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HEPATITIS C

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TABLE OF CONTENTS

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BACKGROUND

In recent years, Hepatitis C has become a familiar disease to most Canadians as a result of the much-publicized scandal about its transmission via blood transfusion or blood products. Although the disease itself is not new, the virus responsible for it has only recently been identified and much work remains for gaining a full understanding of how it affects the progression of the disease. This paper will review some of the major aspects of Hepatitis C and will discuss some of the current research underway for developing an effective method of treatment, a vaccine, and a cure.

TYPES OF HEPATITIS (1)(2)

There is a vast spectrum of diseases all referred to as "hepatitis." Each has a different cause, method of infection, symptomology, progression, and treatment, as well as level of lethality. All hepatitis, however, is characterized by liver (hepatic) inflammation, which usually produces swelling of the liver tissue and, quite often, permanent damage to it. Non-viral agents, such as alcohol, chemical poisons and drugs (both illicit and medicinal) can bring on hepatitis. Infectious agents, viruses, can also produce the disease and there is a growing "alphabet" of the viral forms, from Hepatitis A through to Hepatitis G. Hepatitis C and its cousins A and B are the most common types. Vaccines are available for both Hepatitis A and Hepatitis B.

One method of characterizing the viral forms of hepatitis is to define whether the virus is transmitted via the mouth (food) or via the blood. Forms of hepatitis transmitted through food do not cause chronic (long-lasting) disease and tend to produce serious complications in only a small percentage of cases. Hepatitis A, for example, is spread principally by ingesting water or food that has become contaminated with infected faecal matter; as a result, it is more prevalent in under-developed countries. Hepatitis E is another food-borne viral hepatitis

which is clinically very similar to Hepatitis A, though the patient may be ill for a slightly longer time. Hepatitis F is a recent addition to the list of food-borne forms of hepatitis.

In blood-borne forms of viral hepatitis, transmission of the disease is primarily through contact with infected blood, or, less frequently, other bodily fluids. One such form is Hepatitis B, which is highly infectious, more so than HIV, and is easily transmitted through sexual contact and breastfeeding, or even by casual family contact, as well as through blood-blood routes. Only 5-10% of those infected with the Hepatitis B virus (HBV) become chronically infected; most of those infected successfully fight off the virus and are said to have suffered an acute infection. D and G are other blood-borne hepatitis viruses. The former appears only as a co-infection with HBV and serves to accentuate symptoms. Hepatitis G is a recent addition to this list, about which very little is known at this time.

Hepatitis C, the main subject of this document, is also transmitted primarily through the blood, for example through intravenous drug taking by means of shared needles. Before 1990, transmission took place largely during blood transfusions and the use of blood products. The Hepatitis C virus is not as highly infectious as HBV and it is not easily transmitted through intimate contact or mixing biological fluids. More than 80% of Hepatitis C virus (HCV) infections become chronic, however, and most are believed to lead to liver disease.

CLINICAL DESCRIPTION OF HEPATITIS C

A. Some Details about the Virus

The virus that causes Hepatitis C (HCV) was identified in May 1987 by Chiron Corporation.(3) Until that time, patients who tested negative for both Hepatitis A and Hepatitis B but who still showed symptoms of hepatitis were designated as having non-A, non-B Hepatitis. In 1990, a test became available that specifically tested for the antibody produced against Hepatitis C, but only since 1993 has it been possible to test directly for the virus itself. This is an important distinction, as a person is typically infected with the virus for four to six weeks before antibodies can be detected.

Almost all organisms store their genetic information in the form of DNA (deoxyribonucleic acid). Some viruses are the exception; in two of the six known classes of viruses, genetic information is stored as RNA (ribonucleic acid). This is a much less stable molecule than DNA and is susceptible to mutation at a much greater rate. RNA serves as an intermediary in the replication of our genetic material so that it is not a foreign entity to those organisms that carry DNA. These observations provide the key to the success of the virus in producing chronic infection that eludes the immune system.

