonstrated in multiple studies. In a unique study, designated the Dionysios study, Bellentani et al.[74] attempted to determine the extent and causes of chronic liver disease in the entire population of two small Northern Italian towns. The study enrolled 6,917 of 10,151 inhabitants (69%) and undertook medical and epidemiologic histories, physical exams, and serologic and biochemical testing. Among 1,211 patients diagnosed with chronic liver disease, 58% were attributed to alcohol abuse (>60 g/day), 16% to HCV infection, 3% to alcohol plus HCV, and 7% to HBV. The remaining cases were thought to be due to medications or other rare events. A different pattern emerged when serious liver disease was evaluated. Among 78 cases with cirrhosis, 28% were HCV related, 26% alcohol related, 9% HBV related, and 11% due to combinations of alcohol and virus; the remaining cases were hereditary or cryptogenic. Important to this analysis, among HCV- or HBV-infected patients who did not drink excessively, 11.5% and 8.7%, respectively, developed cirrhosis or HCC. In contrast, among HCV- or HBV-infected patients who drank excessively, 31.2% developed cirrhosis or HCC ($p < 0.001$).

The role of alcohol in exacerbating viral infection was dramatically demonstrated in a study by Corrao and Arico[75] wherein they compared lifetime teetotalers with alcohol abusers (175 g/day) according to HCV status

