CHAPTER 4

Understanding Hepatitis C Disease

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SECTION 1

Liver Disease Progression

Introduction

Throughout this book, you will often read that *chronic hepatitis* C and its treatments affect each person differently. The broad range of variability observed between persons living with hepatitis C is especially true of disease progression. There is no accurate way to predict the course of chronic hepatitis C in an individual person.

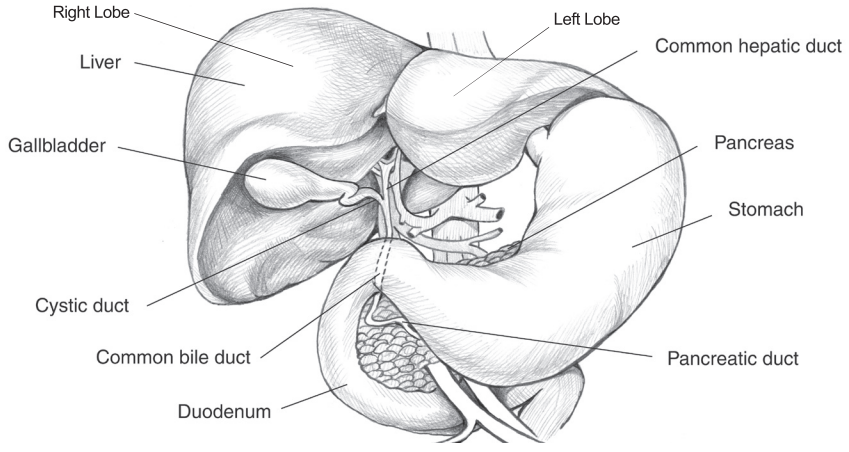
This chapter provides information about possibilities that *might* happen. Remember, none of the situations discussed in this chapter will necessarily happen to you. However, it is important to be aware of the possibilities so that if any of them do occur, you will be prepared and better able to make good decisions.

About the Liver

The liver is the largest internal organ of the body. In a normal adult, the liver weighs 3½ to 4 pounds (1,300 to 1,500 grams). It accounts for about 2.5% of the total weight of the body. The liver is wedge-shaped (see Figure 1). It measures approximately 7 inches (14 cm) across by 5½ inches (18 cm) along its diagonal.

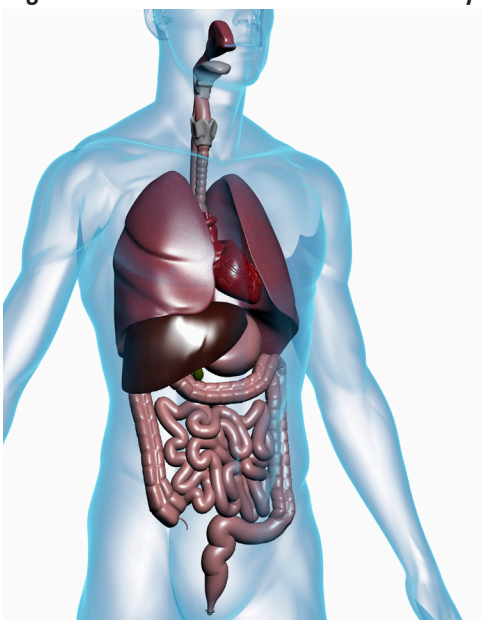
The liver is divided into two main lobes, the right and the left. The right lobe is slightly larger than the left and extends down the right side of the rib cage. The left lobe extends from the right lobe to about the middle of the abdomen. There are also two minor lobes of the liver, the caudate and quadrate lobes. *Fibrous* ligaments separate the lobes. All lobes of the liver perform the same functions. The entire liver is enclosed in a fibrous sheath called Glisson's capsule.

Figure 1. Anatomy of the Liver *



*Courtesy of National Institute of Diabetes and Digestive and Kidney Diseases

Figure 2. Placement of the Liver in the Body



The liver is located on the right side of the abdominal cavity just below the lungs and diaphragm, the muscle that separates the chest cavity from the abdominal cavity (see Figure 2). The liver is packed so tightly into the abdomen that the right kidney, parts of the large and small intestines, and the stomach actually leave impressions on its surface. Even the ribs and muscle bands of the diaphragm make indentations on the surface of the liver.

Approximately 25% to 30% of the blood coming from the heart goes to the liver. Although there are no *lymph nodes* in the liver itself, it produces over ⅓ of the body's *lymphatic fluid*. The fluid drains into *lymph channels* and lymph nodes in the abdomen.

