# IDENTIFICATION OF A RESEARCH AGENDA FOR THE DIAGNOSIS, CARE AND PREVENTION OF HEPATITIS C IN CANADA

**REPORT TO THE**
**MINISTER OF HEALTH:**

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June 1999

MRCCRM
Medical Research Council of Canada
Conseil de recherches médicales du Canada

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# EXECUTIVE SUMMARY

Hepatitis C (HCV) is a health problem with an estimated 170 million people infected around the world. It is quantitatively the first viral pandemic affecting industrialized countries. While there is no direct and representative measurement of the prevalence in Canada, a plausible estimate is 240,000 infected persons (0.8%). As pointed out in a recent Editorial in The lancet, HCV is almost a stealth disease:

1) Tracking its incidence is nearly impossible
2) Symptoms are lacking or are non specific in 80% of newly infected patients
3) It is estimated that only 30% of infected Canadians are aware of their infection
4) There are no reliable clinical or laboratory markers for acute HCV infection
5) HCV - related severe complications such as cirrhosis, end-stage liver disease and hepato-cellular carcinoma develop insidiously and take more than a decade to become manifest

## THE BURDEN OF HCV

HCV is already an important cause of disability, dysfunction, morbidity and mortality. The burden of HCV on the health care system is already considerable and will increase substantially in the next decade (1999-1208). The LCDC model predicts that by 2008, the incidence of cirrhosis and end-stage liver disease will have doubled while liver deaths and liver cancer will have increased by 140% and 70% respectively. Given the current shortage of organ supply, it is difficult to see how it will be possible to increase annual liver transplantations from 217 to 610 during that same decade.

The HCV epidemic is much larger than HIV and its complications are burgeoning. In the face of a remarkable decrease of HIV deaths from 1406 in 1994 to 288 in 1997, it is predicted that liver deaths will number 629 in 1999 and increase to 904 in 2003.

It is clear that the increasingly heavy burden of HCV disease on infected persons and on our health care system will require an improved understanding of HCV infection through basic, patient and population-oriented as well as evaluative research to ensure high quality cost effective care and improved patient outcomes as well as to reduce the probability of infection among those who have not been infected.

## DEFINITION OF A RESEARCH AGENDA

The research agenda identified for Canada during the Workshop is based on current gaps in knowledge, and inventory of hepatitis research completed or underway in Canada, present and future sources of funding and the research capacity which can be mobilized and eventually expanded.

**Biology of the virus and pathogenesis of HCV**. Basic research is the first step in the innovation process. It has its greatest impact if integrated within a full spectrum of research pertinent to HCV.

The development of in vitro (cells) and in vivo models (small animals) of HCV infection is key to progress for better therapeutic strategies and for a vaccine. Other basic research questions, which need to be answered, include the following:

- The virology and immunological basis for persistent infection
- The pathogenetic mechanisms of both acute and chronic liver cell injury
- The factors responsible for progression to cirrhosis and cancer
- The mode of action of current therapies
- The mechanisms by which HCV eludes the immune system
- The viral and virus-induced antigens which elicit protective immunity

**Clinical research and treatment**. Patient-oriented research needs to expand beyond Phase III clinical trials. There is an urgent need for clinical research targeted to the following objectives:

- Elucidation of the basis, for differing clinical presentations, for extrahepatic manifestations and for fatigue as an initial symptom
- Clarification of the natural history of the disease factoring in age, gender and mode of transmission but also genotype, quasispecies diversity and viral load.
- Closing of the gap between basic and applied research by participation in Phase I and Phase II studies and continued involvement in Phase III clinical trials.

**Laboratory testing**. There are a number of unresolved questions concerning the convenience, cost effectiveness and accuracy of current testing methods. The possibility of testing on dry blood and on saliva should be explored.

Reliable, easily accessible and effective lab testing is the foundation for the broad network of research necessary to decrease the burden of HCV. The entire spectrum of basic, clinical, epidemiological and evaluative research is dependent upon an integrated closely linked and accessible national patient database and serum repository.

Ethical concerns raised by patient registries and serum banks will need to be addressed.

