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## Chronic Hepatitis C

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### **1. On May 17<sup>th</sup>, 2002 the press released the following article relating to the manufacturing problems that Schering Plough has been experiencing “Drug Maker Fined \$500 Million”**

Drug maker Schering-Plough will pay the federal government at least \$500 million in fines as it resolves quality control problems at its New Jersey and Puerto Rico manufacturing plants, the company said Friday.

Schering-Plough lowered its 2002 earnings forecast as a result, but analysts said the agreement removes the cloud hanging over the company since regulators spotted problems at the four plants in February 2001. Investors responded positively, pushing Schering stock up nearly 5 percent.

“It's a big issue that was looming out there, and now it's out of the way, so that's good,” said Stephen Scala, pharmaceutical analyst at SG Cowen Securities Inc. “They still have way more to do, (but) they're orchestrating a reasonable course out of this.”

Late last year, the maker of blockbuster allergy medication Claritin set aside \$500 million to cover the consent decree payment. On Friday, it said it expects an earnings-per-share increase this year in the mid-single digits, rather than the low double digits, as previously forecast.

Under the agreement the company signed Thursday night, the manufacturing plants will operate under tighter scrutiny by the U.S. Food and Drug Administration, with extra reviews and reports required, through the end of 2005, an unusually long period. Schering also agreed to have an outside expert ensure that manufacturing methods, procedures and controls at the plants meet FDA's quality standards.

“The FDA wants to make absolutely sure that (Schering-Plough) toes the line and gave them some high hurdles to meet,” said Kenneth Nover, pharmaceutical analyst at A.G. Edwards.” I believe they're committed to that and will make all the deadlines in an orderly fashion.”

Nover said FDA is getting tougher on enforcing manufacturing standards, but that Schering “had major problems that had not been dealt with on a timely basis,” forcing a strong response from the regulators.

The manufacturing plant deficiencies, which have never been disclosed in detail, led FDA to delay for nearly a year the approval of Clarinex, the successor drug to Claritin, battering the company's stock.

Claritin boasts \$3.1 billion in annual sales - one-third of the company's revenues. Analysts expect that to plunge to about \$400 million once the drug faces generic competition and Schering switches it to a nonprescription product, as FDA has pushed it to do. Those changes are expected in 2003 or 2004.

Meanwhile, Schering-Plough disclosed Wednesday that FDA's Office of Criminal Investigation in Puerto Rico is investigating the company. Schering-Plough spokesman Bob Consalvo said Friday the company doesn't know the focus of the investigation or any details. The company said in a statement that all its products on the market are safe and effective.

“The company has worked closely and cooperatively with the FDA throughout this process and achieved two key objectives: keeping our plants open and operating, and continuing to make available our major pharmaceutical products to meet the needs of patients,” said Richard Jay Kogan, the company's chairman and chief executive officer.

The four plants covered by the consent decree - in Kenilworth and Union, N.J., and in Manati and Las Piedras, Puerto Rico - will continue making prescription drugs, including Clarinex, Claritin, asthma inhalers, dermatology products and the hepatitis drug Rebetol.

Schering-Plough will temporarily suspend production of some animal health products at Manati while it upgrades the facility.

The consent decree is subject to approval by the U.S. District Court in Newark, where it will be filed next week, Consalvo said.

Schering-Plough shares were up \$1.10, or 4.5 percent, at \$25.85 in trading Friday on the New York Stock Exchange.

## **2. Additionally on May 17<sup>th</sup> the following press release was issued regarding Schering Plough "Schering-Plough Enters Into Consent Decree With FDA to Resolve U.S. Manufacturing Issues -Company Updates Earnings Projection for 2002, Provides Second Quarter 2002 Earnings Estimate"**

Schering-Plough Corporation today announced that it has reached an agreement with the U.S. Food and Drug Administration (FDA) for a consent decree to resolve issues involving the company's compliance with current Good Manufacturing Practices (GMPs) at manufacturing facilities in New Jersey and Puerto Rico. The agreement is subject to approval by the U.S. District Court for the District of New Jersey (Newark).

"This agreement builds upon the efforts we have undertaken to date to resolve these manufacturing issues," said Richard Jay Kogan, chairman and chief executive officer. "The company has worked closely and cooperatively with the FDA throughout this process and achieved two key objectives: keeping our plants open and operating, and continuing to make available our major pharmaceutical products to meet the needs of patients. We are confident of our ability to move forward under the agreement and complete our improvement programs successfully," Kogan said. He also emphasized that the company is confident that all of its pharmaceutical products currently in the marketplace are safe and effective.

### ***Terms of Consent Decree***

The consent decree agreement formalizes the company's commitment to ensure sustained compliance with current Good Manufacturing Practices at its New Jersey and Puerto Rico manufacturing sites. Under the agreement, the company will retain qualified outside experts in determining that manufacturing methods, procedures and controls at these production facilities comply with current GMP requirements. Schering-Plough said that while these efforts are ongoing, its production facilities will remain open and it will continue to manufacture its human pharmaceutical products. As specified in the consent decree, the New Jersey and Puerto Rico facilities will operate under tightly controlled conditions requiring additional levels of review and reporting.

Under terms of the consent decree, Schering-Plough will pay a total of \$500 million to the U.S. government in two equal installments of \$250 million, the first installment to be paid in the 2002 second quarter and the second in the 2003 second quarter. As previously reported, the company accrued a \$500 million provision for this consent decree payment in the 2001 fourth quarter. In the event agreed-upon actions are not completed on time, the consent decree provides for daily payments of \$15,000 for each deadline missed. These payments cannot exceed \$50 million incurred in any calendar year and have an overall cap of \$175 million incurred through 2005. A royalty payment of 24.6 percent of net U.S. sales can be assessed for each product for which revalidation has not been successfully completed within the timelines of the consent decree. The company is scheduled to complete its revalidation plans by Dec. 31, 2005. The company would expense any such payments if and when incurred.

The consent decree has been signed by the company and the government and will be filed shortly in federal court.

### **3. On May 17<sup>th</sup>, 2002 the press released an article titled “Chemoembolization offers survival benefit for people with liver cancer”**

People with liver cancer that cannot be treated with surgical resection or transplantation could have an increased 2-year survival if they are given chemoembolization, according to a study published in the latest issue of the Lancet. Lancet 2002; 359(9319): 1734

Chemoembolization is a procedure in which blood supply to the tumor, combined with the effect of chemotherapy, inhibits cancer growth. There is no standard treatment for liver cancer when surgery, transplantation, or percutaneous treatment is not possible, which applies to around 75% of all liver cancer cases.

Arterial embolization which is the restriction of blood supply to the tumor is widely used, but there is uncertainty whether it has a survival benefit.

The 2-year survival in this study was as follows:

- ◆ Conservative treatment: 27%
- ◆ Embolization: 50%
- ◆ Chemoembolization: 63%

Jordi Bruix and Josep Llovet from Hospital Clinic, Barcelona, Spain, led a multicenter randomized trial among 112 cirrhotic patients with unresectable liver cancer.

They assessed the survival benefits of arterial embolization which is the use of gelatin sponge to block blood flow to the tumor, or chemoembolization which is the used of gelatin sponge plus the chemotherapeutic drug doxorubicin, compared with conservative treatment.

It became necessary to discontinue the study when it became apparent that chemoembolization had a significant survival benefit compared with conservative treatment.

In this study it was found that 25 of 37 patients (67.6%) assigned embolization, 21 of 40 (52.5%) assigned chemoembolization, and 25 of 35 (71.4%) assigned conservative treatment died.

The probabilities of survival at year 1 and years 2 were 75% and 50% for embolization, 82% and 63% for chemoembolization, and 63% and 27% for conservative treatment, respectively.

Jordi Bruix comments, "While we wait for confirmatory studies, and from now on, chemoembolization should become the standard approach for the selected group of candidates with unresectable intermediate hepatocellular carcinoma and preserved liver function."

### **4. On May 20<sup>th</sup>, 2002 Idun Pharmaceuticals announces that IDN-6556, a caspase inhibitor completes Phase 1 clinical trial for HCV**

Idun Pharmaceuticals, Inc. presented positive results of its Phase 1 clinical trial of IDN-6556 yesterday at the Digestive Disease Week 2002 conference in San Francisco. The drug was safe and well tolerated in the clinical study involving 76 normal adults and patients with mild liver impairment. Statistically significant and clinically relevant improvements in liver enzymes were seen in the patients with mild liver impairment treated with IDN-6556. These patients included individuals with stable hepatitis C virus (HCV) infection. Idun plans to

study IDN-6556 in larger Phase 2 clinical trials in patients with HCV infection and acute alcoholic hepatitis.

IDN-6556 is the first broad-spectrum caspase inhibitor to be studied in humans and acts to preserve the structure and function of cells under stress. The liver damage seen with HCV infection results from the body's defense mechanisms and apoptosis is involved in this process. While IDN-6556 is not an anti-viral drug and will not cure patients of the viral infection, it is thought that treatment of infected patients with IDN-6556 may preserve the cells of the liver and help them to maintain their normal liver function and health.

"There is a considerable and growing need for additional drugs to treat numerous liver diseases. We believe that the protective effects that we have seen with this drug will be useful in several liver diseases," said Dr. David Shapiro, Chief Medical Officer and Executive Vice President at Idun. "Based on the number of people affected, the market potential for this drug is huge and includes hepatitis B virus infection, an enormous medical problem, particularly in Asia."

## **5. On May 22<sup>nd</sup>, 2002 SciClone Pharmaceutical released a press release titled "ZADAXIN(R) Selectively Stimulates Immune System-Related Genes Important In the Fight Against Hepatitis C - Study Presented at the AASLD's Digestive Disease Week"**

SciClone Pharmaceuticals announced the results of a study demonstrating that ZADAXIN (thymalfasin, thymosin alpha 1) up regulates the expression of multiple immune system-related genes in naive, non-responder and sustained responder hepatitis C patients. A combination of ZADAXIN and pegylated interferon is the focus of SciClone's U.S. phase 3 hepatitis C clinical trials involving 1,000 non-responder patients.

The gene expression study was the subject of an oral presentation yesterday at the meeting of the American Association for the Study of Liver Disease's Digestive Disease Week in San Francisco, California. The study, led by David Nelson, M.D., Director of the Liver Unit and Transplant Program at the University of Florida, was designed to examine gene expression in patients with chronic hepatitis C using a gene array with over 850 immune system-related genes. The results indicate that ZADAXIN produces a significant up regulation of many of the genes that are involved in antigen presentation and immune regulation. The addition of pegylated interferon to ZADAXIN did not significantly alter the pattern of up regulation, suggesting that ZADAXIN alone is capable of augmenting the immune response.

