HEPATITIS C.

Donald Jensen, MD

DR. WILLIAM BAKER: Very early this year when we were setting up the program for this meeting, hepatitis C, a subject which is of interest to all of us for risk appraisal and claims adjudication, was the topic that we wanted to include.

I wanted to get a Chicago based physician to talk about this to us and I spoke to a couple of good gastroenterologists who said, when asked who in Chicago is noted and can talk on hepatitis C with authority, they said you've got to get Dr. Donald Jensen.

I called the Association for the Study of Liver Disease which has its meeting here in Chicago every year and they said the man in Chicago you have to talk to and try to get is Dr. Donald Jensen. I called his office and I talked to him and he was very happy to put this on his schedule and we're very happy to have him here this morning to talk to us. He is the associate professor of medicine and chief of clinical hepatology at Rush Presbyterian.

Those of you from the UK will be happy to know that he had part of his fellowship in the liver unit of King's College in London. He's been president of the Chicago Society of Gastroenterology and he's right on the forefront of studying the treatment of hepatitis C with interferon and other modalities. I'd like to welcome Dr. Donald Jensen.

DR. JENSEN: Thank you very much. It's certainly a pleasure to be here with you today. I traveled all the way across town. It took me about 20 minutes. I'm sure many of you came from a lot further than that. I think it's appropriate, in this week of Ken Burns' 18 hour saga of baseball that I start with this quote attributed to Yogi Berra, "Listen up because I've got nothing to say and I'm only going to say it once." I am going to move fairly rapidly through this and as a method of introduction, I've actually decided to start with a little case report.

This is a case that is very typical and very common to practicing physicians, not just gastroenterologists. I'll briefly summarize. A 48-year-old male presents to your office because of an elevated AST level. This was discovered during a life insurance physical. The value is 67 international units per liter. He states he had a normal physical examination three years previously, including normal lab work. He says that he feels well.

When I talk to other physicians and ask them, your next step in evaluation of this patient would be A, perform a comprehensive history and physical examination, which is sort of like motherhood and apple pie; B, repeat liver chemistries; C, obtain hepatitis A, B and C serologic studies; D, order an ultrasound of the liver; E, order other serologic studies for viral hepatitis ANA, ferritin ceruloplasmin.

Well, the right answer is actually repeat the liver chemistries. Don't necessarily do a comprehensive history and physical examination on this patient unless that's what he came to your office for. But he came purely for a single isolated AST elevation, we would repeat the liver chemistries. I'll show you a little later why we would do that.

After we repeat testing the AST is 55 and the ALT is 101. So it's confirmed and the ALT is elevated. The remainder of the chemistry 20 profile is normal. History reveals that the patient notes mild fatigue, no significant past history, drinks three to four cocktails once or twice a week and takes no drugs or medications. The family history is unrevealing. Prior labs reveal that his ALT three years ago was actually mildly abnormal, 47.

So it wasn't completely normal. But it's common that people will tell you that physicians will tell patients not to worry about those minor elevated transaminase and the patients assume that means it's normal. Physical examination reveals that he is 30 percent over his ideal body weight. There are no other cutaneous stigmata of liver disease. The liver span is 11 centimeters and no other abnormalities are noted.

I think the key facts in evaluating abnormal liver enzymes in a patient such as this, we have to go back to some data, actually some from the Journal of Insurance Medicine back in 1984.

Figure One. Biochemical screening of healthy populations reveals that two to six percent, if we use just chemistry panel screening, two to six percent will have abnormal liver enzymes. But the prevalence of liver disease in the population is considerably less than one percent. Many of those patients obviously don't have liver disease that have those elevated liver enzymes.

When we look at those patients with elevated liver enzymes and repeat them later, approximately two thirds, and actually in one study 80 percent, of patients with an isolated AST or ALT elevation will not be confirmed with repeat testing. So the answer to our question, what should we do with that initial presentation,
that initial ALT elevation is actually just a repeat at first because two thirds of those will be negative on repeat testing. Mild single elevations are more likely to be false positive than are more severe elevations, greater than threefold elevated or multiple enzymes are elevated.