The hepatitis C virus (*HCV*) enters the body through the blood stream. It is carried by the blood to the liver where it infects *hepatocytes* (liver cells). HCV reproduces in liver cells. Studies suggest HCV is also reproduced in cells of the blood and bone marrow.

Once diagnosed with hepatitis C, you will have many tests to determine the status of your disease. For detailed information on the tests you may have and why, see *Chapter 6, Laboratory Tests and Procedures*.

Checking blood levels of the *liver enzymes* such as *alanine aminotransferase* (*ALT*) and *aspartate aminotransferase* (*AST*) is one way to tell if liver cells are dying. When liver cells die, ALT and AST are released into the blood. After an abnormal amount of liver cell death, ALT and AST levels rise over a period of 7 to12 days and then slowly return to normal. If liver cells continue to die in abnormally high numbers over time, ALT and AST levels remain elevated.

ALT and AST levels provide information about liver damage, but do not provide information about how much liver repair is taking place. Studies show that liver enzyme levels do not predict disease outcome. You can have normal liver enzyme levels and still have liver damage.

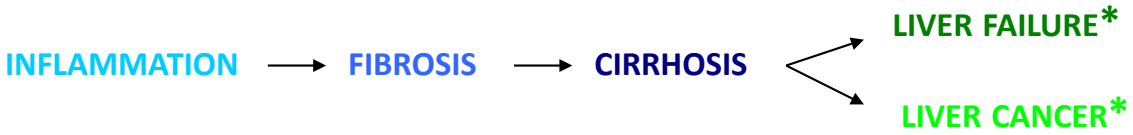
Liver enzymes also provide no information about how well the liver is functioning.[1, 2] Your liver can maintain its many functions despite a remarkable amount of damage. Therefore, it is important to look at the results of other test such as *albumin*, *bilirubin*, *prothrombin time*, and *platelet* count to determine how well your liver is functioning.

Liver enzymes such as AST and ALT reflect liver damage but not liver function. Liver enzymes do not predict disease outcome.

Stages of Disease Progression

Like other liver diseases, HCV disease progresses in *stages*. The usual progression is from *inflammation* to *fibrosis* to *cirrhosis* (see Figure 3). Cirrhosis can progress to end-stage liver disease and/or can give rise to *liver cancer*.

Figure 3. Chronic Hepatitis C Disease Progression



Inflammation

Inflammation is the body's normal response to injury or infection. When the liver is inflamed, there is an overabundance of special cells called inflammatory cells in the liver. Inflammation is labeled chronic when it persists for prolonged period of time.

Chronic inflammation can lead to changes in liver structure, slowed blood circulation, and the death of liver cells (*necrosis*). Prolonged liver inflammation can eventually cause scarring, which is called fibrosis. By controlling liver inflammation, you can potentially control progression to fibrosis.

Fibrosis

Fibrosis is the harmful outcome of chronic inflammation. Fibrosis is scar tissue that forms as a result of chronic inflammation and/or extensive liver cell death. Your healthcare provider uses the amount of fibrosis in your liver as one way of evaluating how quickly your hepatitis C appears to be progressing. Knowledge of approximately when you were initially infected with HCV is a great help in determining your rate of disease progression.

The best way to accurately determine the amount of fibrosis in the liver is to have a *liver biopsy*. No other test can give you and your healthcare providers the important information that is learned from a liver biopsy.

Cirrhosis

When fibrosis becomes widespread and progresses to the point that the internal structure of the liver is abnormal, fibrosis has progressed to cirrhosis. Cirrhosis is the result of long-term liver damage caused by chronic inflammation and liver cell death. The most common causes of cirrhosis include viral hepatitis, excessive intake of *alcohol*, inherited diseases, and *hemochromatosis* (abnormal handling of iron by the body).

Cirrhosis leads to a reduction in blood supply to the liver. The loss of healthy liver tissue and reduced blood supply can lead to abnormalities in liver function. Even when liver disease has progressed to cirrhosis, it may still be possible for the damage to be at least partially reversed if the underlying cause can be eliminated. Cirrhosis progression can usually be slowed or even stopped with effective treatment.

People are often surprised to learn that you can have cirrhosis of the liver and not know it. The onset of cirrhosis is usually silent with few specific *symptoms* to signal this development in the liver.