Certain genes were selectively unregulated by ZADAXIN in patients who had previously not responded to interferon, providing support for the use of ZADAXIN as an addition to interferon treatment. A combination of ZADAXIN and pegylated interferon is the focus of SciClone's phase 3 hepatitis C clinical trials currently in progress in the U.S. Further studies in an in vitro replication model demonstrated the utility of pegylated interferon for the first stage of clearance of hepatitis C (direct antiviral action); the demonstrated effects of ZADAXIN on the immune system should contribute to the critical second stage of viral clearance, a phase mediated by a sustained immune system response.

Dr. David Nelson commented, "The primary mechanism of action of thymosin alpha 1 is via immune modulation (antigen presentation and T cell activation). This would suggest that the addition of thymosin alpha 1 to interferon should improve T cell-mediated clearance of infected hepatocytes and alter the second stage of viral clearance kinetics, which is considered essential for the achievement of a sustained response in hepatitis C patients."

ZADAXIN, an immune system enhancer (ISE), is a synthetic preparation of a natural peptide, thymosin alpha 1, which among other positive actions, enhances the body's Th1 immune response to serious viral infections such as hepatitis B and hepatitis C and to certain cancers. Already approved for sale in 27 countries, ZADAXIN is currently in phase 3 hepatitis C clinical trials in the U.S., a phase 3 hepatitis B clinical trial in Japan and in a phase 2-3 cancer program in Europe. ZADAXIN has been administered without clinically significant side effects to patients for over 10 years.

## **6. Additionally on May 22<sup>nd</sup>, 2002 as a result of data presented at Digestive Disease Week Meeting in San Francisco the press released an article titled “Hepatitis C May Be Transmitted via Toothbrushes”**

The viral infection hepatitis C could possibly be transmitted by common household items such as toothbrushes, researchers warned at the Digestive Disease Week Conference in San Francisco. DDW is an annual meeting attended by gastroenterologists from all over the world.

"This study strengthens the evidence to advise patients with hepatitis C to not share possibly infected household objects," said study co-author Dr. Claus Hellerbrand of the department of internal medicine at the University of Regensburg in Germany.

Hepatitis C is a viral infection of the liver that can lead to cirrhosis and possibly liver cancer. It currently affects around 1% of the US population and can be spread via contaminated blood products or by injection drug use. As many as 10% to 40% of patients diagnosed with hepatitis C had no obvious risk factor or known mechanism for contracting the disease, according to Hellerbrand.

Researchers have theorized these patients may have caught the virus in an unconventional manner, such as via tattooing, piercing or sharing a razor with an infected person. Patients with hepatitis C are currently warned against sharing communal household items that come in contact with blood, such as razors and toothbrushes, with other family members.

In a new study, the researchers examined 30 patients infected with hepatitis C to see whether they contaminated their toothbrushes with the virus. The doctors collected saliva samples from infected patients both before and after they brushed their teeth. After brushing, the toothbrush was rinsed in salt water and inspected for presence of hepatitis C genetic material.

Thirty percent of the infected patients tested positive for traces of the virus in their saliva before brushing their teeth, while 38% of the infected patients tested positive in their saliva after brushing. Forty percent of the rinsing water of the toothbrushes tested positive for the virus, the investigators found.

The patients whose toothbrush water tested positive were not significantly different in their oral hygiene or disease severity than patients whose rinsing water was negative.

Hellerbrand said it was unknown whether these traces of genetic material on the toothbrush could infect another individual, but that it was not impossible. "We can't prove it's alive and could infect another, and we can't exclude that," he noted. "It's probably not easy to be transmitted in this way."

The researchers conclude that publicly used objects such as barbershop razors, which may be vulnerable to infection, should be regulated by health officials

## **7. Additionally on May 22<sup>nd</sup>, 2002 as a result of data presented at Digestive Disease Week Meeting in San Francisco the press released an article titled “Pegasys and Ribavirin Effective at 24 weeks in Patients With Hepatitis C and Advanced Fibrosis/Cirrhosis”**

Swiss researchers say 24 weeks of Pegasys (pegylated interferon alfa-2a) and ribavirin cleared Hepatitis C virus RNA in serum in almost 90 percent of patients with advanced HCV-associated fibrosis/cirrhosis.

The treatment combination is also acceptably tolerated, reported Dr. Eberhard L. Renner, University Hospital, in Zurich, speaking here Monday at Digestive Disease Week 2002, based on interim results in 88 patients of the investigational drug Pegasys (Roche) and ribavirin at the midpoint of the phase III trial. The

treatment phase of the trial continues through to 48 weeks.

The researchers compared efficacy and tolerability of PEG-IFN (180ug sc weekly) and RIBA (1000/1200 mg vs. 600/800 mg po QD) in treatment-naive patients with HCV-associated advanced fibrosis/cirrhosis in an open-label, randomized, controlled, trial in 11 Swiss centers.

Patients had not previously been treated, included both genders with HCV-associated biopsy-proven advanced fibrosis/cirrhosis (Metavir F3-F4) and less than 8 Child-Pugh points, elevated ALT and positive HCV-RNA in serum (Amplicor® HCV Monitor™). Randomization (1:1) was stratified according to genotype (2/3 vs. other; Inno-Lipa®) to PEG-IFN (180ug sc once weekly) and either RIBA (75kg or less: 1000mg, >75kg: 1200mg po QD) or (75kg or less: 600mg, >75kg: 800mg po QD) for 48 weeks with 24 weeks of follow-up.

So far, 88 patients were enrolled including 40 (45 percent) females; 30 (45 percent) genotype two-three, 40 (45 percent) genotype one. Forty-three patients were randomized to higher, 45 patients to lower RIBA dose.

At 24 weeks of treatment, HCV-RNA in serum was negative (<1000 cps/ml) after two, four, eight, 12 and 24 weeks of treatment in 24/71 (34 percent), 36/65 (55 percent), 43/63 (68 percent), 37/53 (70 percent) and 25/28 (89 percent) patients, respectively, with no difference between treatment arms. Treatment prematurely terminated in five (six percent) patients for AEs, of which two were severe (attempted suicide, incidental PEG-IFN over-dose).

Dose reduction was necessary in 38 (43 percent) patients with no difference between treatment arms. In which proportion this high initial response rate translates into sustained HCV clearance remains to be seen. Based on previous studies, Renner, head of hepatology at University Hospital, said he expects a sustained clearance in 50 to 60 percent of patients.

He said the drug is very similar to Peg Intron A, which is already approved in the United States. Pegasys, which could gain FDA approval by the end of the year, is one amino acid different and is pegylated differently so that the drug is cleared through the liver. In contrast, he said Peg Intron A is cleared through the kidneys, Renner said.

Pegasys administration is by ready-to-use syringe. He said he anticipates that Peg Intron A, which now requires the patient to do some preparation of the solution, also will likely adopt a similar system, he said.

Investigators targeted patients with advanced fibrosis/cirrhosis because previous studies have tended to exclude this more difficult population, he said.

The study was supported by Roche Pharma (Schweiz) AG, Switzerland.

**8. Additionally On May 22<sup>nd</sup>, 2002 Achillion Pharmaceuticals reported the successful completion of a Phase 1b/2 clinical trial demonstrating potent antiviral activity of the Company's lead product candidate, ACH-126,443 (Beta-L-Fd4C) in patients with chronic hepatitis B (HBV) infection.**

ACH-126,443 produced rapid, statistically significant and multi-log decreases in HBV DNA levels (viral load) during the study's 14-day dosing period, demonstrating the drug's antiviral activity. Moreover, no apparent drug-related adverse events were observed in the study. Detailed results of the study, which was designed to provide a first clinical assessment of the drug's safety and efficacy in patients chronically infected with HBV, will be presented at scientific meetings in the fall of 2002.

"We are pleased with the profound reduction in HBV levels in the bloodstream that ACH-126,443 demonstrated in as little as 14 days," said Lisa M. Dunkle, MD, Senior Vice President of Drug Development at Achillion.

"Limited treatment options are currently available to treat chronic hepatitis B infection, and a significant unmet medical need exists for new, potent and safe therapeutic agents," said William G. Rice, Achillion's Chief Executive Officer. "Our ongoing Phase 2 study in patients with chronic HBV infection, as well as additional studies already scheduled with ACH-126,443, will provide further clinical data on the potential of this highly promising drug candidate."

Achillion conducted the double-blind study in multiple centers in the U.S. and Canada, evaluating several doses of ACH-126,443 administered once a day for two weeks to 40 patients with chronic hepatitis B infection. The study was designed to evaluate the safety, tolerability and pharmacokinetics of ACH-126,443 compared with a control, as well as to determine optimal doses to achieve antiviral activity.

### ***About ACH-126,443***

ACH-126,443 is an L-nucleoside antiviral agent administered orally once daily that has demonstrated in vitro activity against both wild-type and lamivudine-resistant strains of HBV. In 2002, Achillion plans to conduct several clinical studies of ACH-126,443, including evaluating the efficacy of the product candidate in patients with lamivudine-resistant strains of HBV.

Chronic HBV infection is a life-threatening disease that affects more than 350 million individuals worldwide. It is a common cause of liver damage and the leading cause of liver cancer. The World Health Organization lists chronic HBV as the ninth leading cause of death worldwide.

Pre-clinical studies have demonstrated that ACH-126,443 also effectively inhibits HIV, and Achillion is planning clinical trials to evaluate ACH-126,443 in patients with HIV infection. Over 36 million people worldwide are estimated by the National Institutes of Health to be living with HIV/AIDS at the end of 2000, with approximately 5.3 million new infections having occurred in 2000. Through 2000, the HIV/AIDS epidemic had resulted in over 20 million deaths worldwide.

### ***About Achillion***

Achillion is a privately held pharmaceutical company focused on the discovery, development and commercialization of innovative small molecule drugs that combat drug resistance in infectious diseases, with a particular emphasis on antiviral drugs to treat diseases caused by hepatitis B and C viruses (HBV and HCV), HIV and selected herpes viruses. Achillion's drug development pipeline is led by ACH-126,443 (Beta-L-Fd4C), which is currently in Phase 2 human clinical trials for the treatment of chronic hepatitis B and HIV infections. Achillion's drug discovery expertise embodies both a conventional medicinal chemistry approach directed at classic anti-infective molecular targets and its novel Zinc Finger Targeting (ZFT) drug discovery technology developing small molecules that target zinc finger motifs unique to particular pathogens.