So your next step in evaluating this patient would be to obtain liver ultrasound, advise weight reduction and repeat ALT testing in three months, discontinue alcohol and repeat testing in three months, obtain viral hepatitis A, B and C serologic studies or obtain other studies for iron, TIBC, ferritin and ceruloplasmin. The answer in this case is advise weight reduction and repeat testing in three months.

Now, why weight reduction? Why not discontinue alcohol? Why not do the hepatitis serologic testing at this time? If we look at our algorithm for evaluation of an ALT elevation, or AST elevation, we would first want to do repeat testing and if it's an isolated elevation of the ALT, confirm that it actually is liver origin for the AST elevation.

We know that AST elevations can be found isolated in marathon runners and other exercise program aficionados so it may not indicate liver disease necessarily. Then obtain a comprehensive history and physical examination after you've confirmed that it's truly elevated. And then if there is an alcohol history and the alcohol history is important, because people don't get liver disease from alcohol unless they drink significantly above 50 grams of alcohol a day.

So you have to drink more than three or four beers per day to actually get significant liver damage from alcohol. This is a patient who drank a couple of cocktails twice a week, really is not at high risk for alcoholic liver disease or hepatitis. Obesity present, and we'd certainly want to discontinue any potential drugs or medications that might lead to liver disease.

**Figure Two.** We talk about steatosis, we talk about fatty infiltration of the liver and we talk about overweight individuals. There are some studies that are relevant to this. Necropsies on healthy accident victims age 18 to 58 reveal that hepatic steatosis was present in 15 to 20 percent of these. Half had steatonecrosis, actually had inflammation along with the steatosis. If a person is obese, greater than 75 percent above their ideal body weight, this is associated with steatosis in 90 percent of patients.

So 90 percent of those will have fat in the liver, and this fat may be associated with increased liver enzymes. Another study that's pertinent to this is steatosis is noted in 30 to 75 percent of diabetics, only half of whom have elevations of their AST.

Over the next two months a weight reduction diet was without effect on the serum ALT level or the patient's weight. Subsequent testing revealed hepatitis B surface antigen negative, hepatitis B core antibody negative. His hepatitis C antibody was positive, his ANA was negative, smooth muscle negative, iron TIBC normal, ferritin normal and his oc 1-antitrypsin level normal.

So after three months it's probably appropriate to consider obtaining disease specific testing for that persistent elevation of the AST and ALT. I think this can be individualized for individual patients. You obviously want to know if they have risk factors of hepatitis but many patients who have viral hepatitis actually do not have risk factors for this particular problem.

Metabolic liver disease we want to consider and in particular we want to consider hemachromatosis since this is probably the most common genetic metabolic disease involving the liver. It's estimated that approximately one in 200, one in 300 individuals will have hemachromatosis. So it's a very common metabolic disease for there is a very good cure with phlebotomy therapy.

Ceruloplasmin for Wilson's disease would only be done at somewhat under the age of 45 or so and an oc 1-antitrypsin deficiency, especially if there's a family history. Immunologic disease, more common in women than men, but we certainly wouldn't want to forget about those particular abnormalities.

So in this particular patient a confirmatory test for hepatitis C was performed which was positive which was the RIBA-II. Later in the discussion we'll talk about some of the serologic tests for hepatitis. A liver biopsy was then done after a period of time which revealed evidence of minimal steatosis and mild chronic active hepatitis without fibrosis.

Remember the patient didn't have any symptoms, should this asymptomatic patient be offered treatment with alpha interferon? This is a question that practitioners and gastroenterologists are
faced with fairly commonly. This is a fairly indolent disease, the symptoms are mild. We know interferon can make patients feel sick. So this is a legitimate question that should kick off our discussion today.