As scarring (fibrosis) and liver cell destruction continue, some of the following *signs* and symptoms may occur:

- loss of appetite
- nausea and/or vomiting
- weight loss
- change in liver size
- gallstones
- generalized, persistent itching (*pruritus*)
- *jaundice*

Despite the seriousness of cirrhosis, large numbers of people live many, many years with cirrhosis without symptoms and without progressing to liver failure.

Once cirrhosis develops, it is very important to avoid further progression of the disease. Consumption of alcohol in any form, including such things as certain mouthwashes and cough medicines, must be completely avoided by people with cirrhosis.

If you have cirrhosis, this may be a time to reevaluate your treatment goals. If you have not had *interferon-based therapy*, you may want to consider it or other available treatments that aim to rid the body of HCV. It may also be time to look into other means of improving your liver health.

Liver Cancer

Most people with HCV never develop liver cancer. Nonetheless, people with HCV are at an increased risk for liver cancer. The presence of cirrhosis and/or having been infected with HCV for more than 20 years further increases the level of risk. The development of liver cancer (*hepatocellular carcinoma*) is most commonly seen in people who have cirrhosis,[3] but rare cases of this cancer have been reported in HCV patients without cirrhosis.[4] The reported risk for the development of liver cancer among HCV-positive patients with cirrhosis is 1% to 2% per year.[5]

Liver cancer screening remains controversial in the United State because there are no large scale *clinical trials* to prove that such testing improves overall liver cancer survival rates. However, liver cancer screening among people with chronic hepatitis C is widely accepted and practiced by most *hepatologists* and *gastroenterologists*.

Liver cancer is life threatening, so do not delay telling your healthcare provider about any changes in your symptoms. If you have cirrhosis, you need to be followed closely by a healthcare provider who will monitor you with the appropriate liver cancer screening tests such as liver *ultrasonography* and/or *alfa-fetoprotein* levels.

Liver Biopsy for Determining Disease Progression

Scoring Inflammation and Fibrosis

The most accurate way to check the severity of liver disease is with a biopsy. A liver biopsy is a test in which small pieces of liver tissue are removed and examined under a microscope. The three main things that will be looked for are inflammation, fibrosis, and cirrhosis. The biopsy report may also reveal other *histological* and *pathological* findings such as the presence of lymphoid nodules, damage to small *bile* ducts, and/or the presence of fat.

Many people are surprised to learn it is possible to have normal liver enzymes and still have cirrhosis. (See *Chapter 6, Laboratory Tests and Procedures* for additional information about liver enzymes.) Remember, a liver biopsy is the only way to know with certainty whether cirrhosis has developed.

Liver Biopsy Scoring and Grading

When you receive the results of your liver biopsy, you will hear the terms inflammatory *grade* and fibrotic *stage*. Healthcare providers use these terms to indicate the amount of injury to the liver. Three different methods are used for scoring liver biopsies. This can cause confusion for both patients and healthcare providers. Be aware that the scoring systems are also subject to interpretation by the doctor in the laboratory who examines your biopsy. The three most commonly used scoring systems for liver biopsies in the U.S. are described below.

KNODELL SCORING SYSTEM (ALSO KNOWN AS THE ORIGINAL HAI [HISTOLOGY ACTIVITY INDEX])

This was the first scoring system established to specifically assess the changes (inflammation and fibrosis) seen with chronic hepatitis. It was introduced in 1981 and remains the most commonly used scoring system.[6] The system uses three categories to describe the amount of inflammation and liver cell death present, and a fourth category to assess the fibrosis (which is reported on a scale of 0 to 4).

The tricky part of interpreting a Knodell Score is that the three inflammatory grading numbers and the fibrosis staging number are added together into a single final score. This "problem" is overcome by examining each of the four individual numbers reported instead of just the final score.

ISHAK SCORING SYSTEM (ALSO KNOWN AS THE MODIFIED HAI)

The Ishak scoring system is a modification of the Knodell HAI system. It is reported to be more sensitive and accurate in assessing fibrosis than the original HAI system. Fibrosis staging is scored from 0 to 6 (instead of 0 to 4). The Ishak scoring system is frequently used in the *clinical* research setting because of its detail.

METAVIR SCORING SYSTEM

The METAVIR scoring system was first introduced by a study group out of France in 1996. The METAVIR system has the advantage of being somewhat simpler than the Ishak system to use, but that simplicity is also considered by some to be its greatest disadvantage because it lacks the detailed specificity of other systems. The METAVIR scoring system gives an inflammation score (0 to 4) and a fibrosis score (also 0 to 4).