## **9. On May 23<sup>rd</sup>, 2002 as a result of data presented at Digestive Disease Week Meeting in San Francisco the press released an article titled "Blood Test Successfully Used to Replace Liver Biopsy in Some Hepatitis C Patients"**

There is growing evidence from at least two research groups that a liver blood test rather than a biopsy can be used to distinguish degrees of fibrosis in some hepatitis C patients. These research groups are using blood test results to help them predict which patients qualify for standard combination therapy in lieu of liver biopsy, a feared and expensive procedure for many patients.

Researchers from Australia reported their findings on the FibroTest system at the Digestive Disease Week (DDW) 2002 meeting. Dr. Leon Adams, senior gastroenterology registrar at Sir Charles Gairdner Hospital, in Perth, Australia, said their experience showed a relatively high degree of accuracy in half of the 55 hepatitis C patients they tested.

The sensitivity and specificity of a FibroTest score greater than 0.1 for the presence of fibrosis grades F2-4 was 88 percent and 50 percent, respectively, he said. The sensitivity and specificity of a FibroTest score greater than 0.6 for fibrosis F2-4 was 30 percent and 100 percent, respectively. With a prevalence of 50 percent for the presence of fibrosis F2-4, (as in their population), the negative predictive value of a score less than 0.1 for the absence of such was 82 percent. The positive predictive value of a score greater than 0.6 for the presence of fibrosis F2-4 was 100 percent.

Dr. Adams' group summarized that the FibroTest correlates significantly with the level of hepatic fibrosis in patients with hepatitis C. It can predict the presence or absence of hepatic fibrosis stages F2-4 in up to 50 percent of cases, therefore avoiding the need for biopsy to qualify for treatment.

Still, he notes that the French group achieved predictive values greater than 90 percent. "The next step is to come up with an algorithm for our population," he said. Their experience suggests that the algorithm might need to be adjusted for each population. "That's what needs to be confirmed in centers around the world," he said. For now, he said, "It's a promising test. Unfortunately, we can't apply it to every patient at the moment."

A French group led by Thierry Poynard of the MULTIVIRC group, published results one year ago (Lancet 2001; 357:1069-75), showing that a combination of basic serum markers could be used to substantially reduce the number of liver biopsies done in patients with chronic HCV infection.

For a small fee, physicians can submit the results of blood tests of those biomarkers to the researchers, using a proprietary, FibroTest, protocol. The biomarkers are haptoglobin, gamma glutamyl transferase, bilirubin, alpha 2 macroglobulin and apolipoprotein A1.

## **10. Additionally on May 23<sup>rd</sup>, 2002 as a result of data presented at Digestive Disease Week Meeting in San Francisco Schering Plough issued the following press release titled "Schering-Plough Reports Results Of Clinical Studies Of Peg-Intron And Rebetol Combination Therapy For Hepatitis C - Studies Show Activity in diverse Patient Populations"**

Schering-Plough Corporation reported results of several clinical studies presented here at the 2002 Digestive Disease Week (DDW) conference involving Peg-Intron (peginterferon alfa-2b) Powder for Injection in combination with Rebetol\* (ribavirin, USP) Capsules for the treatment of chronic hepatitis C. In all, 33 studies with Peg-Intron were presented by clinical investigators. Peg-Intron and Rebetol combination therapy received U.S. Food and Drug Administration (FDA) approval in August 2001 for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

In an oral presentation, investigators reported clinical data from one of the largest clinical trials studying African Americans with hepatitis C. The study indicated that the commonly lower response rate to treatment among African Americans is not related to genotype, as previously believed. Researchers have attributed lower treatment response rates in African Americans to the fact that this patient population predominantly contracts genotype 1 virus, which is the most difficult to treat. In this study, which compared the treatment response rate of African Americans to response rates of non-Hispanic whites, 98 percent of all patients studied had genotype 1. In the African American patient group, 28% had a virologic response after 12 weeks of therapy compared to a 58% response rate in the non-Hispanic white patient group. At week 24 of treatment, 25% of African Americans tested negative for the virus vs. 62% of non-Hispanic whites, indicating that factors other than genotype were affecting response to therapy.

Researchers enrolled 100 African Americans and 100 non-Hispanic whites who had not been previously treated with alpha interferon therapy into each group. All patients received Peg-Intron (1.5 mcg/kg/week) for 48 weeks plus Rebetol (1,000 mg/day) for 12 weeks followed by 800 mg/day for 36 weeks. Patients with decompensated liver disease were excluded from the study.

"The low response rate among African Americans has puzzled researchers for years," said Andrew Muir, assistant professor in medicine, division of gastroenterology, Duke University Medical Center. "Even though the response rate in the African American group was lower than in the non-Hispanic white group, treatment with Peg-Intron and Rebetol combination therapy achieved a higher response than had been seen previously. These results bring us one step closer to understanding how the virus behaves in African Americans and how to effectively treat this patient population." Dr. Muir is the lead investigator for this trial.

### ***Additional Peg-Intron Studies Presented at DDW***

Preliminary data from the WIN-R trial, the largest ongoing prospective study to evaluate the safety and efficacy of weight-based dosing with Peg-Intron and Rebetol combination therapy, indicated that patients receiving daily Rebetol dosages (800-1,400 mg) according to their body weight may not have any difference in the rate of significant adverse events than patients receiving a flat daily dose (800 mg) of Rebetol. Both groups were given Rebetol in combination with once-weekly Peg-Intron (1.5 mcg/kg). Although patients receiving the weight-based dose of Rebetol experienced a moderate increase in anemia, there was no incremental anemia in patients receiving 1,400 mg of Rebetol daily compared to the other doses of Rebetol received in weight-based dosing. Researchers also found no clinically important differences or platelet decreases in neutropenia or loss of white blood cells at the higher ribavirin doses. In addition, patients dosed according to body weight had less severe platelet decreases and similar serious-adverse-event and discontinuation rates than those who had been given the standard 800 mg daily Rebetol dose.

"Data from this large patient population reinforces that Peg-Intron and Rebetol combination therapy is manageable in hepatitis C patients," said Ira Jacobson, M.D., chief, division of gastroenterology and hepatology, Weill Medical College of Cornell University, New York. "I am encouraged by these results and believe that studies like the WIN-R trial are critical in helping us better define treatment regimens for the many patients with hepatitis C."

The results of the COPILOT (Colchicine versus Peg-Intron Long-Term) study, which investigated maintenance therapy with Peg-Intron in patients with advanced cirrhosis, were also presented. In this study, 250 patients with advanced cirrhosis who had previously failed interferon-based therapy were randomized to two groups: 130 patients received once-weekly Peg-Intron (0.5 mcg/kg) and 120 patients received colchicine (0.6 mg twice-daily). At the end of one year of treatment, the Peg-Intron group had a reduction in detectable<sup>1</sup> virus (HCV RNA), while the virus levels in the colchicine group remained the same. These findings may be important for patients who have not responded to previous therapy.

"Schering-Plough is committed to offering patients with hepatitis C the best possible treatment option with Peg-Intron and Rebetol combination therapy. The results of studies presented at this year's DDW conference support that commitment," said Robert J. Spiegel, M.D., senior vice president of medical affairs and chief medical officer, Schering-Plough Research Institute. "Through this research, we are achieving a better understanding of the disease and the factors that affect patient response to treatment."

## **11. Additionally on May 23<sup>rd</sup>, 2002 the press released the article titled "NicOx and Axcan Sign Co-Development and License Agreement for NCX 1000 in the Treatment of Chronic Liver Diseases"**

NicOx S.A. (Nouveau Marche: NICOX) and Axcan Pharma (Nasdaq: AXCA; TSE: AXP) today announced the signing of a co-development and license agreement for NCX 1000, a nitric oxide-donating ursodiol (ursodeoxycholic acid) derivative, for the treatment of chronic liver diseases including portal hypertension and Hepatitis C.

Under the terms of this agreement Nicox grants Axcan an exclusive license to commercialize NCX 1000 in Canada and Poland as well as an option to the same exclusive rights for the United States market. The United States option is to be exercised on completion of proof of concept in Phase II clinical development.

NicOx retains rights in the rest of the world including the Far East and Europe with the exception of France where Axcan is granted co-exclusive rights. Axcan and NicOx will share the cost of the future development of NCX 1000 jointly through the completion of Phase II clinical studies.

Axcan will thereafter conduct the required Phase III clinical studies and be responsible for regulatory filings in the exclusive licensed territories. Axcan will make license, option and milestone payments to NicOx following successful completion of key stages of development, totaling up to USD 19 million assuming exercise of the US option and development of both indications of portal hypertension and Hepatitis C.

NicOx will also receive royalties of up to 12% of net sales of the product in the licensed territories for the duration of patent protection.

The scope of the collaboration covers the development and commercialization of NCX 1000 for the treatment of chronic liver diseases including portal hypertension and Hepatitis C. NicOx will have the right to manufacture and supply the active ingredient to Axcan. The two companies may agree in the future to expand the agreement to include other projects in the area of liver and gastrointestinal diseases.

Chronic liver diseases generally progress slowly from inflammation to fibrosis to cirrhosis and liver failure. Severe forms are often associated with scarring and architectural disorganization, which ultimately leads to cirrhosis. Increased portal pressure leads to serious complications such as variceal bleeding, ascites etc. Cirrhosis as a result of chronic liver disease ranks in the top 15 causes of death worldwide. Globally, an estimated 170 million people are infected with Hepatitis C and 350 million with Hepatitis B, and it is estimated that up to 25% of those who are chronically infected will develop portal hypertension and/or cirrhosis.

Michele Garufi, Chairman and CEO of NicOx, said: "We are very pleased to have signed this agreement on NCX 1000 with Axcan Pharma. Axcan is the ideal partner for the co-development of NCX 1000 because of their presence in the field of cholestatic liver disease and their worldwide expertise involving ursodiol.

The combination of our nitric oxide based technology together with the know-how of Axcan will allow us to maximize the value of NCX 1000, which represents a promising approach for the treatment of portal hypertension and Hepatitis C. It is important to underline that the structure of this agreement will help Nicox to meet our strategic objective to retain significant rights for specialist products including NCX 1000, allowing NicOx to market directly in Europe."

Leon F. Gosselin, Chairman and CEO of Axcan Pharma, commented: "Late-stage chronic liver disease represents a true unmet medical need. This combined Axcan -- NicOx endeavor offers the opportunity to develop an effective therapy to decrease portal hypertension and ultimately delay the onset of cirrhosis. We believe NCX 1000 may have significant therapeutic potential and the development plan is designed to give early proof of concept results."