Things we need to know before we can answer this question: We need to know what the natural history of chronic hepatitis really is. What’s the risk that this individual will develop cirrhosis or more advanced liver disease over his lifetime? Can this outcome be modified by interferon? Are we really doing anything when we treat these patients with interferon? And what are the toxicities or side effects of the interferon that we’re giving?

Let’s talk a little about hepatitis C. Hepatitis C was really called non-A, non-B hepatitis until it was discovered by the Kyron Corporation in 1988. In 1988 the first publication of the discovery of hepatitis C was published. It was published in that prestigious medical journal, The Wall Street Journal. It wasn’t until a year later, in 1989, that publication occurred in the scientific journal, the journal Science.

Then we came to realize that this was a 10,000 nucleotide RNA virus, classified as either flavi virus or pesti virus but we’re still not sure what its classification is. It has a worldwide distribution and there are at least two genotypes of the hepatitis C and we now think there may be up to 11 genotypes of hepatitis C. This virus has a strong predilection for mutating quite easily. The more we look, the more different genotypes we can find of this particular virus.

As we said, it has a worldwide distribution. In the US, there are approximately 150,000 to 170,000 new cases occurring each year. This is data from the CDC and it’s probably fairly reliable.

Of all the people infected with the hepatitis C virus, approximately 50 percent will fail to eliminate the virus and remain persistently infected. Now, this 50 percent is probably a fairly conservative figure. I think figures that more people believe in is probably close to 70 percent of people will fail to eliminate the virus and become persistently infected.

It’s the rule, rather than the exception, that those patients infected with this virus will continue to harbor the virus indefinitely. So at least 75,000 people each year will become persistently infected and probably closer to 100,000 or 125,000.

Of all adults in the United States, if we look at blood bank volunteers, and this may not be perfectly represented, the figures seem to be fairly consistent from center to center, about 7 to 1.4 percent have evidence of hepatitis C infection. If you do the statistics, that’s about 1.8 million to two million adults in the United States have evidence of hepatitis C infection.

So it’s actually a fairly common virus, much more common that hepatitis B which actually has more cases per year than hepatitis C but with a high predilection for becoming chronic. There are actually more chronic hepatitis C patients than hepatitis B patients. Of those patients who are persistently infected with the hepatitis C virus, up to 20 percent will develop cirrhosis over a 20 year follow up period and that accounts for about 15,000 cases of cirrhosis per year.

Primary liver cancer occurs in a greater frequency in patients with hepatitis C and cirrhosis and some current suggests that this frequency of liver cancer in patients with hepatitis C and cirrhosis may be as high as ten to 20 percent. So it’s actually not a rare phenomena. Nowadays with screening, transfusion and the risk of developing hepatitis C from transfusion is much less than this two percent figure. The figure now is considerably under one percent of transfused individuals who will develop post-transfusion hepatitis due to hepatitis C. But if we look at those patients that have acute hepatitis C from transfusion, 50 percent or more will go onto develop chronic hepatitis, 20 percent risk of cirrhosis and two to 20 percent risk of developing a hepatocellular carcinoma.

So out of this three and a half million, between 140 and 1,400 patients may develop a hepatocellular carcinoma or less. And this is only looking at transfusion associated. We have to remember that nowadays transfusion associated hepatitis accounts for less than 15 percent of all cases of hepatitis C that we now see in the United States.

Some might argue that if a patient has chronic hepatitis C and mild liver biopsy, in other words, has chronic persistent hepatitis on liver biopsy, that patient is not at any significant risk of developing chronic liver disease.

A study published by Takahashi last year that looked at patients who had liver biopsies performed for hepatitis C over the past 20 years and they looked at the natural history of those patients who had chronic persistent hepatitis on their initial liver biopsy or their initial liver biopsy findings, of those with mild or chronic persistent hepatitis, 50 percent of those patients progressed to more severe liver disease over about a 12 year period of time.