**Epidemiology.** No single discipline will be effective in reducing the burden of HCV. The research questions are complex and have wide ramifications. Productive research teams and centres will be those which can bring together the full range of disciplines.

There is significant strength in epidemiology in Canada but human resources and facilities are problematic. These need to be addressed if epidemiology is to follow progress on the biomedical aspects of HCV. There are a number of urgent epidemiological issues:

- Epidemiological studies have been regional and cross-sectional instead of being national and prospective
- Studies should be targeted not only to high-risk populations but also include those at low risk.
- Between 10% to 40% of infected individuals contracted the disease by a mode of transmission which cannot be positively identified or which is unknown altogether.
- The prevalence associated with high risk sexual behavior, household contacts, sporadic blood to blood contact and vertical transmission is unknown altogether.
- There is under reporting and surveillance is not up to par.

**Primary and secondary prevention**. Effective strategies for both primary prevention aimed at reducing the risk of contacting HIV and secondary prevention targeted to reduce the risk for liver disease and its complications in infected persons are needed. They cannot be devised without the acquisition of new clinical and epidemiological knowledge.

Topics for research into primary prevention include inquiry into undiscovered modes of transmission, IV drug use with emphasis on factors leading to it, effectiveness of current strategies for prophylaxis of HCV with emphasis on aspects of HCV which differ from HIV.

A research background would be necessary before innovative secondary prevention activities can be implemented, this will require the acquisition of information 1) on the relationship between a risk factor and acquiring HCV, 2) on the prevalence of HCV with a risk behaviour, 3) on the way to structure an effective "look back, trace back" program for recipients of blood, blood products and organ transplants prior to 1992 4) on persons who ever Injected drugs or who had a recognized exposure to HCV (e.g. infants born to infected mothers, household contacts, sex partners of infected persons, health care workers).

Finally, HCV specific information, education and prevention messages will need to be profiled after a fact finding research exercise 1) to prevent HCV positive persons 2) to further harm their liver with insults such as alcohol, hepatitis A and B etc and to reduce the risk for transmitting HCV to others and 3) to advocate the need for medical evaluation and treatment.

**Quality of life issues**. HCV has become an important public health issue. Unfortunately, the design and implementation of policies have largely been based on the medical and scientific models of disease and have undervalued psychosocial and quality of life (QOL) issues.

There is an urgent need for studies in the area of QOL. Ongoing issues, which require attention, include:

- Need for better QOL assessment techniques specific for HCV patients
- Does the mode of transmission affect QOL?
- What is the prevalence and impact of co-morbid conditions such as anxiety and depression?
- Is fatigue related to depression and anxiety to the disease it-self?
- What is the impact of the disease on education, employment, insurability, personal relationships and child bearing?
- What are the direct and indirect costs of the disease (e.g. drugs, absenteeism, disability)?
- Will aggressive early patient education programs in HCV infected improve their long term QOL?
- Is the perception of the public for the disease changing in response to education programs?
- What are the iatrogenic consequences of screening and the consequences of a positive test result?

Further attempts at needs assessment of affected communities should be done. A renewed commitment is needed to obtain this information and incorporate it for the formulation of policies and for the allocation of resources. QOL and socio-economic issues should be incorporated into all patient and population-based research. Otherwise, there is a risk that programs will be too narrowly conceived and to poorly implemented to help those people in need.

## HCV RESEARCH IN CANADA: INVENTORY AND SOURCES OF FUNDING

A bibliometric analysis of Canada's contribution to the world literature in biomedical and health sciences places Canada ahead of several larger countries with a percentage of 4.9% of papers published in 1997. However, Canada's productivity in HCV research is disappointing with less than 0.6% of all items published in the past few years.

There are glaring deficiencies not only in terms of the number of studies but also in terms of coverage. Given the size of the pandemic, the burgeoning number of severe complications, the growing public health problem and the enormous burden of HCV, research efforts need to be rapidly intensified and the research capacity expanded.

Current funding of HCV research other than from the private sector is very modest. The MRC currently supports only three grants directly concerned with HCV. NHRDP has not supported any research on HCV since 1996 neither has the Canadian Liver Foundation.