The Hepatitis C virus must attach and infect liver cells in order to carry out its life

cycle and reproduce. The virus injects its RNA into a liver cell, which, perceiving it as its own "transient" RNA ("messenger" RNA or mRNA), proceeds to replicate it. In doing so, the infected cell shuts down most of its normal functions in order to conserve energy. Hundreds or thousands of copies of the viral RNA are produced in the liver cell, at the high rate of mutation of RNA. The host liver cells continue to cooperate by manufacturing the components needed for the viral RNA to assemble into virus particles. These then leave the host cell, eventually killing it, and proceed to infect hundreds or thousands of new host liver cells.

The immune system of the infected individual is quick to recognize the invading virus and attempts to eliminate it. The high rate of mutation, however, ensures that an "evolved" variant will be always able to elude the immune response and go on to replicate without interruption until the immune system makes its next attempt. In this way these viruses can evolve faster than any other organism. This game of genetic hide and seek is also the reason why scientists have so far failed to discover an effective vaccine against Hepatitis C.

B. Transmissibility of the Virus

It is believed that HCV is transmitted only by blood. It is unlike other blood-borne viruses, however, in that any source of blood or blood product appears capable of carrying it, even indirectly via a razor or toothbrush.

In the 1970s and 1980s, many individuals became infected with HCV through blood transfusions. Haemophiliacs were particularly susceptible to contracting the disease, as the blood products they needed were derived from the blood of thousands of donors. Since the virus has been identified and tests for it have become available, the number of transmissions through the Canadian blood system has fallen to a negligible level. The most significant risk behaviour for contracting Hepatitis C is drug use; this accounts for as many as 40% of all cases. Indeed, the majority of IV drug users are HCV positive since the virus is not only transmitted through sharing needles but also through sharing other drug paraphernalia.

Other things shown to carry a significant risk of infection are needlestick injuries, tattooing, body piercing, acupuncture, ear piercing, contaminated medical equipment and sexual activity with multiple partners. Casual day-to-day contact and transmission from mother to child at birth are also implied, but the exact risk through these means remains unknown.

C. Symptoms and Diagnosis of Hepatitis C (4)(5)

In the majority of cases, the patient does not exhibit symptoms when newly infected with the virus (in the acute phase). Any symptoms are sometimes dismissed as the flu or a general malaise and are not followed up appropriately so that the infection can be identified. In a smaller percentage of cases (3-5%),

the infected person experiences an acute reaction two to three weeks after infection, with severe abdominal pain, nausea, vomiting and extreme fatigue. Jaundice, loss of appetite, weight loss, and lethargy usually follow but the severity of these symptoms usually decreases over time.

The most common symptoms of chronic infection, which may not appear for several years, are mild fever, muscle and joint aches, nausea, vomiting, loss of appetite, vague abdominal pain and sometimes diarrhea. Another complaint not uncommon among Hepatitis C sufferers is itchiness of the skin; however, because this symptom is itself poorly understood, its association with HCV status is not clear. Other, less frequently reported, symptoms include dark urine, light coloured stool, and weight loss. As with the milder acute reactions, many individuals dismiss these symptoms as flu-like or may not even recognize them as being sufficiently serious to require medical attention.

In a small proportion of Hepatitis C patients, progression of the disease, usually over several decades, produces symptoms associated with poor liver functioning. In addition to those symptoms already listed, patients may also experience swelling of the arms and feet, readiness to bruise, intermittent confusion, disorientation or inability to carry out complex mental tasks.

Many individuals are diagnosed with the disease when they seek medical attention for chronic fatigue. Others are not diagnosed until severe liver problems prompt them to see a doctor. Some individuals are identified as having Hepatitis C when routine blood tests show abnormally high "liver enzymes"(6) or when they are screened before donating blood.

Elevated liver enzymes will prompt the physician to test for the antibody to the HCV and other conditions associated with liver disorders. A newly infected individual will test negative as it can take three to four months for the immune system to produce any antibody to the virus. A patient found to have the HCV antibody is often said to be "anti-HCV positive." Such a person will generally have acquired a chronic infection, although a very small percentage of people may successfully eliminate the virus from their system. Only very recently has a test become available for the virus itself. This technique, which analyzes for the virus RNA, has now been adopted by Canadian Blood Services for standard screening of blood products. If drug treatment is going to be initiated, or if there is reason to suspect severe liver damage, something that can only be confirmed by analyzing the tissue itself, a biopsy of the liver is required.