Two other systems currently in use to describe the histological activity seen on liver biopsies are the Scheuer system and the Batts-Ludwig system. If your biopsy is reported with either of these systems, talk with your doctor to get the results explained to you in terms you can both understand and use in your decision-making process.

Interpreting Your Liver Biopsy Results

A few key factors will help you understand your liver biopsy report.

- What system did the laboratory use to grade each of your biopsies?
  - A score for a given biopsy characteristic in one system does not mean the same thing in the other systems.
- The scores for all the characteristics of the tissue sample are added together for a final score, except as specified in the notes under the table for that system (see Tables 1-5).
  - If you have had more than one biopsy, you need to look at changes in both the individual characteristics and changes in the overall score.
- A final score from one biopsy may have the same score as that of a follow-up biopsy, but the scores for individual characteristics may have changed. This means your situation could actually be better or worse depending on the individual characteristic scores.

Ask your healthcare provider to explain the results of your liver biopsy thoroughly. Ask for an explanation of the individual scores as well as the final score. Your report should contain a description of the inflammatory grade and fibrotic stage. Ask to speak with the laboratory that evaluated your liver biopsy if your healthcare provider is unable to provide this information.

A liver biopsy is an invasive test that you are unlikely to want or need frequently. It is very important to understand the results of your liver biopsy so you can use this information to help you make decisions about your healthcare. Tables 1 through 5 compare the Knodell (Orginal HAI), the Ishak (Modified HAI), and the METAVIR liver biopsy scoring systems. They are presented here courtesy of David Kleiner, MD at the National Cancer Institute.

Table 1. Comparison of Liver Biopsy Scoring Systems – Periportal Necroinflammatory Changes

Score	Knodell/Original HAI[a(7)]	Ishak/Modified HAI[(8)]	METAVIR[b(9)]
0	None	Absent	Absent
1	Mild piecemeal necrosis	Mild (focal, few portal areas)	Focal alteration of the periportal plate in some portal tracts
2		Mild/Moderate (focal, most portal areas)	Diffuse alteration of the periportal tract in some portal tracts or focal
3	Moderate piecemeal necrosis (involves less than 50% of the circumference of most portal tracts)	Moderate (continuous around <50% of tracts or septae)	Diffuse alteration of the periportal plate in all portal tracts
4	Marked piecemeal necrosis (involves more than 50% of the circumference of most portal tracts)	Severe (continuous around >50% of tracts or septae)	

[a]The periportal component of the Knodell HAI has been split into a periportal piecemeal necrosis and a bridging/confluent necrosis component for better comparison to the other scoring systems. In order to recreate the original scale, the bridging/confluent necrosis component should be added to the periportal piecemeal necrosis component.
[b]The periportal component of the METAVIR score is used with the focal necrosis score to determine overall inflammatory activity.

Table 2. Comparison of Liver Biopsy Scoring Systems – Bridging and Confluent Necrosis

Score	Knodell/Original HAI[a(7)]	Ishak/Modified HAI[(8)]	METAVIR[b(9)]
0	Absent	Absent	Absent
1		Focal confluent necrosis	Present
2	Bridging necrosis (more than two such bridges)	Zone 3 necrosis in some areas	
3		Zone 3 necrosis in most areas	
4		Zone 3 necrosis + occasional portal-central bridging necrosis	
5		Zone 3 necrosis + multiple portal-central bridging necrosis	
6	Multilobular necrosis	Panacinar or multiacinar necrosis	

[a] The periportal component of the Knodell HAI has been split into a periportal piecemeal necrosis and a bridging/confluent necrosis component for better comparison to the other scoring systems. In order to recreate the original scale, the bridging/confluent necrosis component should be added to the periportal piecemeal necrosis component.
[b]The METAVIR score for bridging necrosis is not used in the overall activity determination by this system and is provided only for comparison with other scales.