### ***TECHNICAL NOTE -- NCX 1000***

Preclinical data from several studies was presented during Digestive Disease Week on May 20, 2002 in San Francisco, California. One study demonstrated the effectiveness of NCX 1000 in lowering portal pressure in animals without adversely affecting systemic arterial pressure (Abstract #M1318, S. Fiorucci et al). Other data suggest the potential of NCX 1000 to protect the liver from acetaminophen induced toxicity (Abstract #235, S. Fiorucci et al).

Preliminary studies carried out with NCX 1000 demonstrate that this compound is significantly effective in modulating inflammation and tissue damage in animal models of liver inflammation. NCX 1000 was found to inhibit apoptosis in vivo and in vitro, in models where ursodiol is non-effective and inhibits pro-inflammatory cytokine production from inflamed tissues.

Experimental animal data indicate an activity of NCX 1000 different from ursodiol in lowering portal blood pressure without affecting systemic blood pressure. This activity appears to be related to the influence on the dynamic component of portal hypertension and to structural hepatic changes. These studies suggest that the addition of the nitric oxide moiety has dramatically improved the potential pharmacological profile of ursodiol.

Taken together, these early preclinical data suggest that NCX 1000, by releasing nitric oxide into the liver microcirculation, may provide a novel approach for the treatment of portal hypertension.

NicOx is an emerging pharmaceutical company using recently-discovered properties of nitric oxide to design and develop safer and more effective drugs. NicOx is targeting several major pharmaceutical markets including pain and inflammation, cardiovascular diseases, respiratory disorders, inflammatory bowel diseases, urinary incontinence, osteoporosis, certain dermatological disorders, certain liver diseases, Alzheimer's disease and colon cancer. Headquartered in Sophia-Antipolis, France, NicOx is a Public Company listed on the Nouveau Marche of Euronext Paris (segment: Next Economy).

Axcan Pharma is a North American specialty pharmaceutical company involved in research, development, production and marketing of innovative products in the field of gastroenterology. The company markets a broad line of prescription products sold for the treatment of symptoms in number of gastrointestinal diseases and disorders such as inflammatory bowel disease, irritable bowel syndrome, cholestatic liver disease and complications related to cystic fibrosis. Its products are marketed in Canada, the United States of America, France and Poland. Axcan just celebrated its 20th anniversary in April, 2002

## **12. On May 24<sup>th</sup>, 2002 the press released the following article titled “Liver fibrosis progression in HCV-infected patients”**

Factors predicting the progression of liver fibrosis in HCV-infected patients have been identified, claim researchers from Sweden and England. The team evaluated the progression of liver fibrosis in untreated patients with hepatitis C virus (HCV) infection, and reported their results in the latest issue of Liver. Liver 2002; 22(2): 136-44

A total of 98 patients with HCV were included in the study. Two liver biopsy specimens, obtained prior to antiviral therapy, were taken from each patient. These biopsies were scored and evaluated using statistical methods appropriate for ordered categorical data.

Greater progression of fibrosis was seen with increasing time between the biopsies. Likewise, the change in fibrosis score was significantly more pronounced in the 11 patients whose first biopsy was obtained within the first year after acquiring HCV.

A multivariate logistic regression analysis showed that interface hepatitis in both biopsies, the time interval between the biopsies, and age at first biopsy, were associated with change in the fibrosis score. In addition, the authors found that older age at the time of infection was associated with development of cirrhosis.

The greatest factors linked with fibrosis progression were:

- ◆ Interface hepatitis
- ◆ Older age at diagnosis
- ◆ Alcohol intake

Furthermore, moderate intake of alcohol was associated with fibrosis progression.

An inflammatory response, in the form of moderate interface hepatitis in the first biopsy, was not necessarily associated with greater progression of fibrosis if the second biopsy showed mild interface hepatitis. However, having moderate interface hepatitis later in the course of infection, as reflected by the second

biopsy, may be detrimental.

Author L. Martin Lagging, of Goteborg University, Goteborg, Sweden, concluded on behalf of his colleagues, "If moderate interface hepatitis occurs early in the course of the disease, and is followed by less interface hepatitis later on, there is less fibrosis." However, if moderate interface hepatitis persists, there is more fibrosis eventually."

### **13. Additionally on May 24<sup>th</sup>, 2002 the press released an article titled "Disease rages behind bars"**

On Dec. 1, 1998, health officials at the Oregon State Penitentiary learned that inmate Rodger Anstett had elevated liver enzymes, an indication that he might be infected with hepatitis C, according to a lawsuit against the Department of Corrections.

It took two more years until prison doctors ordered a blood test that confirmed Anstett had the viral disease. To date, Anstett has received no treatment for the disease, and his health is failing.

Inmate Larry Vaughan, 63, gives Phyllis Beck a hug as she and other visitors enter the prison to talk about the disease. Below: Inmates listen to John Bergland of Eugene during a recent visit to the Oregon State Penitentiary in Salem as he tells of coping with hepatitis C.

"They won't treat the hepatitis C. They're dragging their feet," said Anstett, who is serving a 20-year sentence for multiple counts of arson and attempted murder out of Washington County. "The problem in prisons is, they really want to look the other way. They have an intentional policy to misdiagnose consistently until you leave."

Or die.

That's the central allegation in the \$17.5 million lawsuit, filed last fall by Portland lawyer Michelle Burrows on behalf of 10 inmates, including Anstett, and one former inmate.

"The state of Oregon, through the DOC, has a de facto policy of not treating hepatitis C," Burrows said. "I've had four inmate clients die from hepatitis C-related issues."

Anstett is one of three plaintiffs whose disease has reached an advanced stage and could die at any time, Burrows said.

Burrows is trying to get the suit, filed last fall, certified as a class action complaint. Attorneys for the state are preparing to fight the class action request.

Although state lawyers won't discuss the merits of the case, the Corrections Department's top medical official contends that most people who get the disease suffer few serious health problems and that it's appropriate for the department to take a cautious approach to treatment.

But the sheer numbers of prisoners with the disease shows that the state has a growing, costly health problem on its hands.

An estimated one in three Oregon prisoners is infected with hepatitis C, a chronic, potentially deadly disease that's costly to treat. Although the numbers are startling, they're similar to numbers found in prisons across the country, said Phyllis Beck, director of the Eugene-based National Hepatitis C Prison Coalition.

"In essence, our state prisons have become a state-sponsored incubator for HCV, by default," Beck told Hepatitis magazine.

Prison officials said about 30 percent of the nearly 11,000 inmates in the 14 Oregon prisons, work camps

and release centers - 3,300 prisoners - have hepatitis C. Burrows believes that the number could be closer to 40 percent.

Hepatitis C is the fourth-leading cause of death in Oregon prisons, after heart disease, cancer and suicide, Burrows said, citing Corrections Department death reports.

About 4 million Americans are infected with the hepatitis C virus, many of whom don't know they have the disease. Hepatitis C is spread through blood-to-blood contact, often through injection drug use and from needles used to inscribe tattoos. Some people got the disease through blood transfusions or organ transplant before 1992 when better testing of the blood supply became available.

The virus can lurk in a body for years without detection, slowly wrecking the liver. Federal health officials report that 10,000 people die each year from hepatitis C, a number expected to triple by 2010.

The Department of Corrections won't say how many inmates are being treated for hepatitis C. Burrows said she's aware of eight inmates who are receiving treatment.

Burrows alleges that treatment decisions are being made for financial, not medical reasons. The disease is expensive to treat, with a single course of the recommended combination therapy, interferon and ribavirin, costing \$17,000 to \$20,000, she said. One course of treatment can take 25 to 45 weeks. The expense doesn't include liver biopsies, which are required to assess the amount of liver damage and cost several thousand dollars.

Measure 11, which mandated tough sentences for violent offenders, has exacerbated the problem, Burrows said.

A guard tower, seen from outside the prison, looms over the Oregon State Penitentiary in Salem. Prison officials said about 30 percent of the nearly 11,000 inmates in the 14 Oregon prisons, work camps and release centers - 3,300 prisoners - have hepatitis C.

"We put people in prison for a very long time, and we expect that to be the end of it," she said. "We don't want to deal with it. ... The unfortunate thing is, you have to take care of them. These are captive, vulnerable people."

However, Corrections Department medical director Dr. Steve Shelton said the state adequately cares for inmates who have hepatitis C, most of whom probably won't experience serious health problems.

"Over 80 percent of the people with hepatitis C will not show evidence of health problems during the course of their full lifetime," he said.

Knowledge about hepatitis C has evolved rapidly in recent years and doctors have not settled on a single standard of evaluation and treatment, Shelton said.

"It is reasonable to take a very careful, reasonable medical evaluation, though some people want it to move faster," he said.

Treatment decisions are based on medical evaluations that seek to identify patients for whom it appears to be a progressive disease, he said.

"For those people for whom it is not a progressive disease, is it a problem? I think you'd probably have to say it is not a problem for those people," he said. "Everyone who has chest pain doesn't get taken to open heart surgery."

Hepatitis C attacks different bodies in different ways, depending on the strain of the virus and the strength of the person's immune system, according to the National Institutes of Health.

According to the federal Centers for Disease Control and Infection, 70 percent of hepatitis C patients suffer chronic liver disease and 15 percent may develop cirrhosis of the liver over a period of 20 to 30 years. The risk is greater for people who have abused alcohol.

Dr. Hugo Rosen is a liver specialist at the Veterans Affairs Medical Center and Oregon Health & Science University in Portland. He said for the "vast majority of patients," hepatitis C is a progressive disease, albeit one that progresses slowly.

"If you follow patients, many will develop progressive liver disease," he said. "The ultimate progression is a point where they die or need a transplant."

He favors treatment in most cases, though not for patients with psychiatric problems because the combination therapy can cause side effects, including depression, anxiety and flu like symptoms.

In some cases, the combination therapy can cause the virus to go into remission.

"If you treat someone with less degree of injury you may prevent them from developing cirrhosis," he said.

For Anstett, it may be too late to treat his disease. If he has cirrhosis, as Burrows suspects, drug therapy may do more harm than good.

Anstett said he's never injected drugs and believes that he contracted the virus while serving in Vietnam. He said the disease has given him a skin rash that feels "like acid coming up from under my skin," leaves him constantly achy and fatigued, and fogs his brain so it's hard to think clearly or carry on coherent conversations.

"I do not consider any of the treatment I have received to be responsible or responsive," he wrote in an affidavit prepared for the lawsuit. "I believe the various delays and denials are simply calculated to see whether I die or are released first."