So the chronic persistent hepatitis or mild liver lesion is not necessarily so benign when we’re talking about hepatitis C. If they had moderate histologic activity, mild chronic active hepatitis, 60 percent of these progressed to more severe chronic active hepatitis or cirrhosis over a nine year period of follow up. If they had severe chronic hepatitis when first seen, 71 percent progressed to cirrhosis over a mean time period of seven years.

So this is not a benign disease. This is a disease that has the potential of progressing to more severe liver disease even though the patients may be mildly symptomatic or asymptomatic and even though the initial liver histology may be fairly mild.

What are the risk factors for hepatitis C? Clearly this is blood borne infection and intravenous drug use is a major risk factor. Blood transfusion recipients nowadays accounts for about 50 percent of the patients we see with hepatitis C, and because of the more effective screening this figure is decreasing with time.
We're seeing less and less patients presenting with a history of blood transfusion.

Sexual transmission of this disease is possible but seems to be uncommon. Unlike hepatitis B, where 60 or 70 percent of sexual contacts may become exposed to hepatitis B, with hepatitis C the figure is markedly reduced. Original studies suggested it was between zero and five percent of sexual contacts would become exposed to the hepatitis C virus. A more recent paper suggested it may be as high as 30 percent in people who had been married for a long period of time, where the relationship was constant and the individual who had the hepatitis C had a high level of circulating virus in his blood stream, over time there was about a 30 percent risk in some of those sexual partners.

Forty to 50 percent of cases had no known risk factors. We call those sporadic. So when we evaluate patients with hepatitis C and we go through whether they've had intravenous drugs or blood transfusions or IV drug use or sexual transmission, we end up coming up blank about 50 percent of the time.

Many patients with chronic hepatitis C have no symptoms of their liver disease as in the patient that we presented here today. He was totally asymptomatic and had chronic hepatitis on his liver biopsy. When we do question these patients we find that the most common symptom that they do have is usually fatigue. But fatigue is such a ubiquitous symptom in our society that it's not very specific for hepatitis C. Now, we can say in retrospect that it may have been due to hepatitis C. If we treat that patient for their symptoms, then the fatigue symptom goes away.

We can say retrospectively that that fatigue was likely due to hepatitis C. The presence or absence of symptoms does not predict severity of the liver disease or the risk of progressing to cirrhosis and there are very good studies to support this, that even though a patient may be mildly a symptomatic doesn't mean that they don't already have severe histologic disease or liver biopsy and doesn't predict whether they're going to go on to develop more severe histologic disease in the future. So it makes it very difficult for us as clinicians to evaluate these patients and give them an accurate prognosis.

Symptoms and blood test abnormalities are poor predictors of liver biopsy findings, as we just said, and cirrhosis may be present with few clinical or laboratory abnormalities. In my practice about 30 percent, 40 percent of the patients I see are referred to me for hepatitis because of hepatitis C. Many of those patients when we biopsy them have cirrhosis and many I would not have predicted would have had cirrhosis ahead of time. So as hepatologists we're wrong because the clinical and biochemical findings don't really mesh with what we find histologically.

The other thing to keep in mind, and we're going to talk about this at the end, is that liver transplantation is being performed for hepatitis C and at most centers around the United States. About 25 percent of all liver transplants done in the United States are done for cirrhosis due to hepatitis C and its complications.

Let's talk a little about testing. I don't want to get too fancy with this and I don't want to spend too much time with this because it's really not that relevant to your applications. But realize that there are several recombinant proteins that are produced from the hepatitis C virus RNA. The first was the 511 protein, later the C100 and these others.

These have been recombinantly produced and are capable of being used for testing. The test, which was the enzyme linked assay to detect antibodies against hepatitis C. It was directed against this C100 protein. This test is not currently being used.

The problems with this first generation EIA was it was only positive in 20 percent of patients with acute hepatitis C, 80 percent of those with chronic hepatitis C and false positive results occurred any time there was increase in gamma globulin concentrations. So it suffered from both sensitivity and specificity problems.