D. Progression of the Disease

Although the progression of Hepatitis C is relatively slow, the consequences can be quite debilitating or even fatal. As yet, because of the relatively short time since the virus has been identified, the percentage of sufferers who progress to liver disease and death is not known. The chronic inflammation of the liver associated with Hepatitis C leads to scarring ("cirrhosis") as the liver attempts to

protect itself from the inflammation. Approximately 20% of those chronically infected will develop cirrhosis after 20 years of infection. Of these, 1-5% will develop cancer of the liver (hepatocellular carcinoma) each year.(7) Hepatitis C also exacerbates co-existing liver conditions. Once the disease has progressed to cirrhosis or cancer, a liver transplant is the only option for survival. Liver disease caused by HCV infection is the leading cause for liver transplantation in Canada.(8)

Many additional complications have also been linked to this disease, although the relationships are at present not entirely understood. It is believed that as many as 20% of Hepatitis C patients may also suffer from disorders of the thyroid, intestine, eyes, joints, blood, spleen, kidneys or skin.(9) Many of these complications are suspected of being associated with the interferon therapy itself.

CURRENT TREATMENTS AND MANAGEMENT

Once diagnozed, the individual must consider whether treatment or management of the disease, by means of drugs, alternative treatment, or lifestyle modification, is appropriate. In cases where the patient is not suffering any physical symptoms and the liver enzymes are clinically stable, doctors frequently do not advocate aggressive treatment.

A. Conventional Drug Therapy

Since Hepatitis C was identified, the only approved drug therapy has been an interferon given the trade name Intron-A®. Interferon is a family of glycoproteins derived from the human cells normally involved in fighting viral infections by preventing virus multiplication in cells. Interferon therapy is aimed primarily at patients with HCV infection and where persistent elevation of the liver enzymes indicates chronic hepatitis. Interferon is not considered a cure. Only 25% of infected patients may be candidates for this therapy and, of those treated, only 10-25% will show prolonged reduction of liver enzyme and virus levels.

Advances in drug therapy have always included interferon, in varying dosages and perhaps in conjunction with a second drug. Recent interferon therapy consisted of injections three times weekly over a 12-month period or longer. This therapy is discontinued if no improvement in liver enzymes is seen after a reasonable time (two or three months). Of those individuals who show improvement while on therapy, a large proportion will relapse upon discontinuation of the drug. Higher doses of interferon can be given by increasing either the amount of the drug or the frequency of administration; this approach appears to have more success in viral eradication during therapy and a higher post-treatment success. Even here, unfortunately, the incidence of relapse remains high and larger doses do not appear to improve sustained response rates substantially. Interferon itself is a harsh drug to take, with many debilitating

side effects, and several physicians have questioned its use, given the very low long-term remission rates.

Recently, the Therapeutic Products Programme at Health Canada approved the use of Rebetron ®. This is a form of therapy in which interferon is combined with a drug called ribavirin, which, like interferon, acts by modulating the immune response. This therapy combination does increase the percentage of patients showing sustained decrease of virus levels in the blood. Of individuals with a certain strain of the HCV, however, only 25-30% show sustained response following therapy.(10) Significant adverse effects from ribavirin can limit the use of combination therapy for many individuals.(11)

B. Alternative Drug Therapy

Many herbal medicines are claimed to be helpful in treating liver diseases in general and some are said to be effective specifically for Hepatitis C. Studies confirm that the most widely acclaimed, silymarin, also called Milk Thistle, helps liver cells regenerate and stabilizes liver cell membranes. It also boosts the ability of the liver to filter blood and prevents damage to it from toxins, including solvents, alcohol, drugs, most pesticides and herbicides, and bacterial compounds such as those associated with food poisoning. Silymarin may help treat cirrhosis, hepatitis and other liver diseases.(12)

C. Lifestyle Management

Many individuals suffering from Hepatitis C feel that they can minimize fatigue by having healthy sleeping habits, allowing for short naps, eating wisely, and maintaining a constant modest level of physical exercise. In terms of diet, patients are encouraged to ensure they have the adequate protein intake essential for repairing liver cells, consume complex carbohydrates liberally, and restrict fat, while still having an adequate intake of essential fatty acids. Calorie intake should not be limited unless there is a need for the patient to lose weight. HCV positive individuals are advised against being overweight as this is associated with some other liver abnormalities such as fatty deposits, which can lead to its inflammation.(13)

Because any additional stresses on the liver will exacerbate the effects of the virus, it is recommended that patients avoid unnecessary substances that require liver metabolism. In this regard, many medications should be kept to a minimum. Common medications such as aspirin, and ibuprofen can be toxic if used habitually by someone with compromised liver function.(14) Alcohol should clearly be avoided as it has been shown to increase the chances of developing cirrhosis.