FIGURE

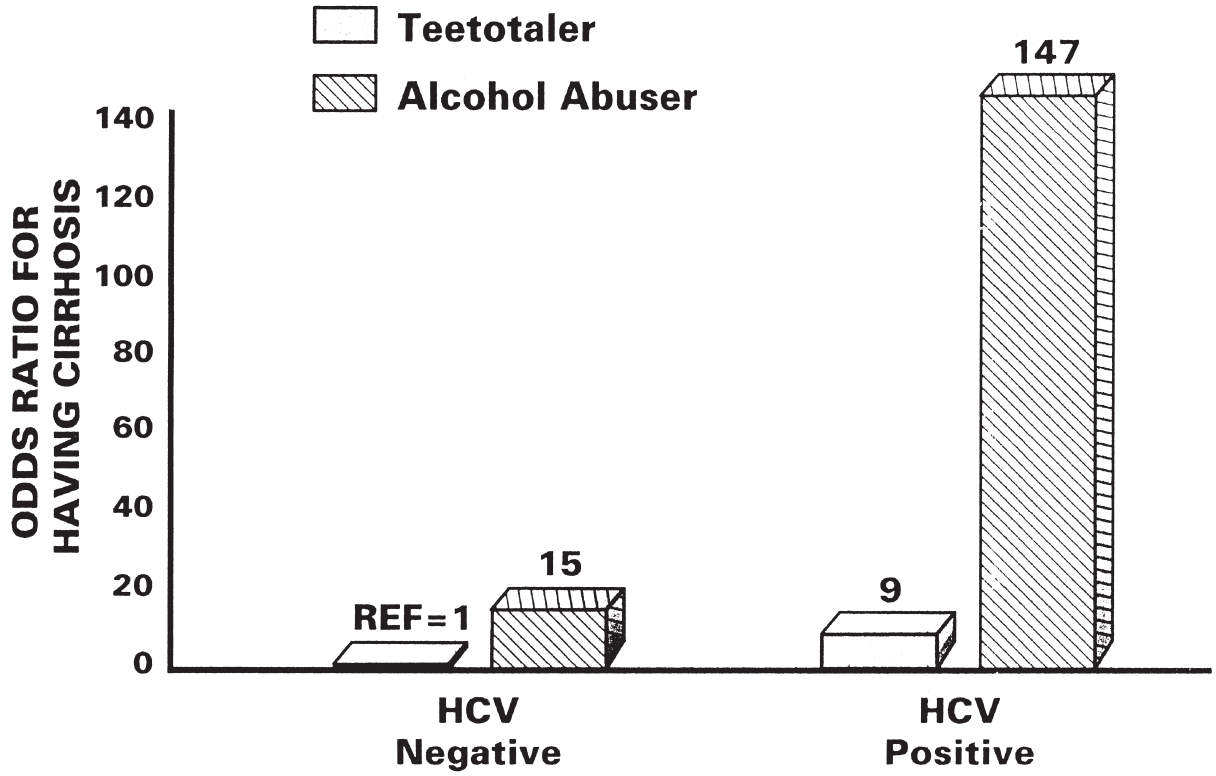

FIG. 2. Comparison of the risk of developing cirrhosis in relation to both alcohol abuse and HCV status. Persons who do not drink and are HCV negative are the referent group. Abusing alcohol in the absence of HCV imposes a 15-fold increased risk of cirrhosis. A nine-fold increased risk was observed in persons who were HCV-infected but abstained from alcohol. A marked increased risk (147-fold) was observed in patients who were HCV-infected and drank excessively. Thus, the combined deleterious effects of alcohol and HCV infection were substantially more than additive.

(Fig. 2). Subjects who did not drink and were HCV negative served as the reference population. The relative risk for developing cirrhosis in alcohol abusers who were not HCV infected was 15 and that for persons HCV infected who did not drink was 9. In contrast, in patients who were both HCV infected and abused alcohol, the relative risk of developing cirrhosis was 147. These studies, and others,[76–78] have led to the accepted conclusion that HCV-infected patients should abstain from alcohol or limit their intake to no more than one drink per day.

CONCLUSIONS

There is an incontestable association between HCV infection and the subsequent development of cirrhosis, HCC, and end-stage liver disease. At present, 30% of liver transplants in the United States are a consequence of underlying HCV-related cirrhosis. These are somber associations that are well publicized and create considerable fear in those diagnosed with hepatitis C, even though most such individuals have a clinically silent infection. It is important to provide this "silent majority" with a balanced perspective that incorporates probabilities not only of dire outcomes, but also long-term survival and successful therapy. When these elements are balanced, the patient is not only better informed but also generally relieved.

Although HCV infection is rarely encountered in the acute stages, it is important to ascertain outcome in those who are recognized during incipient infection. It has become increasingly clear that at least 15% of HCV-infected individuals have a spontaneous recovery, generally within the first year. The 15% recovery rate, based on the absence of HCV RNA in sequential samples and normalization of ALT, has been documented in prospective studies[7] and confirmed in population-based screening.[41] This spontaneous recovery in HCV infection is as unequivocal as is the progression to cirrhosis. Further, data now suggest that spontaneous recovery rates may be even higher than initially described. When cohorts known to have been HCV infected from a defined exposure are recalled decades later, the percent that maintain antibody but have lost HCV RNA has ranged from 26% to 45% (Table 3). It is probable that on average the recovery rate in acute HCV infection is closer to 20% than to the commonly cited 15%. The key issue then becomes the clinical outcome in the 80% who develop persistent HCV infection. There is an accumu-