The currently licensed test measuring antibody responses to the hepatitis C virus, the second generation assay, which is now the routine assay used in the United States, is 65 percent sensitive to patients with acute infection and over 90 percent in chronic infection. And what they've done for the second generation assay is extend this protein to the C200, make this a larger protein and add a structural protein, the C22, to gain more protein sites for the antibody to react against. So assay is currently quite sensitive for hepatitis C, but still not perfect. False positive tests may occasionally occur particularly in patients with immunologic diseases, even with the second generation assay.

Before we treat anyone with interferon we want to confirm that this antibody is a true positive and not a false positive and we therefore do supplemental tests which are either the RIBA-II or the matrix assay. I'll tell you a little about what RIBA-II is. The RIBA-II are recombinant immuno-block assay, takes these four proteins, C22, C33, C100, 511, immobilizes them on a nitrocellulose strip and looks for antibody reactivity against each of these specific antigens.

So if we take these four proteins immobilized on nitrocellulose, include a control, super oxide dismutase and then looking for binding to each of these specific antigens, if there are two or more bands present, that's a positive result. It's less likely that a person with just hyperglobulin anemia will have antibody reactivity strong enough to these isolated bands to become false positive. So this test is much more specific than the EIA-II or second generation EIA and is currently our confirmatory test.

If we compare these tests, EIA-I, EIA-II and RIBA-II, in terms of sensitivity we see that the EIA-II and RIBA-II have comparable sensitivity but the advantage of RIBA-II is more specific. The presence of hepatitis C virus, now, remember all the tests that we've talked about up to now measure antibody to hepatitis C.

We can measure the virus directly by measuring the RNA of the virus in either liver or plasma. The way we measure the RNA of the virus is by polymerase chain reaction or PCR, but this test is
not licensed. It’s extremely sensitive, the most sensitive and specific test we have but is quite expensive, about $200 to $300 per test to do PCR to measure this virus directly. So it’s not something that’s practically used on a day to day basis. For most purposes it’s not something that we need on a day to day basis.

We’re going to shift gears a little bit and talk about treatment now, since we’ve talked about diagnosis. Patients with chronic hepatitis C, since it’s a viral infection, may be candidates for treatment with alpha interferon.

Natural interferons represent the body’s major defense against viral infections. Alpha interferon has been genetically produced in a highly purified form for administration and it is approved by the FDA. There’s only one currently approved interferon and that’s the alpha II-B interferon. There are other interferons, alpha II-A, beta interferon and census interferon which are undergoing clinical trials but all seem to be comparably effective.

Interferons act in the somatic cells of the body by a number of different mechanisms. They have anti-tumor effects and the first use of interferon in humans was actually against hairy cell leukemia and other solid tumors.

The effects that we’re interested in are these two effects, antiviral effects, it actually decreases viral entry on coding, RNA synthesis and protein synthesis by the virus in the cell, and its immuno-modular effects, it actually can induce or increase the immune effects of the host against viral infected liver cells. So it works in two different mechanisms.

The goals of treatment in hepatitis C might include any one of these particular goals. We don’t get all of these goals. Sometimes we don’t get any. We want, ideally, to eradicate the virus or decrease viral replication, decrease hepatic necrosis, reduce symptoms of liver disease and ideally halt progression to cirrhosis and hepatocellular carcinoma. Those are the goals that we look for.

If we look at the studies of patients that were treated with interferon, three million units three times a week for six months, it’s given by subcutaneous injection, three million units TIW for six months, liver enzymes and liver biopsy improve in approximately 50 percent of the patients during this six month course of therapy. Hepatitis C RNA may or may not disappear along with normalization of the ALT level.

**Figure Three.** An example of a patient with persistently elevated ALT levels. The saw-toothed pattern of ALT is shown in Figure Three. This is typical of hepatitis C. The patient treated with interferon, the ALT level promptly goes to normal, also typical. Often within several weeks of initiating therapy the ALT will be normal, the hepatitis C RNA becomes negative, the ALT stays normal, the interferon discontinued, the patient remains hepatitis C RNA negative and ALT normal. This is the ideal situation.