#### **14. Additionally on May 24<sup>th</sup> as a result of an article published in *Gastroenterology* the following article was released: "Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C"**

Rate of liver fibrosis progression in hepatitis C patients is significantly reduced by the combination of pegylated interferon and ribavirin. This data was published in *Gastroenterology* 2002; 122:1303-1313.

This multicenter international study for the PEG-FIBROSIS Project Group, headed by Thierry Poynard and colleagues from the University of Paris VI, Paris, France, established the effect of using these two agents together on liver fibrosis, a key prognostic factor in these patients. The researchers pooled individual data from 3,010 naïve patients with pre- and post treatment biopsies from four randomized trials and compared 10 different regimens combining standard interferon, pegylated (PEG) interferon and ribavirin.

The percentage of patients with at least one grade improvement in necrosis and inflammation (METAVIR score), the percentage with at least one stage worsening in fibrosis METAVIR score and fibrosis progression rate per year were used to estimate the impact of each regimen. Necrosis and inflammation improvement ranged from 39 (with interferon 24 weeks) to 73 percent (optimized PEG 1.5µg/kg and ribavirin). Fibrosis worsening ranged from 23 (interferon 24 weeks) to 8 percent (optimized PEG 1.5µg/kg and ribavirin).

Post-treatment fibrosis progression rates in all regimens were significantly reduced in comparison with those before treatment. Reversal of cirrhosis was seen in 75 (49 percent) of 153 patients with baseline cirrhosis.

The following factors were independently linked with the absence of significant fibrosis after treatment:

- ◆ baseline fibrosis stage
- ◆ sustained viral response
- ◆ age of less than 40 years
- ◆ body mass index less than 27 kg/m<sup>2</sup>
- ◆ no or minimal baseline activity and
- ◆ viral load of fewer than 3.5 millions copies per milliliter.

**15. Additionally on May 24<sup>th</sup> as a result of data published in *Liver* an article titled “Hepatic Stellate Cell Marker Tied To Degree of Hepatitis C Liver Injury” was issued.**

Severity of liver fibrosis in patients with chronic hepatitis C virus infection is associated with intrahepatic expression of the hepatic stellate cell marker fibroblast activation protein. This is the finding of an investigation of the link between expression of hepatic stellate cell markers and liver damage in these patients in Sydney, Australia undertaken by Miriam T Levy and colleagues from the Centenary Institute of Cancer Medicine and Cell Biology and other centers. The results of the investigation are published in *Liver* Volume 22 Issue 2 Page 93 - April 2002.

Recognized by their smooth muscle actin immunoreactivity, activated hepatic stellate cells (HSCs) are primarily responsible for liver fibrosis. However, presence of smooth muscle actin positive HSCs are not always associated with development of this condition. Recently, other markers of human HSCs, including the gelatinase FAP and glial fibrillary acidic protein have been identified.

The researchers used immunohistochemistry to examine liver tissue from 27 patients. Staining scores were then compared with the stage and grade of liver injury (using linear correlation analysis). FAP expression, seen at the tissue-remodeling interface, was found to be strongly and appreciably associated with severity of liver fibrosis. A weaker correlation was seen between glial fibrillary acidic protein expression and fibrosis stage. This contrasted with the absence of a link between smooth muscle actin and fibrotic score. A correlation was also observed between FAP expression and necroinflammatory score.

Thus, FAP expression identifies an HSC subpopulation at the tissue-remodeling interface that is related to the severity of liver fibrosis, these authors conclude.

**16. Additionally on May 24<sup>th</sup>, 2002 based upon data published in the *Journal of the Association of Physicians of India (JAPI)* the following article was released “Liver Disease Worsened By Dual Infection of Hepatitis B and C”**

Chronic liver disease is more aggressive in patients infected with both hepatitis B and hepatitis C than in those with only one of these viruses. This finding was published in *J Assoc Physicians India* 2002; 50:651-655

More severe liver disease also tends to occur in patients, in whom the hepatitis B virus (HBV) is the more active of the two infections, suggests a study from New Delhi, India.

Clinical and biochemical profiles of chronic liver disease due to infection with both HBV and hepatitis C virus (HCV) are sketchy, and reports vary on the severity of the disease in these patients. R C Guptan and colleagues from the Departments of Gastroenterology and Pathology, GB Pant Hospital analyzed the course of liver disease in patients infected with both viruses versus those with either one of the two.

Among 186 histologically proven non-alcohol chronic liver patients, 30 (16.1 percent) were serologically diagnosed with HBV and HCV dual infection. Researchers compared the clinical profile of this group with that of 30 consecutive patients with HBV-related and 30 with HCV-related chronic liver disease. Those with both infections were also further grouped according to the predominance of activity of HBV versus HCV.

Dually infected patients were found to be younger than those with chronic HCV infection and to be predominantly male. They also had significantly more disrupted liver function than did those in the other two groups. However, the duration of their illness was shorter than that in the chronic HCV group.

Patients with chronic HCV infection more often presented with low-grade fever than did the dually infected group, and those with HBV-related disease commonly presented with ascites and variceal bleeding.

When patients with dual infection were sub grouped on HBV DNA and HCV RNA positivity, there was a tendency for increased biochemical derangement with active HBV infection.

### **17. On May 28<sup>th</sup>, 2002 the press released the following news article “Market for Hepatitis C Treatments Poised for Dramatic Growth. Decision Resources Forecasts That Pharmaceutical Sales For HCV Treatment Will Increase Threefold”**

Decision Resources announced today the availability of a new report entitled Hepatitis C, which finds the market for Hepatitis C treatments to be poised for dramatic growth. The report forecasts that sales of pharmaceuticals to treat people infected with the hepatitis C virus (HCV) will increase almost threefold between 2001 and 2011 in the major pharmaceutical markets (the United States, France, Germany, Italy, Spain, the United Kingdom, and Japan), growing from \$1.7 billion in 2001 to a projected \$6.6 billion in 2011.

The report concludes that there are three major reasons for the significant growth of hepatitis C treatments: widespread acceptance of pegylated interferons in treating HCV-infected patients; improved clinical efficacy of HCV drugs; and higher treatment rates among HCV-infected patients.

#### ***Major Market Players***

Schering-Plough's PEG-Intron and Hoffmann-La Roche's Pegasys (both are pegylated interferons) will compete for HCV market leadership between 2001 and 2011. According to the report, Schering-Plough currently appears to have an edge, due to the earlier launch of its pegylated interferon, PEG-Intron, in 2001. However, Hoffmann-La Roche's Pegasys, which will launch in 2002, could capture 50-60% of interferon sales for hepatitis C in the seven major pharmaceutical markets by 2011.

"Pegasys from Hoffmann-La Roche, even though it is second to market, is going to give Schering-Plough a formidable test of its marketing muscle when the agent is launched later this year," says Julia Bradsher, Decision Resources' therapeutic area director for infectious disease. "Pegasys will have an upper hand because of its effectiveness in difficult-to-treat patient groups."

### **18. Additionally on May 28<sup>th</sup>, 2002 as a result of data published in *Liver* an article titled “Ongoing Interface Hepatitis C May Signal More Fibrosis Later” was issued.**

Liver fibrosis in untreated patients with hepatitis C infection worsens with increasing time between biopsies. Likewise, change in fibrosis score is significantly more pronounced in people whose first biopsy is obtained within the first year after acquiring hepatitis C virus (HCV). These are among findings of a study by L. Martin Lagging and colleagues from Goteborg University and Chalmers University of Technology, Goteborg, Sweden and Royal Free and University College Medical School, London, England. The data is published in *Liver* Volume 22 Issue 2 Page 136.

To evaluate progression of fibrosis linked with HCV infection; these researchers obtained, and then scored and evaluated, two liver biopsy specimens from 98 HCV patients prior to antiviral therapy. Interface hepatitis in both biopsies, the time interval between the biopsies and age at first biopsy were all found to be associated with change in fibrosis score. In addition, higher age at the time of infection was linked with development of cirrhosis, and moderate intake of alcohol was associated with fibrosis progression.

If the second biopsy showed mild interface hepatitis, the authors note, an inflammatory response in the form of moderate interface hepatitis in the first biopsy was not necessarily linked with greater progression of fibrosis. However, having moderate interface hepatitis later in the course of infection, as reflected by the second biopsy, may be detrimental.

If moderate interface hepatitis early in the course of the disease is followed by less interface hepatitis later, there is less fibrosis; and if moderate interface hepatitis persists, there is more fibrosis eventually, study authors conclude.

### **19. On May 29<sup>th</sup>, 2002 based upon recent data published in *Hepatology* the press wrote an article titled “Daily Interferon Effective in Hepatitis C”**

Daily interferon induction treatment for 12 weeks plus combination therapy for another 24 weeks is as effective in hepatitis C patients as is 48-week combination therapy without induction treatment. This is the finding of a multi-centre study in France comparing the efficacy and safety of daily interferon alfa-2b in combination with ribavirin with that of interferon alfa-2b three times a week alone or in combination with ribavirin. The results of this study are published in *Journal of Hepatology*, Vol. 36 (5) (2002) pp. 672-680

The effectiveness of daily administration of interferon has been suggested by data on hepatitis C virus (HCV) dynamics and on the effect of interferon in blocking virion production in chronic HCV patients.

Three hundred and twenty one chronic HCV patients participated in this study by Victor de Lédighen and colleagues from the Service d'Hépatologie-Gastroentérologie, Centre Hospitalier Universitaire, Pessac.

The patients were randomly assigned to receive standard-dose interferon alfa-2b alone or in combination with ribavirin for 48 weeks or daily interferon alfa-2b (3 million units per day for 12 weeks followed by 3 million units three times per week for 24 weeks) and ribavirin (36 week treatment).

The rate of sustained virologic response (an undetectable serum HCV-RNA level 72 weeks after initiation of treatment) was higher in patients on combination therapy with three times weekly interferon (51.7 percent) and daily interferon (46.1 percent) than in those on interferon alone (25 percent).

Combination therapy, weight, genotype and viral load were found to be independent predictive factors for sustained virologic response.

### **20. On May 30<sup>th</sup>, 2002 Human Genome Sciences Updated the Press on the Phase 1 Trial of Albuferon-alpha for HCV**

Human Genome Sciences, Inc., (HGSI) recently told financial analysts in New York that the company expects to file four investigational new drug (IND) applications in 2002, seeking clearance from the U.S. Food and Drug Administration (FDA) to begin clinical trials of its new drugs.