There is a clear need for a large increase in publicly funded research. Progress for the education, patient support and care programs are dependent on the acquisition and application of new knowledge. Two future sources of funding will become available:

1) **The Hepatitis C disease, Prevention, Research and Community - based Support Program of health Canada.** Of the $10M/year available through the Minister's proposal in September 1998, it would be appropriate for this program to allocate a substantial proportion to the full spectrum of HCV research. The spectacular gains made for the control of the AIDS epidemic cannot be isolated from the growth and international caliber of Canadian HIV/AIDS research. It should be noted that 30% of the $42.2M annual budget of the HIV/AIDS federal program goes to research.

2) **The Canadian Institutes of Health Research (CIHR).** The creation of CIHR in February 1999 represents a landmark in the history of Canadian biomedical and health research. It will increase the amount of public money available for research, bring together diverse sources of funding, coordinate isolated research efforts and link them more closely to health care and to the health care system. As the MRC, soon to be subsumed into CIHR, has a renewed commitment to partnerships, negotiations should be undertaken to create a partnership between the Hepatitis C Disease Prevention, Research and Community - based Support Program of Health Canada and the MRC/CIHR. Contributions should also be sought from other governmental agencies, disease-related foundations and the private sector.

## FRAMEWORK FOR A COORDINATED AND INTEGRATED NETWORK FOR RESEARCH AND CARE

**New Research Paradigm**. To improve the outcomes of the 240,000 Canadians who are infected and to reduce the probability of infection among those who are not infected will require more than money and an expanded research capacity. A three-pronged knowledge strategy needs to be put in place:

- Knowledge generation to expand the stock of relevant knowledge
- Knowledge transfer to assemble, package and deliver it to the right person
- Knowledge use so that best practices are adapted

Integration is key to the success of the undertaking. It will not occur unless there is a profound transformation of the research landscape:

- Isolated research efforts should be integrated across the country
- Disciplinary separation should be replaced by integration across disciplines, institutions and sectors
- Lag between knowledge and its application should be shortened
- Fragmented multi-agency funding should be coordinated through CIHR.

**Strategic Plan.** There is time and resource - limited funding available for research prevention and community support through the Hepatitis C disease Prevention, Research and Community based Support Program. Thus, it is imperative to:

1) Prioritize certain research themes and build on existing strengths
2) Expand Canada's capacity for research and care
3) Give undivided attention to the creation of national Centers of Excellence for education, prevention, care and research
4) Form a large consortium of diverse funding sources around CIHR for a multi- pronged attack on HCV

The programmatic approach should favour investigator-initiated projects but under well defined themes framed by multidisciplinary programs, which foster cross-disciplinary and inter-sectoral (academic, public health, private sector) collaboration. As pointed out above, the research performance of Canada in the field of HCV research is quantitatively insufficient. HCV research needs to attract productive investigators from related fields of enquiry and to develop new talent. Salary and training programs will be necessary to increase the research capacity for Hepatitis C.

In view of the urgent need for a well orchestrated effort to increase disease awareness, education of the public, training of health professionals, patient support, quality of care and prevention, there is a consensus for the creation of a national network of Centers of Excellence. Anchored in Academic Health Sciences Centres, these Centres of Excellence would be the hubs for smaller satellite centers. Accreditation of these HCV Treatment and Education Centres and the availability of Clinic incentive grants would ensure the quality of the programs and facilitate close monitoring and access to new treatment approaches.

With expansion of Canada's research capacity over the wide spectrum of HCV research and maturation of productive interdisciplinary and intersectoral linkages, it would be appropriate to apply to the NCE program for a National Centre of Excellence dedicated to HCV research.

# IDENTIFICATION OF A RESEARCH AGENDA

# FOR THE DIAGNOSIS TREATMENT AND PREVENTION

# OF HEPATITIS C IN CANADA

## REPORT TO THE MINISTER OF HEALTH

### INTRODUCTION

A workshop on Hepatitis C (HCV) was held in Ottawa January 15 and 16, 1999 to define a research agenda for Canada. Initiated by the Medical Research Council of Canada (MRC) it was co-sponsored by the MRC, Health Canada and the Canadian Blood Services.