**Figure Four.** Unfortunately that doesn’t occur all the time, and of those 50 percent of patients who respond, 50 percent of those relapse during the next six months. Some may relapse even later. The studies were only carried out to six months. But some have shown to relapse even later. If re-treated 86 percent again will respond to interferon therapy. So we don’t see to induce mutations that make the virus less responsive over time.

A patient that relapsed and is hepatitis C RNA positive, treated with interferon, ALT came to normal, but when interferon was discontinued, the ALT came back to its pre-treatment level and the hepatitis C RNA again became positive. This is the typical response of interferon in those who relapse. So we can say that 50 percent responders, 25 percent of those will be continued responders and another 25 percent will relapse after interferon is discontinued.

Patients without cirrhosis seem to respond better than patients with cirrhosis and excessive iron in the liver diminishes the response to interferon. Those are investigational things that we’re looking at right now. High pre-treatment hepatitis C RNA is associated with a lower response rate.

So the more virus you have, the less likely you are to respond to this particular form of therapy. Flu-like symptoms may occur with interferon therapy. Transient bone marrow suppression can occur. Thyroid abnormalities, which now seem to be reversible, can occur in less than one percent of patients, and depression or irritability can occur and this may lead to discontinuing the medication. So who should we treat?

We should consider treatment for patients with elevated liver enzymes for at least six months, a liver biopsy demonstrating
chronic hepatitis, a positive test for hepatitis C antibody that's confirmed with an assay such as RIBA-II and well compensated liver function. We don't want to treat patients with cirrhosis.

I'd like to stop there and thank you all for your attention. I'd be happy to entertain a question or two if you'd like.

(Appause.)

AUDIENCE MEMBER: I was very interested to see you use the transaminase throughout your talk and never mention GGTP. Most of the people in this room represent companies that use a blood panel that includes the GGTP. I had our company eliminate that test a year ago because of its horrid specificity. I feel we're penalizing up to 90 percent of people with isolated GGTP elevations. I'd appreciate your comment.

DR. JENSEN: Well, I have the same problem. Up until about two years ago, three years ago, our hospital didn't even put GGTP on its inpatient panel of laboratory tests. We finally did it at the urging of the transplant surgeons because they like to look at GGTP as an early predictor of rejection. But since it's been on the panel, we've spent countless investigations of patients with elevated, isolated elevated GGTPs that turned out to be red herings. It turned out to be they were associated with a drug or medication, associated with some alcohol. It's a very sensitive enzyme for induction by alcohol.

So a few drinks can induce moderate levels of GGTP in the blood and don't necessarily indicate underlying liver disease. So I don't like to use GGTP for a screening test. I think it's better left as a confirmatory test for liver disease. I think you end up spending a lot of time and money chasing down elevated GGTPs that aren't specific. I actually agree with you in that particular regard.

AUDIENCE MEMBER: At what point after an apparent successful treatment with interferon would you feel comfortable that the patient is unlikely to relapse and therefore, if there was no cirrhosis on the biopsy, might then become insurable?

DR. JENSEN: That's a very important question. There are some studies now that are trying to get at that very point. If we look at those patients, and it seems to be about 20 percent, there was a study recently in the Lancet that had about 20 percent of their complete responders had long lasting, in other words, three or four years later, long lasting normalization of their ALT and negative hepatitis C RNA.

So of those complete responders, about 20 percent of those may have been "cured" of their disease. I would feel that a year follow up, we're going to see relapse within a year, biochemical relapse within a year. I'm not sure what it means and there's a small percentage of patients that have persistently normal ALT level who relapse virologically.

So a small number of patients may have virus come back after six months but the ALT level stays normal. When we do liver biopsies on those patients, many of them, their liver looks pretty good. So I think those patients are probably insurable from that point of view.