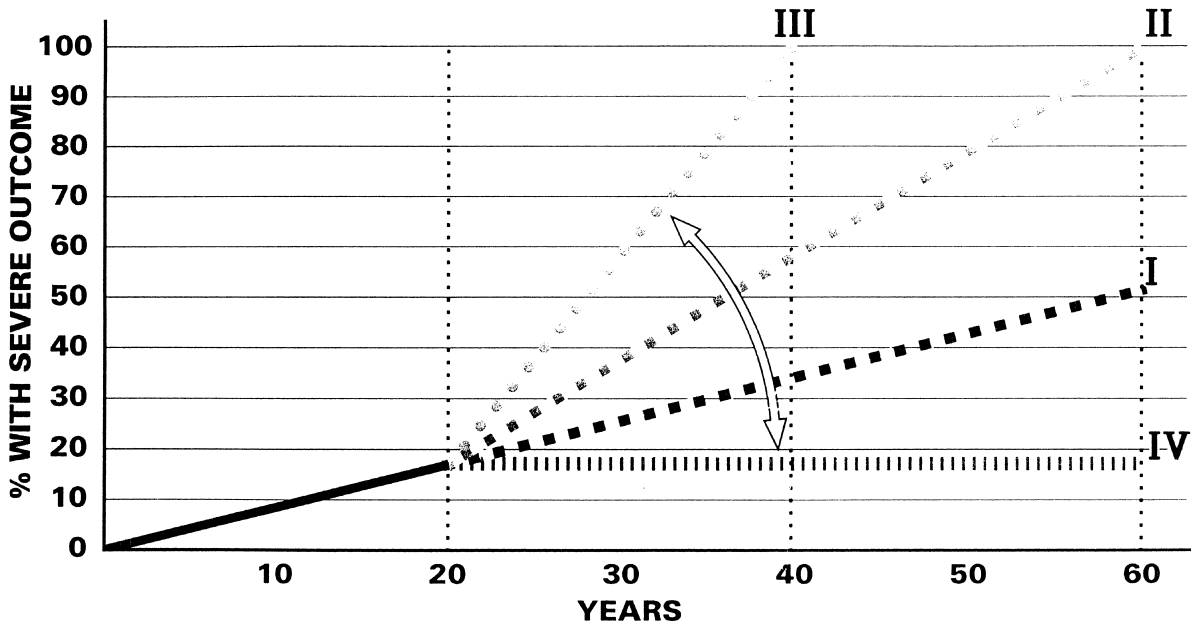

FIG. 3. Projection of the severe outcomes of HCV infection. The percent with severe outcomes in the first two decades of infection is based on a considerable body of evidence (see text) and appears to be less than 20%. Curve I assumes that the development of severe disease (fibrosis progression) will be linear and that approximately 50% of infected individuals will have severe outcomes 60 years after the onset of infection. Curves II and III assume that every HCV-infected individual will develop severe liver disease if they do not die of another illness in the 40–60 years that might be required for this indolent progression. Curve IV assumes that if severe disease has not developed in 20 years, it generally will not occur. The relative probabilities of these assumptions are discussed in the text, and it is the author's speculation that the "true" outcome will reside below curve I.

lating and consistent body of evidence that during the first two decades of HCV infection, fewer than 20% of patients followed prospectively from the time of acute infection or recalled subsequent to a known exposure have evidence of severe liver disease (Table 1). Indeed, in persons infected as children and young adults, the proportion with severe liver disease in the first two decades appears to be less than 5%.

Thus, at the end of 20 years, approximately 80% of HCV-infected individuals have either recovered, have stable chronic hepatitis, or have died of an intercurrent illness. To estimate the long-term outcome of HCV infection, attention must focus on the majority of infected individuals who have apparent stable or very slowly progressive liver disease. Figure 3 is databased for the first 20 years, showing a less than 20% incidence of severe disease during this interval, and then projects a series of potential long-term outcomes. In projection I, progression of liver disease is considered linear, advancing at a constant pace so that after 60 years of HCV infection, approximately 50% will have developed severe liver disease. Projections II and III assume an acceleration of fibrosis after the first 20 years of infection, in which case every HCV-infected individual would ultimately develop severe liver disease if they survived 40–60 years from the onset of infection. Projection IV makes a very different assumption, namely that if severe disease has not occurred in 20 years, it may never occur. The dilemma is to decide where the truth lies in these assumptions that project beyond our database? Conclusions drawn from these projections are clearly speculative and tenuous, but worthy of comment.

TABLE 3. Studies Indicating High Rates of Spontaneous Recovery* in HCV Infection

Author (Reference)	*Country*	*Percent Recovery**	*Setting*
Alter (15)	USA	26	Population survey (NHANES III)
Kenny-Walsh (43)	Ireland	45	Contaminated Rh immune glob.
Seeff (38)	USA	26	TAH—Adult
Vogt (45)	Germany	45	TAH—Pediatric

*Recovery based on the sustained loss of HCV RNA, generally with normalization of ALT and persistence of RIBA-confirmed antibody.
TAH, transfusion-associated hepatitis; NHANES III, National Health and Nutrition Epidemiologic Survey III.