CURRENT RESEARCH INTO THE DISEASE

Hepatitis C research focuses on two areas, treatment of the disease and

prevention of infection. Below is a brief description of the current state of research in these broad categories.

A. Treatment

Treatment of the disease can encompass several areas, including strategies to alleviate or eliminate symptoms, slow down or reverse tissue damage (with or without symptoms), or cure the disease through elimination of the virus. Most current research is focusing on the last two categories.

A significant amount of research continues on existing drug therapies. Interferon therapy has proved to be helpful in a very limited proportion of HCV infections, but the proportion appears to rise when interferon is combined with ribavirin. The harshness of these drugs detracts from their appeal as possible treatments, however. Researchers have been interested in identifying which hepatitis C sufferers would be most likely to benefit from them, in order to minimize the application of ineffective therapies. Other research consists of analyzing and overcoming possible reasons for non-response to interferon.(15)

Research into a cure for the disease has focused mainly on genetically engineered therapeutic vaccines and drugs that could "overwhelm" the virus before it was able to mutate sufficiently to elude treatment. Most recently the emphasis has been on antisense gene therapy.(16)(17)

B. Prevention

Research into the prevention of HCV infection centres on developing a vaccine. This research has proved to be very frustrating because of the mutative nature of the virus. It is hoped that biotechnology will make a genetically engineered vaccine a reality in the near future. Any successes in the race to produce a vaccine against HIV would speed the search for a vaccine against HCV.(18)

HOW IMPORTANT IS THE HEPATITIS C ISSUE FOR CANADA?

A. How Many People Suffer?

According to one report, just under 300,000 people in Canada (more than 1% of the population) may be infected with HCV(19) and as many as 20,000 new infections are reported each year.(20) The prevalence of HCV infection in Canada is thought by some to be even higher; the Centers for Disease Control and Prevention in Atlanta report the American prevalence to be about 1.8%. (21) Many of the infected individuals are as yet undiagnosed because of the high proportion of asymptomatic, or slightly symptomatic, infected persons who are not identified for diagnosis. Hepatitis C is thus referred to as the "silent epidemic." From the estimate of 300,000, it can be projected that approximately 60,000 cases (20% of cases) will progress to cirrhosis, which, based on 1% to 5% per year, could result in between 600 to 3,000 cases of hepatocellular

carcinoma a year.

B. Compensation for Tainted Blood Victims

1. The Debate over Surrogate Testing (22)

In the early 1970s, donated blood began to be screened for Hepatitis B, the only form of chronic viral hepatitis known at the time. It was expected that this would eliminate all post-transfusion hepatitis; however, hepatitis continued to be associated with transfusion. Many scientists felt that occurrences of post-transfusion hepatitis would be significantly reduced as a result of screening donated blood for an elevated level of the liver enzyme alanine amino transferase (ALT) and for the antibody to the Hepatitis B core antigen (anti-HBc). Such screening, which does not test specifically for the infectious agent, is referred to as surrogate testing. Other scientists and authorities believed that the benefits of such testing were questionable, and that it would be ethically and morally difficult, if not impossible, to design the research studies needed to confirm its usefulness. Nevertheless, the United States ordered surrogate testing of all donated blood by 1986, although many centres within the country had done this independently as early as 1982.

Canada followed this issue as it developed in the United States and on several occasions considered surrogate testing of all donated blood. Conflicting opinions among different authorities (such the Canadian Red Cross Society, The Bureau of Biologics and the Canadian Blood Authority) however, in addition to budgetary considerations, delayed a decision on implementing such testing. When a study of surrogate testing (a study having been considered unacceptable in the United States) was begun in Canada in 1989, the Red Cross was required not to implement surrogate testing while the study was in progress. Eventually, with the introduction of a specific test for the Hepatitis C virus in early 1990 and the subsequent availability of Chiron's first generation anti-HCV test kit, the debate about whether to implement surrogate testing in Canada became obsolete.