I think the final common thing that we look at is histology in terms of determining progression to their liver disease at that particular point. So I think, yeah, I think there's a lot of data that we still need on this, but I would say between six months and a year, if they haven't shown signs of relapse that they're probably in pretty good shape.

AUDIENCE MEMBER: You mentioned in your slide on transfusion, would you care to comment on blood products such as gamma globulin?

DR. JENSEN: The risk of hepatitis C from other blood products other than red cells seems to be extremely low. It's low enough now even with red cells, with the current screening. Gamma globulin preparations, I've not aware of any studies that have implicated gamma globulin studies in the transmission of hepatitis C. It seems to be very safe.

The preparation of gamma globulin, the cold cone fraction, seems to be free of hepatitis C RNA in those preparations. So other than blood product, platelet, red cells, there doesn't seem to be much risk in the other products.

AUDIENCE MEMBER: May I just comment that such cases of gamma globulin are being investigated in Sweden at this time.

AUDIENCE MEMBER: Saturday I was privileged to present some data to the medical management committee and show that over the past five years, we have seen an increase in GGT from five percent to about nine percent of our proposed insured.

These were data that were confirmed by commercial laboratories that were present in the room. I was really worried about this before I presented the data, so I called the New York City blood center and asked them if they have seen a rise in the ALT's that they have measured over the past years, where in 1981 it was five percent.

And indeed they confirmed that they've seen these non-specific rises to the point that they've not going to permanently defer individuals who have an isolated ALT; but allow them to reapply as blood donors in a year.

So I think we see a lot of transient changes in these liver function tests, but is it potentially a risk in your mind that we might be admitting some people with elevated ALT's, especially when you see the saw-toothed pattern that you presented?

DR. JENSEN: Well, I think we've all seen patients with ALT levels, there's two aspects to this question. Number one is we've seen patients with the saw-toothed pattern whose ALT levels may transiently go to normal. So it's conceivable that we could...
patients were on the average 50 years of age when they got their transfusions. So we're looking at a disease with a long natural history, and if we're starting at age 50, a lot of those patients are going to die, particularly if they were transfused in the late 1960s.

Most of them had open heart surgery and other things, so the death rate due to other causes could obscure an increased death rate due to their underlying liver disease. There's been a lot of criticism of that. People are now going back and looking at patients that are younger, saying we'd like to look at patients that have hepatitis C from the age of 30 on, or the age of 20 on. Is their life impacted by this hepatitis C?

On the opposite side of the coin, is that at transplant centers— and there are now over 100 liver transplant centers in the United States, 25 to 30 percent of the transplants that are done in this country, are done for complications of liver disease due to hepatitis C.

There are 3,000 to 4,000 liver transplants done, so you're saying 800 to 1,000 liver transplants in this country are done each year for patients with end-stage hepatitis C and a life threatening complication. So it's not a benign disease. Where's the middle ground? How can we predict? We don't know that yet.

I think that data that we need to still generate but it clearly has the capability of causing end-stage liver disease and its complications. How often, we don't know. And over what period of time, we don't know. It's still open for question.

AUDIENCE MEMBER: I deal primarily with disability claims. I'd be very interested in your clinical observations as to if and when in the progress of the disease you see fatigue effecting productivity and two, do you ever recommend rest, do you feel that rest will affect the outcome of this disease?

DR. JENSEN: I find two things. I find that disability claims, the patients request going on disability because the fatigue is incapacitating. Yet on those patients that are on disability, they come back to me and they're playing golf, they're traveling. So I have a real problem and I've become a "hard ass" when it comes to disability claims with my patients.

(Applause.)

DR. JENSEN: I don't know what the right answer is. There are clearly patients that have incorrectible fatigue that can't work. I found that a lot of those patients when I've treated them with interferon, have their fatigue improve. What I offer those patients is treatment to see if they'll improve and off treatment, after the treatment is discontinued. Otherwise you're stuck. It's a subjective symptom and unless they can prove that it interferes with their lifestyle and sometimes I talk to their employer to see how much it is interfering with their work.