The meeting was chaired by Dr. Morris Sherman who, with the help of a broad-based Steering Committee which met on October 4, 1998 in Montreal, laid down the following objectives:

1) Review critically the full spectrum of HCV research, from basic science to public Health and psychosocial aspects, carried out in Canada,

2) Identify knowledge gaps in the understanding of the pathogenesis, epidemiology, transmission, clinical and psychosocial aspects, complications, management and prevention of HCV,

3) Define a research agenda which takes into account the burden of the disease, the research capacity of the science community, and present as well as potential future sources of funding,

4) Propose research, training and salary support programs which will have maximum impact on the acquisition of new knowledge and on the management and prevention of the disease.

This was a closed meeting attended by representatives of the Hepatitis C Society of Canada, the Canadian Hemophilia Society, the Thalassaemia Foundation, the Canadian Blood Services, Héma-Québec, the Canadian Liver Foundation, the Canadian Association for the Study of the Liver, provincial epidemiologists and laboratory directors, the Laboratory Centre for Disease Control, the National Health Research Development Program (NHRDP) of the Information, Analysis and Connecting Branch, MRC, the Hepatitis C Division of the Health Promotion and Programs Branch, the Correctional Service of Canada, the Health Policy Division of the Programs and Consultation Branch of Health Canada, representatives from the Human Immunodeficiency Virus (HIV) research community, and from the pharmaceutical and biotechnology industries involved in HCV research as well as several academic clinician investigators and scientists involved in hepatitis C care and research. The workshop consisted of plenaries, breakout groups and report back sessions, thereby encouraging interactive discussion periods and the development of recommendations. The Appendix provides the detailed program of the workshop, a list of members of the steering Committee and of the attendees.

This report, while largely based upon deliberations which took place during the workshop, is also the result of discussions with stakeholders and of the perusal of relevant literature. It was prepared by an Editorial Committee composed of:

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# THE BURDEN OF HCV

## BURDEN OF HCV INFECTION

HCV is a global health problem with an estimated 170 million people (31%) infected around the world. It is quantitatively the first viral pandemic in all industrial countries. While there is no direct and representative measurement of the prevalence of HCV infection for Canada, a plausible estimate, based on expert review of available data, is 240,000 infected persons in Canada in 1998, i.e. 0.8% of the population. This contrasts to the directly measured prevalence of 3.9 million persons (1.8%) in the United States (US). While caution in interpretation is necessary, the estimated prevalence of HCV infection in Canada varies by province with British Columbia being the highest (1.4%) and Newfoundland the lowest (0.1%). Nearly two-thirds of infected Canadians are in the 20-39 year age group. Prevalence in males is nearly twice as high as in females. It is estimated that only 30% of infected Canadians are aware of their infection.

## BURDEN OF HCV DISEASE

The burden of HCV disease is considerable since in the large majority of cases it is a chronic disease which may progress to severe complications. The majority (60% to 80%) of infected persons are asymptomatic after the initial infection. Eighty-five percent of persons with initial infections continue to be chronically infected. Following a long latency period of one to three decades, one third are expected to develop cirrhosis followed by end stage liver disease and hepatocellular carcinoma (HCC) will develop in 1% to 5%. However, HCV infection is often silent even when the disease is progressive hence many infected persons are unaware of their status. The burden of HCV disease for the decade 1998-2008 is expected to escalate dramatically (see table below).

**PREDICTION OF HCV BURDEN IN CANADA (1999-2008)**

| | | 1999 | 2003 | 2008 |
|---|---|---|---|---|
| MILD CHRONIC HEPATITIS | P* | 164,279 | 135,926 | 106,556 |
| | I ** | —— | —— | —— |
| CIRRHOSIS | P | 20,223 | 29,130 | 39,312 |
| | I | 2,974 | 3,771 | 4,120 |
| END-STAGE LIVER DISEASE | P | 2,366 | 3,575 | 5,555 |
| | I | —— | —— | —— |
| HEPATO-CELLULAR CARCINOMA | P | —— | —— | —— |
| | I | 313 | 393 | 534 |
| LIVER TRANSPLANTS | P | —— | —— | —— |
| | I | 217 | 316 | 610 |
| LIVER DEATHS | P | —— | —— | —— |
| | I | 629 | 904 | 1,522 |