Thus, between the 1986 implementation of surrogate testing in the United States and the introduction of the anti-HCV kit in 1990, blood in Canada was not screened at all for "non-A, non-B post-transfusion hepatitis." It is on this ground that those who contracted the disease through blood products in Canada between those dates demanded compensation from the federal and provincial governments.

2. Federal Compensation Package

On 27 March 1998, the federal government announced a compensation package of $1.1 billion for those who had contracted Hepatitis C through the Canadian blood supply between 1986 and 1990. These were estimated to number as many as 10,000 individuals,(23) although the figure could well be

less.(24) This compensation arrangement had been forged with the provincial and territorial governments and was made up of $300 million provincial/territorial dollars and $800 million federal dollars. This figure was reduced slightly on 16 December 1998, when it was decided that about $58 million of it would go to compensate secondarily infected HIV victims.

On 18 December 1998, details of the package were revealed after much negotiation between a federal-provincial-territorial legal negotiating team and the counsel for the class action suits. In May 1999, a final settlement, valued at $1.118 billion plus interest, was reached; this included compensation for those individuals secondarily infected with HIV. The proposed settlement calls for an initial payment of $10,000 to every person who became infected with HCV through the blood system between 1 January 1986 and 1 July 1990. Individuals would also be eligible for additional compensation, depending upon the severity of their disease. Claimants might also be eligible to receive compensation for loss of income, loss of services in the home, costs of care, costs of HCV drug therapy, costs of uninsured treatment and medication and out-of-pocket expenses. They would be able to apply for more compensation as their disease progressed, up to a maximum payment of $240,000. In addition, a death benefit category would compensate the patient's estate, should death be directly attributable to Hepatitis C contracted through the blood supply between the relevant dates.(25) The award would not be taxable and would not affect social assistance benefits. In return, those accepting the offer would have to sign a waiver giving up their right to sue the Red Cross and the federal, provincial or territorial governments. This offer has been filed in the courts of Ontario, British Columbia and Quebec and is now going through the process for appeal, which is expected to be heard by the fall of 1999.(26) Upon acceptance of this package, the terms would be binding and cover all class action and non-class action suits filed so far, including lawsuits in all other provinces. Generally, all claims must be submitted prior to 30 June 2010.

3. Provincial Compensation Packages

When the federal compensation package was initially announced in March 1998, it was with the cooperation of all provinces and territories, the provinces having expressed support for compensating only those individuals infected between 1986 and 1990 through their endorsement of the federal package. Over the next several months, however, some provinces began to speak of expanding the compensation to all those who had acquired HCV infection through the blood system, regardless of when. Most of these provinces felt that such expanded compensation should come from federal funds. In November 1998, the Ontario government announced that it would compensate these victims; before the end of December, it began to distribute lump-sum payments of $10,000.(27) Ontario is at present the only province to be compensating individuals infected in the pre-1986 and post-1990 time frame; but, Quebec and British Columbia have stated that they may be considering similar action.

4. Liability of the Canadian Red Cross Society

The Canadian Red Cross, just prior to relinquishing its control of the blood supply in the fall of 1998, filed for bankruptcy protection so that it could restructure its finances in the face of $8 billion in lawsuits filed primarily by those who had contracted Hepatitis C through the blood system outside the 1986-1990 timeframe. The charity has expressed a desire to fulfil its moral obligation to these victims but emphasizes its financial constraints in offering compensation. It had hoped to create an acceptable special compensation fund for Hepatitis C victims; however, in March 1999, its offer of $60 million to victims excluded from the federal compensation package was rejected.(28)

CONCLUSION

The slowness of Hepatitis C in progressing to its potentially fatal end has led it to be labelled the "silent epidemic." Now that the disease has been identified and many people are known to have suffered from it for many years, however, the associated health problems are receiving more attention. Each year, more cases of infection are reported. This does not point to a surge in new infections, but rather to increased diagnoses of chronic infection after symptoms finally emerge. Hepatitis C is a major contributor to liver disease, cirrhosis and liver cancer.

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(1) "Hepatitis C — An Epidemic for Anyone," Internet site: www.epidemic.org

(2) S.D. Shafran and J.M. Cooly, "ABCDEFG…," *The Canadian Journal of Infectious Diseases*, Vol. 7, No. 3, May/June 1996, p. 181-182.