AUDIENCE MEMBER: At this point do you recommend treating people with chronic persistent hepatitis with interferon and if you say yes to that...
Audiencemember: So you treat both chronic active and chronic persistent. Do you therefore do liver biopsies on everybody pre-treatment?

Dr. Jensen: Yes. The reason for that is, and I showed you a slide of the natural history saying that chronic persistent hepatitis, that biopsy, a mild histologic lesion, has a 60 percent chance or 50 percent chance of progressing to more severe liver disease in a 12 year follow up period of time. So it's not a benign lesion.

I think in the '70s we assumed that chronic persistent was a non-progressive benign lesion, didn't go to cirrhosis. We now know that that's patently untrue, that's false. It's so untrue that in the past six months the American Association for the Study of Liver Disease and other groups have come to abolish the term chronic persistent hepatitis. The hepatologists are no longer using that term. It's either mild-moderate or severe chronic hepatitis. So chronic active, chronic persistent is thrown out the window. We don't even use it.

Audiencemember: That's regarding hepatitis C or all hepatitis?

Dr. Jensen: All hepatitis, but particularly for hepatitis C. And the chronic persistent, that mild lesion does progress, so I do treat them.

Audiencemember: Why do a liver biopsy if you're going to treat all people?

Dr. Jensen: I do a liver biopsy really to find other factors. One, I want to find if they have cirrhosis already and find out if they're going to be a good responder or poor responder. Second, I want to make sure they don't have some other condition. And we found patients with hepatitis C that also had other lesions, hemachromatosis, granulomatis disease, steatosis from alcohol, other things that may impact on their response to interferon. My personal bias is they all should be biopsied, unless there's a contra-indication to doing biopsy.

Audiencemember: My question is related to how do you sell your patients on the interferon versus waiting for the next wave of treatments or taking their chances and what proportion are you successful in? I've had that problem in practice, trying to convince the patient and even the gastroenterologist that the patients ought to be treated.

Dr. Jensen: I think that's the art of medicine. What I tell the patients is I explain exactly what I've explained to you. I don't tell them anything different. I spend a lot of time. I tell them what the results are, how they're going to feel on interferon. But having treated almost 1,000 patients with interferon, different types of interferon over the last ten years, what I see is different than what the people's expectation is. In other words, they've come from their gastroenterologist or their primary physician who tell them, boy, it's a terrible medicine. It's going to make you feel sick as a dog.

When I follow those patients, I find they're able to work, those flu-like symptoms get better after a couple of doses and they're able to get back to work. There are a handful of patients, 30 percent who actually feel better on interferon. So one, I tell them, you may have this. You may have these terrible symptoms, and if you do and it's intractable and you can't work, we can stop interferon.

We haven't lost anything. But if you have the beneficial effect, if you're in that one in five that's going to have a long term beneficial effect, most of those patients not only do well on interferon during the later courses, but do well afterwards and feel better. I think if you hold that out to a patient, say you have a one in five chance of potentially having this disease regress or go away or get markedly better, most of these people will take it, even if they feel fine.

They understand that if you're 30 years old, and I ask doctors. I say, okay, you're 40 years old. You have hepatitis C. You have a 35 year life expectancy and you're going to live 35 more years with this virus. Twenty percent are going to develop cirrhosis in 20 years. What's the percentage that are developing cirrhosis in 35 years? What are the chances that you're going to need a liver transplant before your 75th birthday?

I think when you put it in those terms, they say, gee, I don't want to live with this disease for 35 years. If I have a chance to get rid of it, I'll take that chance. I think we need to do cost effective analysis of that. We don't have that data right now. I think there are studies being done to look at that. Thank you very much.

(Applause.)

Dr. William Baker: After hearing that splendid presentation, Dr. Jensen, we know why you were recommended to us nationally and all over Chicago.