*Annual Prevalent Cases **Annual Incident Cases

(Based on unpublished work in progress at the Blood-borne Pathogens Division, LCDC with assistance from Robert Remis)

By 2008, the number of HCV cases with cirrhosis and end-stage liver disease will have doubled while liver deaths and HCC are expected to increase by 140% and 70% respectively. In the US, a large epidemiological study has already noted a 70% increase in HCC over the past two decades. Also noted is the prediction that the number of liver transplantations done in Canada will increase by a factor close to 3 by the end of the decade. In the face of a remarkable decrease in HIV deaths from 1406 in 1994 to 288 in 1997, it is predicted that liver deaths will number 629 in 1999 and increase to 904 in 2003.

## BURDEN OF HCV ON THE HEALTH CARE SYSTEM

Although the LDCD model has its limitations, it does deliver a clear message. HCV is already an important cause of disability, dysfunction, and morbidity as well as mortality. The burden of HCV on the health care system, already considerable, will increase substantially over the next decade. While in the US the incidence of acute hepatitis C infection started to fall in the 90s, no such decrease has yet been observed in Canada. Even though the model shows a 35% reduction by 2008, it is not expected that complications of HCV will decrease before 2018.

## WHAT CAN BE DONE TO DECREASE THE BURDEN OF HCV

The direct consequences of HCV disease on the health care system are considerable and immediate action is necessary to deal with this looming crisis. It is necessary to estimate the resources necessary to meet the needs of people with HCV, as well as those of the health care system. Canada must swiftly plan studies, establish policy and commit resources commensurate with this burgeoning public health challenge. In moving this challenging agenda forward it is imperative to keep people affected by HCV at centre stage and empower them to make informed decisions on issues pertaining to public awareness, screening, diagnosis, treatment options, access to care, prevention programs and research strategies in order to decrease the burden of HCV.

HCV AWARENESS: Despite its significantly higher prevalence, hepatitis C has long been overshadowed by HIV. While much media attention has been given to HCV, (primarily related to blood supply compensation issues) there is a need for a broad-based public education campaign to increase the public's understanding of HCV risks, their avoidance or minimization, symptoms, complications and burden. Further a primary target for focussed information should be populations at particular risk, e.g. recipients of blood products prior to 1992, IV drug users, immigrants from areas of high prevalence, individuals with high risk sexual behaviour. School programs could do much to equip the next generation with current knowledge.

For health care providers, special attention should be given to education programs designed to optimize the timely recognition and up-to-date management of HCV infection and to training programs for the recruitment and training of gastroenterologists and hepatologists with a special interest in HCV.

SCREENING AND DIAGNOSIS: State-of-the-art technology should be accessible for the screening of all Canadians at risk as well as for those who feel that they have the disease. Timely access to a specialized HCV care team should be available for confirmation of the diagnosis, information and patient support in a spirit of shared decision making.

TREATMENT: Effective treatment should be available to everyone who needs it in an environment where options are discussed along with risks and benefits. All efforts should be applied to make sure that exemplary care is provided across the country.

PREVENTION: Much remains to be learned with regard to primary and secondary prevention. A massive effort should be deployed to develop innovative strategies in collaboration with the HIV community not only for obvious risks but also to address sexual, perinatal and household transmission, the importance of which are not well established.

Community based organizations are often on the front line when it comes to the identification of emerging problems. Furthermore, because they have direct access to at risk populations, they are key partners, their work will help ensure the improvement of community health. Harnessing the power of science, technology and medicine to the resolution of HCV will not be successful unless it is recognized that science needs to be an integrated part of health services. Moreover, the resolution of HCV is not within the reach of a single scientific discipline. In view of the fact that, beyond determinants, there are social, economic and environmental factors that play, they will require investigation.

## DEFINITION OF A RESEARCH AGENDA

It is clear that the increasingly heavy burden of HCV disease on infected persons and our health care system will require an improved understanding of HCV infection. We need to focus on the biology of the virus and the pathogenesis of HCV, a shortened lag between "precept and practice" through patient- and population-oriented research, and a fresh commitment to evaluative research, in order to put in place policies and structures which will ensure high quality, cost effective care and improved patient outcomes.