Phase 1 studies of Albuferon-alpha are in progress with patients who have failed interferon treatment for hepatitis-C (HCV) and continue to test positive for active serum hepatitis-C virus. Levels of the enzyme, 2', 5'-oligoadenylate synthetase (OAS), provide a surrogate marker for interferon- alpha activity. A single dose of Albuferon-alpha has been demonstrated to be capable of inducing elevated OAS levels for up to 28 days.

More remarkably, the HCV viral load was reduced by half a log in some patients treated with a single dose. Along with continued escalation of single-dose exposure, repeat dosing has been initiated to further assess safety and the durability of biological activity. Once again, it is important to stress the relatively small number of patients studied and the preliminary nature of the data.

Albuferon-alpha and Albuferon-beta are new long-acting forms of interferon-alpha and interferon-beta, respectively. The drugs were created by fusing the genes for the parent drug to that for human albumin. Preclinical studies show that both drugs are active and have longer half-lives than do the original compounds.

Human Genome Sciences has initiated human trials for Albuferon-alpha for the treatment of patients with hepatitis C. Interferon-alpha alone has been shown to be an effective antiviral drug. We hope that Albuferon-alpha will be more effective and perhaps better tolerated than interferon-alpha. Albuferon-alpha is also the subject of clinical study for use in treating chronic myelogenous leukemia

**21. On May 31<sup>st</sup>, 2002 an article was released titled “Accelerated hepatic fibrosis in patients with both hereditary hemochromatosis and HCV” as a result of data published in the *Journal of Hepatology***

Hereditary hemochromatosis patients with HCV present with advanced fibrosis at a younger age, and at a lower hepatic iron concentration, compared to hereditary hemochromatosis patients without HCV, finds a study published in May's *Journal of Hepatology*. *J Hepatol* 2002; 36 (5): 687-91

A team from St. Louis, Missouri, USA, investigated patients with both hereditary hemochromatosis (HH) and chronic hepatitis C virus (HCV) infection. Both of these conditions can result in hepatic fibrosis and cirrhosis.

The researchers assessed whether these conditions together result in patients presenting with hepatic fibrosis/cirrhosis at a younger age and at a lower hepatic iron concentration, compared to patients with HH or HCV alone. In the study, 10 patients with combined HCV and HH were compared to 13 patients who had HH alone and 24 patients who had HCV alone. All patients had advanced fibrosis/cirrhosis on liver biopsy.

It was found that fibrosis in HH patients with HCV:

- ◆ Occurs at younger age
- ◆ At lower hepatic iron level

All HH patients were homozygous for the C282Y mutation. At presentation with advanced fibrosis/cirrhosis, the mean age of the HH/HCV group was significantly lower than that of the HH group and the HCV group. The authors also found that mean hepatic iron concentration was lower in the combined HH/HCV group, compared to that of the HH group.

Hari H. Diwakaran, of the Saint Louis University School of Medicine, said on behalf of the group, "HH patients with HCV present with advanced fibrosis/cirrhosis at a younger age, and at a lower hepatic iron concentration, compared to HH patients without HCV".

"These findings support the concept that the combination of HH-induced iron overload and HCV has a potentiating effect on hepatic fibrogenesis," it was concluded.

Hereditary hemochromatosis patients with chronic hepatitis C infection develop advanced fibrosis and cirrhosis earlier and at a lower hepatic iron concentration than do those without this infection. This combination of haemochromatosis (HH)-induced iron overload and hepatitis C virus (HCV) does appear, as has been suggested in earlier reports, to have a potentiating effect on hepatic fibrogenesis.

Both HH and HCV infection can independently result in liver fibrosis and cirrhosis.

This study, from a team at the Saint Louis University School of Medicine, St. Louis, Missouri, United States, sought to determine the effect of the combination of HH and HCV infection on hepatic function.

Hari H. Diwakaran from the Division of Gastroenterology and Hepatology, with colleagues from the

Departments of Internal Medicine and of Pathology, compared 10 patients with combined HCV and HH to 13 patients with HH alone and 24 with HCV alone. All 47 of these patients had advanced fibrosis/cirrhosis on liver biopsy, and the 13 HH patients were homozygous for the C282Y mutation.

On presentation with advanced fibrosis/cirrhosis, the mean age of the HH/HCV group was significantly lower than that of the HH group and of the HCV group. Furthermore, the mean hepatic iron concentration was lower in the combined HH/HCV group than in that of the HH group.

These findings thus support the concept that the combination of HH-induced iron overload and HCV has a potentiating effect on hepatic fibrogenesis, these authors conclude.

## **22. Additionally on May 31<sup>st</sup> as a result of data published in the *Journal of Viral Hepatitis* the following article was released by the press “Immunoglobulin/ Antiviral Combination Fails To Block Hepatitis B Virus Infections”**

Passive immunization with immunoglobulin in patients infected with the hepatitis B virus is only likely to be effective in those on antiviral treatment who have low pre-treatment levels of the hepatitis B surface antigen (HBsAg), a small trial published in the *Journal of Viral Hepatitis*, 2002; 9(3): 221-228 suggests.

Researchers from the Erasmus Medical Centre in Rotterdam, The Netherlands, concluded that it was not practical to immunize all HBV DNA negative patients with specific hepatitis B immunoglobulin (HBIg).

In the study, two of the six HBV infected patients on the antiviral lamivudine, who also had passive immunization, developed levels of surface antigen (HbsAg) that were so low as to be undetectable by the assay used. These low levels persisted for 31 and 7.5 hours for each of the two patients. Peak anti-HBs concentrations were 5100 and 4648 IU/l. The researchers found that, in vitro, it was possible to neutralize HbsAg with HBIg. There were 50 percent inhibition concentrations of 100-250 IU/l, with surface antigen levels varying from 68 to 120ng/ml. But, response was poor in the other four patients where surface antigen levels were higher to start with - in fact, they hardly changed after treatment. Overall in the six patients, there was no statistically significant overall fall in HbsAg levels. However, in four of the six, a fall in HbsAG levels of between 18 and 66 percent was observed.

The researchers came up with the idea of combining lamivudine with passive immunization because its efficacy is limited, and because of the success of immunization in preventing infection in the newborn.

Adding HBIg immunization to antiviral therapy is only likely to work if agents inhibiting viral proteins and Dane particles are developed.

## **23. On June 2<sup>nd</sup>, 2002 the press released an article titled “Gates Donates to Combat Hepatitis B”**

A charity created by Microsoft billionaire Bill Gates will donate \$37.5 million to combat hepatitis B in China, where two-thirds of the disease's victims live.

The Vaccine Fund's gift will be used to help immunize 35 million infants over the next five years against the potentially lethal blood-borne ailment, fund Executive Vice President James Jones told The Associated Press on Friday.

The Chinese government will spend another \$37.5 million on the project, which will buy vaccines to immunize newborn children in poor rural areas.

The money will also buy 500 million self-disabling syringes - specially designed to be used only one time. Reuse of dirty needles and syringes has been a leading cause of hepatitis B infection in China.

Jones said Chinese officials estimate the disease has infected more than 700 million Chinese. Every year, as many as 400,000 people in China die from liver cancer and other liver ailments caused by the disease, he said.

#### **24. On June 4<sup>th</sup>, 2002 as a result of data published in the *Journal of Viral Hepatitis* the press released an article titled “Low to Moderate Alcohol Intake Increases Fibrosis Progression in Hepatitis C”**

Total abstinence from beverage alcohol should be recommended to patients infected with hepatitis C virus as even at moderate levels, alcohol use appears to increase fibrosis progression in these patients.

For patients unable to achieve abstinence, then occasional alcohol use is probably less harmful than is low or moderate daily consumption, suggest J. Westin and colleagues from Goteborg University and Chalmers University of Technology, Goteborg, Sweden, and the Royal Free Hospital, London, England. The information is published in *Journal of Viral Hepatitis* Volume 9 Issue 3 Page 235 - May 2002

Excessive drinking in combination with hepatitis C virus (HCV) infection is known to increase liver cirrhosis risk. Until now, however, the effect of moderate alcohol intake in patients with this condition has not been elucidated.

In this study, 78 patients with HCV infection and moderate alcohol consumption were analyzed retrospectively and their lifetime drinking history recorded. All of the patients had had two liver biopsies, with a median time between biopsies of 6.3 years, and none had received any antiviral therapy. Except for one patient, all participants had daily consumption of below 40 g of ethanol in the period between the biopsies.

Those patients whose liver fibrosis had deteriorated were found to have higher total alcohol consumption and higher drinking frequency between biopsies than did the other participants. In patients with a total alcohol intake and drinking frequency above the median level for the group, degree of fibrosis progression was found to be greater.

Further analysis (multiple logistic regression) showed drinking frequency and time between biopsies were independently linked with progression of fibrosis.

#### **25. Additionally On June 4<sup>th</sup>, 2002 the press released an article titled “Iron Removal May Improve Effectiveness of Interferon for Chronic Hepatitis C”**

In patients with chronic hepatitis C, iron removal by phlebotomy appears to improve the sustained response rate to interferon, according to a recent report by Italian researchers. Previous reports have suggested that iron removal can improve the histologic and virologic response to short-term interferon therapy. However, it has been unclear whether iron removal would lead to an improved sustained response when longer courses and/or higher doses of interferon therapy were used.

Dr. Silvia Fargion, from the Ospedale Maggiore in Milano, and colleagues assessed the outcomes of 114 patients with chronic hepatitis C who were randomized to receive interferon alone or interferon preceded by phlebotomy. In both groups, interferon was given at a dose of 6 MU three times a week for 4 months, followed by 3 MU three times a week for 8 months.

The researchers' findings are published in the May issue of *The American Journal of Gastroenterology*. *Am J Gastroenterol* 2002; 97:1204-1210.

The virologic sustained response rates in the interferon only and the iron depletion groups were 15.8% and 28.1%, respectively ( $p = 0.17$ ). Multivariate analysis revealed that HCV genotypes 2 and 3 and a baseline

ALT level greater than 120 U/L were independent predictors of a sustained response.

Patients who underwent phlebotomy tended to respond better to interferon therapy than patients who did not ( $p = 0.082$ ). The difference in sustained response rates between the treatment groups was nearly significant for patients with hepatic iron concentrations no greater than 1100 micrograms/g dry weight ( $p = 0.059$ ).

"To our knowledge, this is the first randomized, controlled study on the effect of phlebotomy before long duration and high-dose interferon therapy in naive patients with hepatitis C virus-related chronic liver disease," the authors point out. "Our data indicate that iron removal by phlebotomy is able to improve the rate of sustained responses to interferon, especially in patients with lower hepatic iron concentrations."