(3) Chiron Internet site: www.chiron.com/patients/education/hepatitisFrame.html

(4) Paul R. Gully and Martin L. Tepper, "Hepatitis C," *Canadian Medical Association Journal*, Vol. 156, No. 10, 1997, p. 1427.

(5) World Health Organisation, Hepatitis C fact sheet at Internet site: www.who.int/inf-fs/en/fact164.html

(6) Liver enzymes are enzymes specific to the liver and normally found in the blood. Any assault on the liver can result in higher levels of these enzymes, which are always present in low amounts due to the normal death of liver cells and release of the enzymes into the blood.

(7) World Health Organisation, Hepatitis C fact sheet at Internet site: www.who.int/inf-fs/en/fact164.html

(8) Canadian Organ Replacement Register (CORR), Annual Report 1996, Vol. 2, Canadian Institute for Health Information, Ottawa, 1996, p. 3-11.

(9) "Hepatitis C — An Epidemic for Anyone," Internet site: www.epidemic.org

(10) HepNet Internet site: www.hepnet.com/hepc/news042999.html

(11) Mitchell Schiffman, "Hepatitis C: Dilemmas in Treatment," Presented at the Digestive Disease Week 1999 Annual Meeting, 17 May 1999.

(12) M.I. Thabrew, "Phytogenic Agents in the Therapy of Liver Disease," *Phytotherapy Research*, Vol. 10, No. 6, September 1996, p. 461-467.

(13) "Relationship between Diet and HCV," American Liver Foundation Internet site:
http://gi.ucsf.edu/alf.html

(14) T.R. Riley 3rd and J.P. Smith, "Ibuprofen-Induced Hepatotoxicity in Patients with Chronic Hepatitis C: A Case Series," *American Journal of Gastroenterology*, Vol. 93, No. 9, September 1998, p. 1563-1565.

(15) W. Wayt Gibbs, "In Focus: R_x for B and C," *Scientific American* Internet site:
www.sciam.com/1999/0399issue/0399infocus.html

(16) In antisense gene therapy, viral reproduction is inhibited by administering man-made copies of DNA into affected cells engineered to inhibit one or more of the processes of the virus and thus prevent it from surviving.

(17) Kenneth B. Chiacchia, "Looking to the Future," HepNet Internet site:
www.hepnet.com/charge/chap12.html

(18) David B. Weiner and Ronald C. Kennedy, "Genetic Vaccines," *Scientific American*, Vol. 281, No. 1, July 1999, p. 50-57.

(19) Health Canada, Health Protection Branch, *Report of the Expert Panel on Hepatitis C Epidemiology*, Ottawa, 24 July 1998.

(20) Personal communication with the Federal Laboratories for Health Canada, Bureau of Microbiology, Laboratory for Human Viral Infections, June 1999.

(21) Hepatitis C fact sheet, Centers for Disease Control and Prevention Internet site:
www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm

(22) This section is adapted from Mr. Justice Horace Krever, "Commission of Inquiry on the Blood System in Canada — Final Report," Volume 2, Chapters 23 and 24, Minister of Public Works and Government Services Canada, 1997, 1, 138 p.

(23) Hepatitis C Class Action — Class Counsel Statement, Canada News-Wire, 15 June 1999.

(24) Health Canada, *Report on the Meeting of the Expert Panel on Hepatitis C Epidemiology*, 24 July 1998.

(25) "Proposed 1986-1990 Hepatitis C Settlement Agreement — Summary Overview," Health Canada Internet site: www.hc-sc.gc.ca/main/hc/web/english/archives/releases/9984ebk1.htm

(26) "Proposed 1986-1990 Hepatitis C Settlement Agreement: Chronology of Key Developments," Health Canada Internet site: www.hc-sc.gc.ca/main/hc/web/english/archives/releases/9984ebk.htm

(27) Government of Ontario Press Release for 15 June 1999 at Internet site: www.newswire.ca/government/ontario/english/releases/June1999/15/c5064.html

(28) Mark Kennedy, "Blood Victims Reject $60M Offer: Hep-C Victims Say Red Cross Proposal Not Enough," *The Ottawa Citizen*, 30 March 1999, p. A7.