Is HCV-related liver disease linear in its progression as depicted in curve I? The dramatically variable outcomes among HCV-infected patients argues against linear progression as do studies in blood donors,[42] blood recipients,[7,38] or unique cohorts.[40] The large METAVIR analysis of fibrosis progression by Poynard et al.[49] derives fibrosis units that assume a linearity of progression. Nonetheless, the authors recognize that fibrosis progression is neither linear nor normally distributed.

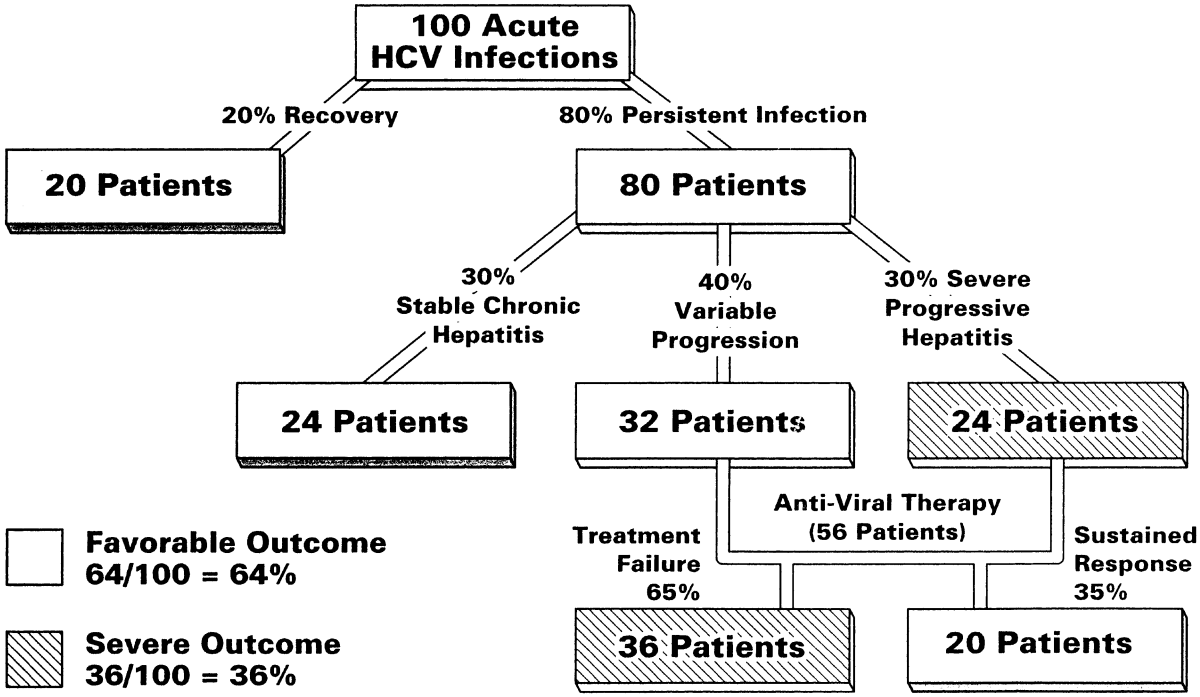

FIG. 4. Projected outcome in a hypothetical cohort of 100 individuals with acute HCV infection. Existing data (see text) suggests that 20% will spontaneously resolve their acute infection. Natural history studies suggest that of the residual 80 patients, 30% would manifest progressively severe liver disease, 30% would have stable chronic hepatitis that did not progress to cirrhosis, and 40% would have a variable outcome that might or might not eventuate in cirrhosis. The natural history of HCV infection is now tempered by therapeutic intervention. Because the ultimate outcome in an individual patient cannot be predicted accurately , most patients with chronic hepatitis are now being treated. The figure projects that of the 56 patients who might have advanced to cirrhosis during the natural history of their infection, 35% (20 patients) will be "cured" by existing combination therapy. The figure assumes that the 24 patients with stable chronic hepatitis will do well whether or not they are treated. Hence, of the total population of 100 acutely infected individuals, 64% will have a favorable outcome either through spontaneous recovery, an inherently stable chronic hepatitis, or a sustained treatment response.