The research agenda and strategic approach which follow are based on current gaps in knowledge, the inventory of hepatitis research either completed or underway in Canada, present and future funding sources, and the research capacity (human resources) which can be tapped. Attention is also given to the identification of research themes in terms of the impact for the diagnosis, treatment, and prevention of HCV in our country.

### BIOLOGY OF THE VIRUS AND PATHOGENESIS OF HCV

Understanding the biology of the virus and the pathogenesis of HCV is key to progress in decreasing the burden of the disease. Basic research is the first step in the innovation process. It can have the desired impact if integrated within a full spectrum of research pertinent to HCV.

MODEL SYSTEMS: The identification of HCV was a triumph of modern molecular biology. Clearly, the combination of reverse-transcriptase polymerase chain reaction (RT-PCR) and PCR amplification of viral complementary DNA (cDNA) has played a pivotal role in the identification of the virus responsible for the vast majority of non-A non-B hepatitis cases. This very sensitive technology permits the detection of low-level replication of the virus which take place in hepatocytes and possibly in a range of other tissues. However, formal proof of replication in all culture systems has not been easy to obtain. The development of in vitro viral propagation systems to study the mechanisms of cell infectivity would be of great help. The development of such technology would facilitate the study of cellular immune mechanisms, neutralizing antibodies and epitopes. It is the key to the search for new antiviral agents.

At this time, the only animal model available is the nonhuman primate. Small animal models of acute and chronic infection for characterization of the replicative cycle of the virus, of the host's immune response, mechanisms of recovery and persistence as well as of liver injury are badly needed.

VIROLOGIC AND IMMUNOLOGICAL BASIS FOR PERSISTENT INFECTION: The mechanisms by which a high rate of persistent infection are established appears to be related to the genetic diversity of the virus and the host response.

Like other RNA viruses, the substantial heterogeneity of the HCV genome is the result of mutations which occur during viral replication. Within an infected individual, HCV consists of a population of closely related yet heterogeneous sequences (quasispecies) which result from the rapid development of mutations. By the time a humoral immune response is mounted, there is a new generation of mutants which is not recognized by the preexisting antibodies.

Studies are needed to elucidate the immunological and virologic basis of recovery from HCV as opposed to persistence of viral infection. Also needed is research targeted to identification of factors independent of HCV load and dynamics which account for severe versus mild liver damage.

LIVER CELL INJURY: The pathogenetic mechanisms of both acute and chronic HCV infection are still poorly understood. These are key to the design of better therapeutic strategies.

In the acute stage of the disease, a strong CD4+T proliferative and cytokine response has been documented in chimpanzees with viral clearance. In humans with mild HCV-induced liver disease, it has been shown that the CD4+ cell response is associated with control of the viral infection. The role of Th1 and Th2 and of their cell receptors remains to be defined. The level of HCV specific CD8+ cytotoxic T lymphocyte response also deserves attention, as it appears to contribute to viral replication and disease activity as well as to the response to d-interferon therapy. Whether it also is predictive to successful combination therapy (interferon-ribavirin) is unknown.

The mechanisms by which HCV induces liver cell injury are largely unknown. There is little evidence for direct cytopathic damage. However, histological features suggest that apoptosis is present and host immune cytotoxic (e.g. T lymphocyte-mediated) pathways of apoptosis are activated. Furthermore, HCV viral proteins have recently been shown to modulate apoptosis. The mechanisms that lead to the formation of lymphoid aggregates, and to steatosis are unclear. Particularly intriguing is the epithelial damage to bile ductules. As HCV is not detected in bile duct cells, it could be immune damage. It is clear that progress in characterizing the response of the host's liver cells will not come about until liver cell culture systems fully permissive for viral replication are available.

FIBROGENESIS: Clinicians are intrigued by the observation that 30% of chronically infected HCV patients never develop fibrosis which ultimately leads to bridging fibrosis and cirrhosis.