Table 3. Comparison of Liver Biopsy Scoring Systems – Focal (Spotty) Lobular Necrosis and Hepatocellular Apoptosis

Score	Knodell/Original HAI[a](7)	Ishak/Modified HAI[8]	METAVIR[b](9)
0	None	Absent	Less than one necroinflammatory focus per lobule
1	Mild (acidophilic bodies, ballooning degeneration, and/or scattered foci of hepatocellular necrosis in less than 1/3 of lobules/nodules)	One focus or less per 10x field	At least one necroinflammatory focus per lobule
2		2 - 4 foci per 10x field	Several necroinflammatory foci per lobule or confluent/bridging necrosis
3	Moderate (involvement of 1/3 to 2/3 of lobules/nodules)	5 - 10 foci per 10x field	
4	Marked (involvement of more than 2/3 of lobules/nodules)	More than 10 foci per 10x field	

Table 4. Comparison of Liver Biopsy Scoring Systems – Portal Inflammation

Score	Knodell/Original HAI[7]	Ishak/Modified HAI[8]	METAVIR[b](9)
0	No portal inflammation	None	Absent
1	Mild (sprinkling of inflammatory cells in less than 1/3 of portal tracts)	Mild, some or all portal areas	Presence of mononuclear aggregates in some portal tracts
2		Moderate, some or all portal areas	Mononuclear aggregates in all portal tracts
3	Moderate (increased inflammation in 1/3 to 2/3 of portal tracts)	Moderate/marked, all portal areas	Large and dense mononuclear aggregates in all portal tracts
4	Marked (dense packing of inflammatory cells in more than 2/3 of portal tracts)	Marked, all portal areas	

[a] The METAVIR score for bridging necrosis is not used in the overall activity determination by this system and is provided only for comparison with other scales.

Table 5. Comparison of Liver Biopsy Scoring Systems – Fibrosis

Score	Knodell/Original HAI[a](7)	Ishak/Modified HAI[8]	METAVIR[b](9)
0	No fibrosis	No fibrosis	No fibrosis
1	Fibrosis portal expansion	Fibrosis expansion of some portal areas, with or without short fibrous septa	Stellate enlargement of portal tracts without septae formation
2		Fibrosis expansion of most portal areas, with or without short fibrous septa	Enlargement of portal tracts with rare septae formation
3	Bridging fibrosis (portal-portal or portal-central linkage)	Fibrosis expansion of most portal areas, with occasional portal to portal bridging	Numerous septae without fibrosis
4	Cirrhosis	Fibrosis expansion of portal areas, with marked bridging (portal to portal as well as portal to central)	Cirrhosis
5		Marked bridging with occasional nodules (incomplete cirrhosis)	
6		Cirrhosis, probable or definite	

Table 6 shows how the HAI inflammation scores relate to the grade of histological injury. In the HAI system, the various inflammation scores are added together. These numbers are directly related to the descriptive grade of inflammation.

Table 6. Relationship of Aggregate Inflammation Scores to Grade of Activity[10]

Sum of inflammation Scores in HAI or Modified HAI systems	Description of Activity
0	None
1-4	Minimal
5-8	Mild
9-12	Moderate
13-18	Marked

Other Liver Biopsy Findings

FATTY LIVER (STEATOSIS OR STEATOHEPATITIS)

Fatty liver is a general term indicating the accumulation of fat in liver cells. *Steatosis* is the presence of fat in liver cells without inflammation. *Steatohepatitis* is the presence of fat in liver cells with inflammation. You may hear other terms to describe fatty liver, depending on your medical condition.

- *NAFL – nonalcoholic fatty liver*
- *NAFLD – nonalcoholic fatty liver disease*
- *NASH – nonalcoholic steatohepatitis*

Fatty liver is emerging as a major medical problem. Obesity affects up to 35%[11] of adults in the U.S. population and 17% to 33% have NAFLD.[12] Approximately one-third of people with NAFLD will have progressive liver disease.[13]

For the hepatitis C patient, fatty liver is another factor that may accelerate in the progression of fibrosis.[14] A liver biopsy can determine both the presence of fat in the liver and the level of fibrosis. This information will allow your healthcare provider to counsel you about your risk of progressive liver disease.

Alcohol consumption can increase the amount of fat in the liver and is the most common cause of fatty liver. The association between fatty liver and alcohol is another very important reason for you to refrain from drinking any alcohol. However, not all cases of fatty liver are caused by alcohol use. Diabetes and high *triglycerides* are also associated with fatty liver and should be managed closely by your healthcare provider.

The liver must *metabolize* any fat that is not eliminated through the intestinal tract. If you eat excessive amounts of fat, the amount that goes to your liver may be too much for it to metabolize. Excess fat that is not metabolized begins to accumulate in the liver. This accumulation of fat can cause inflammation. Inflammation can lead to scarring, which may eventually lead to decreased liver function. Therefore, it is important not to have excessive amounts of fat in your diet. It is particularly important to limit your intake of animal fat because animal fat is especially difficult for the liver to metabolize. See *Chapter 15, Nutrition and Hepatitis C* for suggested dietary guidelines.