## **26. Additionally on June 4<sup>th</sup>, 2002 the press announces that "Stanford Researcher Identifies Genes Pointing to Liver Cancer; Advocates Screening for Asian Populations"**

Cancerous liver cells rely on a different set of genes than normal liver cells in order to function. Now researchers at Stanford University Medical Center have identified genes needed by cancerous liver cells but ignored or used at different levels by normal liver cells. This discovery could lead to more effective treatments and screening tests for liver cancer, which is usually not detected until the disease is too advanced to treat effectively. A screening test would be of particular benefit to Asian and Pacific Island populations, which have roughly 10 times the risk of liver cancer than Caucasians because of high rates of chronic hepatitis B infection.

There's a real opportunity to use this information to develop better and cheaper tests for diagnosis and treatments," said Samuel So, MD, director of Stanford's Asian Liver Center and an associate professor of surgery at the School of Medicine. Last year, So launched the Jade Ribbon Campaign to draw attention to the high rate of hepatitis B among Asian Americans. Chronic hepatitis B infection can lead to liver cancer.

Surgically removing the tumor is considered the only effective treatment for liver cancer, but less than 20 percent of liver cancer patients are diagnosed when surgery is still an option. Of those who undergo surgery, 50 percent experience a relapse. "Most of the time, if you wait until the patient has symptoms, the diagnosis is too late," said So, who also oversees the medical center's liver cancer program. Because of late discovery, he added, many liver cancer patients survive only four to six months after diagnosis.

To identify the genes in this study, So and his colleagues compared the genes being used in more than 200 normal and tumor samples. First they isolated RNA from the samples (RNA is produced by active genes - the more active the gene, the more RNA is produced). Then they tacked a fluorescent molecule onto the RNA and washed it over the surface of a glass slide dotted with 17,400 human genes. Any RNA that corresponded to a gene on the array stuck, creating a fluorescent spot. A brighter spot meant more RNA and more gene activity.

By comparing the pattern of fluorescent spots created by both normal and tumor samples, the researcher determined which genes were being used at either high or low levels in the tumor samples. They reported these findings in the June issue of the journal *Molecular Biology of the Cell*. Many of the genes they found were well-known cancer genes; however, "many were not known to play a role in liver cancer," So said. Of these, he hopes to find genes that make proteins that are secreted from the tumor and are present in the bloodstream of individuals with liver cancer.

"If that protein is only present or produced in high levels in people with liver cancer, maybe we can develop a better blood test to detect the cancer," So said. He added that other proteins could be targets for new drugs to treat the disease once it's diagnosed.

So said many Asians are exposed to hepatitis B at birth and roughly 10 to 15 percent become chronic carriers of the disease. Overall, 400 million people worldwide have chronic hepatitis B. Although infected

individuals may feel healthy, the disease can cause scarring of the liver (cirrhosis) or liver cancer in people as young as 30. So recommends that all Asian Americans be screened for hepatitis B and get vaccinated if they test negative.

Hepatitis B carriers should be screened for liver cancer every six months by having their blood tested for a protein called alpha-fetoprotein, which is sometimes at higher levels in people with liver cancer. These individuals also should undergo a liver ultrasound annually to look for tumors. So said neither technique is completely accurate nor are the precautions inexpensive enough for widespread use in poor countries, highlighting the need for a better screening tool.

So's colleagues include Xin Chen MD, PhD, research associate at the Asian Liver Center and the department of surgery; Pat Brown MD, PhD, professor of biochemistry; David Botstein, PhD, professor of genetics; Chris Barry, MD, PhD, resident in surgery; and his collaborators from the University of Hong Kong. Other Stanford investigators are John Higgins, MD, assistant professor of pathology; Matt van de Rijn, MD, PhD, associate professor of pathology; and Kin-man Lai, MD, resident in surgery.

## **27. On June 5<sup>th</sup>, 2002 based upon data from the University of Sao Paulo, the medical press released an article titled "Hepatitis C Viral Load Is About More Than Numbers"**

Hepatitis C viral (HCV) load does not correlate with the histological evolution of the disease, and use of viral RNA quantification as a predictor or determinant of severity of this disease is incorrect and of relative value.

These are the views of Evaldo Stanislau Affonso de Araujo and colleagues following an analysis of 58 patients at the Hepatitis Outpatient Clinic, Department of Infectious and Parasitic Diseases, Faculty of Medicine, University of Sao Paulo, (DMIP/FMUSP), Sao Paul, Brazil. This data is published in Rev. Inst. Med. trop. S. Paulo vol.44 no.2 São Paulo

Participants all had chronic hepatitis C confirmed by liver biopsy and detection of viral RNA in serum by nested polymerase chain reaction (PCR). They were followed from 1997 to 1998.

They received interferon-alpha subcutaneously three times per week for 12 months, blood samples were collected and processed before treatment, and six and 12 months after. The virus was serotyped.

A predominance of male patients with a mean age of 40 years was found and although most patients acquired the infection through blood transfusion and blood derivatives or through drug use, one third of the cases did not report any suspected epidemiology. Diagnosis was mainly made upon blood donation.

Genotype 1 was the most common HCV subtype (30 cases, one co-infected with genotype 4); although 34 percent of the patients were non-1 (4 were type 2 and 16 type 3). In most cases, viral load was below 500,000 copies/ml.

There was a predominance of patients with elevated HAI and slight structural alterations. Median viral load decreased during the first six months of treatment, but this reduction did not persist to the end of treatment. A virological response was obtained in 21 cases and was sustained in 10 (17.2 %), and a biochemical response was obtained in 19 cases and sustained in nine (15.5 %).

Histological analysis revealed a reduction in inflammatory activity and maintenance of the favorable architectural profile.

These researchers conclude HCV RNA quantification plays a role in viral dynamics and can provide an early prediction (24h to 48h) of a sustained virological response. However, disease progression is more complex and does not simply depend on viremia.

## **28. On June 6<sup>th</sup>, 2002 Schering Canada Inc. released a press release titled "Pegetron**

## **(Peginterferon Alfa-2b/Ribavirin) Receives Health Canada Approval for the Treatment of Chronic Hepatitis C**

Schering Canada today announced the approval by Health Canada of the first pegylated interferon-based combination therapy, Pegetron™, (peginterferon alfa-2b powder for solution plus ribavirin 200 mg capsules) for the treatment of adult patients with chronic hepatitis C.

Pegetron is the only pegylated interferon combination therapy approved in Canada. This new combination treatment, representing the most significant advance in the treatment of hepatitis C, was granted centralized marketing authorization by the European Commission in March 2001 and approved by the U.S. Food and Drug Administration in August 2001.

"I am pleased that this next generation of treatment for hepatitis C is now available in Canada," said Dr. Morris Sherman, Chairman of the Canadian Viral Hepatitis Network (CVHN). "We expect to see improved treatment response rates with easier administration of medication."

A recent published study demonstrated that Pegetron increased the sustained virological response (SVR - undetectable hepatitis C virus (HCV) in the blood at 24 weeks following treatment), resulting in an overall response rate for Pegetron that was 30 percent higher compared to Rebetron™, the previous standard of care therapy for chronic hepatitis C. Health Canada has approved Pegetron to be prescribed based on each patient's body weight. This optimal "weight-based dosing" may result in an overall SVR of 61% compared to 47% with Rebetron. (1)

"With response rates for the first time exceeding 50 percent, access to this new combination therapy will result in a significant increase in the number of patients who have eradicated their virus", said Dr. Victor Feinman, Director of the Liver Study Unit at Mount Sinai Hospital in Toronto. Pegetron will also provide patients with more convenient dosing by allowing for a once- weekly self-injection of pegylated interferon alfa-2b compared to three times weekly with Rebetron.

### ***THE "SILENT EPIDEMIC"***

Health Canada estimates that as many as 275,000 Canadians may be infected with hepatitis C with 4,000 to 5,000 new infections occurring each year. Dr. Urs Steinbrecher, Professor of Medicine at UBC, says the approval of Pegetron is welcome news for his province. "This is good news for the many patients with hepatitis C who have been waiting for this new treatment, especially in British Columbia where we have one of the highest rates of newly identified HCV cases in Canada."

HCV is transmitted through contact with infected blood. Key risk factors include intravenous drug use and body piercing/tattooing with non-sterile needles. Most people are unaware that they have the disease because there may be no symptoms until it has reached an advanced stage. The disease causes inflammation of the liver that can lead to scarring (cirrhosis), and may progress to liver cancer or liver failure. Hepatitis C is one of the leading causes of liver transplantation in Canada.

"I am very pleased that this significant breakthrough in treatment is now approved", said Tim McClellmont, Executive Director of the Hepatitis C Society of Canada. "Canadian patients can now receive the best therapy available." Regulatory approval by Health Canada is the first step in the process for enabling patient access to Pegetron. People with hepatitis C depend on coverage for their medicine through provincial formularies or employer drug plans. Schering Canada will be working with these drug plans to ensure that patients have timely access to the treatment they need when this new combination becomes commercially available in July.

The frequency and type of adverse events reported in clinical trials were similar to those reported with Rebetron. The most frequently reported adverse events with Pegetron were fatigue, fever, headache, rigors, myalgia and insomnia. Other common adverse events included application site inflammation and reaction, arthralgia and nausea.

All alpha interferons, including Pegatron, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping Pegatron therapy.

Ribavirin may cause birth defects and harm to the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. (See Pegatron product monograph for additional information and other warnings.)

## **ABOUT SCHERING CANADA**

Schering Canada's commitment to hepatitis C treatment is reflected in more than a decade of research, continuing medical education and cooperative educational efforts with organizations that represent the interests of people with hepatitis C.

Schering Canada's head office is located in Pointe-Claire, Quebec and the company also has a distribution centre in Kirkland on the West Island of Montreal. Schering Canada is a wholly owned subsidiary of Schering-Plough Corporation, a research-based company engaged in the discovery, development, manufacturing and marketing of pharmaceutical products worldwide.

### **References:**

(1) MP MANNES ET AL. "Peginterferon alfa-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C : a randomized trial", The Lancet Sept 22, 2001: 358: 958-965.

## **29. On June 7<sup>th</sup>, 2002 based upon research data from Revista do Instituto de Medicina Tropical de São Paulo the medical editor community released an article titled "Hepatitis G Adds No Anti-Liver Action To Hepatitis C In Coinfected"**

Liver histology adds weight to growing evidence that in people co-infected with hepatitis C virus, hepatitis G is not pathogenic and does not induce a more aggressive liver disease. High prevalence of hepatitis C virus (HCV) infection and related morbidity is well documented. For the more recently described hepatitis G virus (HGV), however, there is little evidence of related morbidity and many questions about its etiologic role in liver disease.