They considered the likelihood that there are three populations consisting of rapid fibrosers, intermediate fibrosers, and slow fibrosers (we would add a category of nonfibrosers). Based on this, the investigators projected that about one third of HCV-infected individuals would advance to cirrhosis in 20 years, that a third would advance more slowly, and that a third would either never develop cirrhosis or require 50 or more years to do so. When combined, this even distribution of diverse outcomes could give the impression of a linearity that does not indeed exist. It is of interest that the METAVIR projections are not inconsistent with the ultimate outcome predicted by curve I wherein 50% would develop severe disease in 60 years.

Is there reason to suspect that liver disease progression will accelerate after the first 20 years due to increasing duration of infection or age-related changes in the host environment? Clearly, as indicated in this review, there is an established relationship between disease duration and disease severity and evidence that liver disease is more severe in the elderly.[9,49] Increasing disease severity over time is indeed integral to the assumptions of slope I (Fig. 3). In contrast, scenarios II and III are predicated on acceleration, a distinct change in the slope of the curve, at some point in time. Although this could occur, to date, there has been no published evidence to support an acceleration of fibrosis progression after any given number of years of infection or any given age. Rather there are early data that the liver disease can be nonprogressive for up to 50 years.[40] Overall, curve I appears more likely and more evidence based than curves II or III.

Curve IV suggests that patients who have not demonstrated progression to more intense inflammatory activity or fibrosis by 20 years may never do so. There is little published evidence to support the flat trajectory depicted in curve IV, but anecdotally, long-term follow-up of HCV-infected patients in NIH prospective studies has demonstrated that some have late spontaneous normalization of ALT levels and diminution in anti-HCV reactivity despite the continued presence of HCV RNA and others have persistently normal or near-normal ALT with minimal histologic lesions in repeat biopsies obtained over the course of two decades. More detailed studies are required to determine if there is a true "burnout" or complete long-term stabilization of HCV-related

liver disease, as also suggested in the METAVIR analysis.[49] Based on the above considerations, it is our speculation that in the absence of treatment, the natural history of HCV infection will lie somewhere between curves I and IV, perhaps closer to curve I. Successful treatment would, of course, lower the slope as it improves outcome; highly effective therapy would flatten the curve.

Clearly, these long-term projections are speculative, but it seems reasonable, based on the data in this review, to conclude that of 100 persons acutely infected with HCV (Fig. 4), 20% (20 patients) will spontaneously recover and 80% (80 patients) with develop persistent infection. Of the 80 persons with persistent infection (chronic hepatitis C), based on the composite data presented in this review, it would appear that up to 30% (24 patients) will have progressively severe liver disease culminating in cirrhosis and/or HCC and another 30% (24 patients) will have stable liver disease that will not progress to cirrhosis and its serious sequelae whether or not treatment is given. The remaining 40% of those chronically infected (32 patients) will have a slowly evolving infection whose outcome cannot be predicted (Fig. 4). This results in 56 patients who are either highly likely to progress to cirrhosis or who have a variable and unpredictable likelihood of fibrosis progression. Of these 56 patients, approximately 35% (20 patients) can be "cured" by existing combination therapy,[79] leaving only 36 (36%) from this theoretic cohort of 100 acutely infected individuals who will have progressive HCV-related liver disease not responsive to therapy. In addition, the slow pace of HCV progression will allow time for the development of improved treatments that will further diminish long-term morbidity and mortality.

Although this perspective allows reasonable hope for the individual HCV-infected patient, it is not intended to ignore the large number of persons who may die or require liver transplantation as a result of HCV infection. This individualized perspective is also not intended to diminish the enormous global impact of HCV infection engendered by the sheer magnitude of the infected population. The absolute number of dire events on a global scale is staggering even if the proportion that encounters those events is encouragingly small.

ABBREVIATIONS

ALT alanine aminotransferase
CTL cytotoxic T lymphocyte
HAI histologic activity index
HBV hepatitis B virus
HCC hepatocellular carcinoma
HCV hepatitis C virus
HIV human immunodeficiency virus
PCR polymerase chain reaction
RIBA recombinant immunoblot
VA Veterans Administration

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