Achieving or maintaining your ideal body weight (a *body mass index* [*BMI*] of approximately 20 to 25) and limiting the amount of fat in your diet are important for your liver health. Your BMI is calculated by taking your weight (in kilograms) and dividing by your height (in meters) squared. A free BMI calculator is available on the Internet at www.nhlbisupport.com/bmi/bmicalc.htm. Normal body weight not only helps your liver but can also improve your energy level, reduce *hypertension*, and lower your risk of heart disease. Regular exercise can help you maintain a normal body weight and avoid the development of fatty liver.

If you are considering interferon-based therapy, obesity may play a role in your response. One study showed an 80% decrease in *sustained response* to interferon therapy in obese patients compared to those with normal body weight.[15] Your doctor may suggest weight loss before beginning interferon-based therapy if you are significantly above your ideal body weight. Healthcare providers have also begun to *advocate* for individualized weight-based dosing of *pegylated interferon* alfa-2b (PegIntron®) plus *ribavirin* to improve the chance for response to treatment One large study showed that heavier patients were much more likely to achieve an SVR with weight-based ribavirin dosing versus flat-dosed ribavirin (64% versus 25%).[16]

People with fatty liver often have high *blood sugar* and *lipids* such as *cholesterol* and *triglycerides*. If you have a fatty liver, your healthcare provider should monitor you for the development of these problems.

Some medications and other substances can cause fatty liver. Be sure to review all of your medications with your healthcare provider and avoid the following, if possible.

- alcohol
- amiodarone (anti-arrhythmia medicine)
- methotrexate (arthritis medicine)
- high doses of *vitamin A*
- tetracycline (antibiotic)
- cortisone (steroid medicine)
- prednisone (steroid medicine)

Systemic Complications of Hepatitis C

Although the effects of HCV on the liver are most visible, the virus can affect other body systems and organs. This results in *extrahepatic* (outside the liver) conditions or manifestations of *chronic hepatitis* C.

Many *autoimmune* diseases occur as secondary diagnoses after a primary diagnosis of chronic hepatitis C or in association with hepatitis C. Some examples of these diseases include:

- type 2 diabetes
- mixed *cryoglobulinemia*
- *thyroiditis*
- *erythema nodosum*
- erythema multiforme
- *glomerulonephritis*
- *hypothyroidism*
- *lichen planus*
- polyarteritis
- *urticaria*
- *porphyria cutanea tarda*
- *polymyalgia*
- *B cell lymphoma*
- Mooren corneal ulcers

There is much controversy regarding the true cause of the many so-called HCV-related conditions that have been reported. Some of them probably are related to hepatitis C. Others probably are not, and occurred by chance in a few individuals unrelated to HCV. Many studies on this topic come from clinics that treat only specific diseases, which may skew the study findings.

The way HCV produces extrahepatic conditions and the true prevalence of these conditions is the subject of ongoing research. The link to type 2 diabetes has been studied by numerous groups and it appears that HCV causes *insulin* resistance.[17-20] In other HCV-related extrahepatic conditions, HCV stimulates the *immune system* to produce *autoimmune antibodies*, *antibodies* against the body's own tissues. This appears to be the mechanism for HCV-related *thyroid* and blood disorders.

We are hopeful that ongoing research will help clarify both the mechanism of these potentially debilitating conditions and new treatments to help alleviate the suffering caused by them.

Summary

The question of whether it is the virus or the person infected by the virus that determines how HCV disease will progress is an active area of medical research. At this point, several personal factors and several viral factors have been identified that may influence the rate of HCV disease progression.

Personal factors related to disease progression include some variables you can control. The consumption of alcohol can markedly affect disease progression. The amount of fat in one's diet, and body weight can also influence disease progression and treatment outcomes. Your environment, diet, exercise plan, lifestyle, and support system may all be important factors that could affect the course of your HCV infection.

In terms of viral characteristics, the existence of multiple *quasispecies* can accelerate disease progression. HCV *genotype* affects response to interferon-based therapy and is therefore an important factor in halting disease progression by *viral clearance*.

Progression of chronic hepatitis C in any given person cannot be predicted. The majority of people will not progress to cirrhosis. However, the seriousness of this disease for people with advanced cirrhosis is beyond question. If you follow the progression of your disease with all the tests available to you, you will be in a better position to make informed decisions about your treatment options.

We are confident that ongoing research will improve the ability to predict disease progression and intervene more effectively.

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