Although co-infection by HCV and HGV has been studied in a wide range of conditions and in different ways, histopathological variables have rarely been analyzed. Because prevalence of HGV is high in Brazilian blood donors, and HCV infection is usually mild in these asymptomatic patients, these researchers reasoned this was an interesting group in which to investigate a possible synergism of these viruses in producing liver damage.

Forty-six blood donors with hepatitis C were investigated for HGV RNA in this study from the Divisao de Anatomia Patologica da FMUSP and LIM 14, Sao Paulo, Brasil; Centro de Tecnologia en Salud Publica, Universidad Nacional de Rosario, Argentina; and Fundacao Pro-Sangue Hemocentro de Sao Paulo. The results are published in Rev. Inst. Med. trop. S. Paulo vol. 44 no. 2 São Paulo

In seven of the 46 patients, HGV-RNA was detected, for a prevalence of HGV/HCV co-infection of 15.2 percent. Liver biopsy was indicated and done in 22 patients. Six of them had HGV/HCV co-infection, and 16 had HCV isolated infection.

As well as staging and grading of inflammation at portal, peri-portal and lobular areas (Brazilian Consensus), Edna Strauss and colleagues calculated the fibrosis progression index in both groups, i.e. those with

HGV/HCV co-infection and those with HCV isolated infection. Although none of the patients had symptoms or signs of liver disease, most had mild liver disease.

The fibrosis progression index, calculated only in patients with known duration of infection, was 0.110 for co-infection and 0.130 for isolated HCV infection, characterizing these patients as "slow fibrosers". There were no statistical differences found between the groups, although a lesser degree of inflammation was always present in the co-infected.

The finding that HCV/HGV co-infection does not induce a more aggressive liver disease supports the hypothesis that HGV is not pathogenic, study authors conclude.

### **30. On June 10<sup>th</sup>, 2002 the editors for AIDS weekly released an article titled "Protease inhibitors may reduce hepatitis C load in people coinfectd with HIV".**

People coinfectd with hepatitis C virus (HCV) and human immunodeficiency virus may see reductions in HCV loads in the liver as a result of taking HIV treatment regimens containing protease inhibitors.

A research team in France reported that finding after evaluating 37 individuals coinfectd with HIV and HCV. According to the researchers, who work at the Centre Hospitalo-Universitaire (CHU) of Bordeaux, France, each of the study enrollees had controlled HIV, with HIV plasma loads of less than 10,000 copies/ml, and CD (superscript)+ counts greater than 250/(micro sign). Thirty-five of the study participants were on antiretroviral treatment regimens for HIV.

After performing different serological and pathological evaluations of the study group participants, P. Trimoulet and colleagues detected several common elements within the cohort. "All patients had serum and liver HCV RNA, and both levels correlated," Trimoulet and coauthors said. Neither age, sex, genotype, fibrosis, or duration of disease corresponded with HCV load in the liver, the group noted. METAVIR scores, used for staging liver fibrosis, were lower in patients with lower levels of hepatic HCV RNA, which also correlated with patient concentrations of the liver enzyme aspartate aminotransferase (AST)

The data on the intrahepatic HCV RNA loads in 37 HIV -HCV coinfectd patients with controlled HIV infection was published in the Journal of Medical Virology, June 2002;67(2):143-151) . "Highly active antiretroviral therapy (HAART), including protease

inhibitor (PI)-treated patients had significantly lower HCV load," said Trimoulet and associates. Researchers suggested PI might be responsible for lowering HCV levels, "supporting a protective effect of PI-induced immune restoration."

In summary this study showed that:

- ◆ In patients coinfectd with HCV and controlled HIV, liver fibrosis tended to correlate with liver HCV load
- ◆ Coinfectd individuals on protease inhibitors demonstrated lower liver loads of HCV RNA
- ◆ Protease inhibitors may induce immune system activation that curbs HCV replication

### **31. On June 12<sup>th</sup>, 2002 at the NIH Consensus Conference on Management of HCV it was determined that "Drug users, children and HIV patients should not be excluded from treatment for hepatitis C"**

Drug users, children and HIV patients should not be excluded from treatment for hepatitis C, a blood-borne virus that has infected an estimated 4 million Americans and is a leading cause of liver cancer, a federal advisory panel says.

A 12-member committee of experts selected by the National Institutes of Health said Wednesday that

treatment for hepatitis C has improved in recent years and that groups that previously were excluded from therapies should now receive treatment.

The committee made the recommendation in a report that reviewed the current medical consensus on the diagnosis and treatment of hepatitis C. Such reports influence the way doctors treat patients in the United States.

About 4 million Americans are infected with hepatitis C, making it the most common blood-borne infection in America. The virus is spread most frequently through the shared needles of drug users, but it can also be spread by high-risk sex and transplantation of infected organs, and an infected woman can give it to her infant.

Blood transfusions were once a common source of the infection, but blood screening tests started in the early 1990s have almost eliminated that risk. However, many patients infected before the tests began may be diagnosed in coming years as they develop symptoms.

About 85 percent of people infected with hepatitis C develop chronic disease; the other 15 percent are able to eliminate the virus. Chronic disease over a 10- to 20-year period can lead to cirrhosis, liver failure and cancer. It is estimated that 3 percent to 20 percent of chronically infected patients will develop cirrhosis, making hepatitis C is the leading cause of liver transplants.

Dr. James Boyle, a liver expert from the Yale University School of Medicine and chairman of the panel, said clinical studies that led to development of drugs to treat hepatitis C excluded children, drug users, the elderly, people infected with HIV, alcoholics and those with depression.

As a result, he said, there was no clinical evidence that people in these groups responded to the hepatitis C therapies and doctors tended to not treat such patients.

"We now know that these patients can respond to the standard treatment so we are recommending that they receive it," said Boyle.

New tests can now detect hepatitis C infection at a high degree of accuracy and can be suitable for screening virtually all at-risk patients, the panel said.

To treat the virus, a combination of drugs that includes interferon and ribavirin has been shown to be the most effective, the panel found.

Patients who do not respond after a year of this therapy, however, "present a significant problem," the committee said. The group report said a large drug trial is underway to determine if long-term maintenance therapy with interferon alone can prevent progression of cirrhosis or development of liver cancer among chronically infected patients.

## **32. Additionally on June 12<sup>th</sup>, 2002 the following press release was issued from the NIH "Progress and Future Directions for Management of Hepatitis C"**

Substantial advances in treatment for chronic hepatitis C and a decline in the number of new infections were highlighted by a panel convened by the National Institutes of Health (NIH). Nonetheless, a fourfold increase in persons with chronic hepatitis C infection is projected over the next decade, as a result of unsuspected infection from contaminated blood and blood products, occupational exposure, and injection drug use prior to the advent of routine screening in the early 1990s. These chronic infections are now leading to significant increases in cirrhosis, end-stage liver disease, liver cancer, and are the most common causes of liver transplants.

"However, the good news is that new combination therapies are having a beneficial impact on this disease,"

noted panel chair Dr. James Boyer, Ensign Professor of Medicine and Director of the Liver Center at Yale University School of Medicine. "In addition, preliminary research indicates that this approach may prove useful in treating important subgroups of patients including children and injection drug users previously ineligible for treatment. Up to now, the majority of studies have focused on what is actually a narrow segment of the patient population. Thus, we still have a lot to learn."

More than 4 million Americans are infected with hepatitis C, and of this group, the majority experience chronic infection, defined as detection of the virus in blood over at least a 6-month period. The hepatitis C virus (HCV) is the most common blood-borne infection, and transmission now occurs primarily by injection drug use, high-risk sexual behaviors and occupational exposures such as accidental needle sticks, and mother-to-infant transmission.

Clinical trials are providing persuasive evidence that treating HCV with a combination of pegylated interferon and ribavirin produces a considerably better sustained viral response (SVR) than monotherapy or standard interferon-ribavirin combination. Unfortunately, patients with genotype 1 HCV, who account for 70-75% of infected persons, require longer duration of therapy and have a lower SVR.

Although SVR has not yet been correlated with improved survival because of the need for long-term follow-up, the absence of detectable HCV provides a significant benefit in terms of resolution of liver injury, reduction of liver fibrosis, and a lower likelihood of HCV reinfection. The best treatments are less clear for non-responders and relapsers.

The independent, nonadvocate, non-Federal panel issued its statement at the conclusion of a two-and-a-half-day NIH Consensus Development Conference on Management of Hepatitis C: 2002 held on the NIH campus in Bethesda, Maryland. The meeting was convened to provide an update to a 1997 conference on the same topic. This consensus panel broke away from its 1997 predecessors by expanding the scope of patients eligible for treatment to include those who use injected drugs, consume alcohol, suffer from co-morbid conditions such as depression, or who are coinfecting with HIV. Similarly, panelists cautioned against the exclusion of children and older adults from treatment and further research.

Among its recommendations for future research, the panel gave top priority to the development of reliable and reproducible HCV cultures, which will advance the understanding of its biology, mechanisms of drug resistance, and aid vaccine development. The panel urged the establishment of a hepatitis research network that would conduct research into the natural history, prevention, and treatment of hepatitis C. Studies to determine the efficacy of alternative medicines are also needed. The panel also recommended the development of strategies to better prevent, diagnose, and treat the disease in injection drug users and the incarcerated population.

The 12-member consensus panel included representation from internal medicine, gastroenterology, infectious diseases, pediatrics, family practice, oncology and the public. The panel members heard presentations from 28 hepatitis C experts, and reviewed an extensive body of medical literature, as well as an evidence report prepared by the Johns Hopkins University School of Medicine Evidence-based Practice Center (EPC) under contract to the U.S. Agency for Healthcare Research and Quality (AHRQ).

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH Office of Medical Applications of Research (OMAR) sponsored the conference. Co-sponsors included the National Cancer Institute (NCI), the National Center for Complementary and Alternative Medicine (NCCAM), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA), the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), the U.S. Department of Veterans Affairs (VA), and the U.S. Food and Drug Administration (FDA).

The panel's statement is an independent report and is not a policy statement of the NIH or the Federal Government. The NIH Consensus Development Program, of which this consensus conference was a part,

was established in 1977 as a mechanism to judge in an unbiased, impartial manner controversial topics in medicine and public health. NIH has conducted 116 consensus development conferences addressing a wide range of issues.

The full text of the panel's statement will be available in draft form following the conference at <http://consensus.nih.gov>. Statements from past conferences are available at the same Web site, or by calling 1-888-NIH-CONSENSUS (1-888-644-2667).