Studies are needed to investigate mechanisms of fibrogenesis induced by HCV. The creation of small animal models would be most helpful to characterize not only the effect of HCV on liver matrix deposition and hepatic fibrosis, but also the effect of alcohol. It is interesting to note that a high percentage of alcoholic cirrhotics (15% to 50%) are known to have chronic HCV. Does alcohol make hepatocytes more sensitive to the fibrogenic effects of mediators of inflammation (i.e. cytokines, oxidants, iron etc.)? Insights on the effect of HCV on stellate cells are crucial to our understanding of the factors mediating the enhanced fibrogenesis leading to end stage HCV liver disease. Surrogate markers for liver fibrosis are necessary so as to avoid the need for repeated liver biopsies to evaluate the severity of the disease.

CARCINOGENESIS: Hepatocellular carcinoma (HCC) is a dire complication of HCV and surveillance testing technique for its early detection are inadequate. The development of the techniques such as more sensitive and specific blood tests or imaging would be most helpful. Basic research is needed to elucidate the mechanisms of development of HCC. Is it the consequence of a chronic inflammatory response with extensive fibrosis or is it related to genetic factors of the host, HCV species, subtypes and quasispecies?

TREATMENT: Great strides have been made in the past year with combination therapy. It has led to the approximate doubling of the response reported with intermittent, short acting interferon monotherapy. Even among those patients with the more resistant genotype I, the response is between 25% and 29%. Despite this success, research applications are needed to identify and develop new therapeutic modalities based upon HCV's replication cycle, protein structures and host response. The mechanisms of action of existing therapies and how the combination exerts a synergic effect requires investigation. Canadian expertise in crystallography of proteins and in the design of proteases may lead to new therapeutic molecules.

Before new strategies of intervention become available, better means of predicting responses, and of defining viral eradication versus repression also call for fundamental approaches in close collaboration with patient and population-oriented researchers.

VACCINE DEVELOPMENT: The ultimate goal of HCV research is the development of a vaccine. This cannot be envisaged unless permissive tissue culture systems, reliable animal models, identification of viral and viral induced antigens eliciting protective immunity, better understanding of the molecular determinants of both cellular and humoral immunity to HCV, knowledge of the nature of antigenic variation as related to quasi-species, and information on the mechanism by which HCV eludes the host immune system become available.

**CLINICAL RESEARCH AND TREATMENT:**

CLINICAL PICTURE: Elucidation of the basis for differing clinical presentations (i.e. silent acute hepatitis, cholestacic hepatitis, chronic active LKM-positive hepatitis, post-liver transplant hepatitis) is needed. In depth studies to elucidate the cause of the fatigue associated with HCV infection are needed.

Determination of the basis for extra hepatic autoimmune manifestations including cryoglobulinemia, lymphoma, anti-LKM positive proliferative glomerulonephritis and Sicca syndrome may throw light on understanding the immunopathology of the virus and of the host's response.

NATURAL HISTORY: The natural history of the disease requires further work. The long-term morbidity ( >20 years) and mortality of chronic HCV infection have not been fully determined. The extent of initial liver injury is greater in post-transfusion cases. Post-transfusion infection may account for a higher incidence of progression to end stage liver disease and cancer. Viral load, genotype and quasispecies diversity need to be factored into all studies examining the outcome of chronic HCV infection. Long-term follow up studies are needed to find out if other factors are involved, as well as to elucidate the reason why infection in the younger age group appears less likely to progress than in older individuals particularly of the male gender.

Besides mode of transmission, age, and gender, environmental factors other than alcohol, such as smoking, nutrition, geographic location, medications, and co-infections with other viruses need to be investigated. The pediatric age group deserves special attention since rapid progression of fibrosis has been observed in the absence of other factors (such as alcohol or drugs). Further inquiry should also be made into the progression of the disease in patients with haematologic disorders who received, and are continuing to receive blood and blood products. It is quite clear that a prerequisite for undertaking studies on the natural history of the disease, and on the identification of prognostic factors, is the creation of a country wide network of databases and serum banks.

TREATMENT: At a time when substantial progress is being made for the treatment of HCV, it is difficult to accept that none the less access to care is limited. Furthermore, because of an insufficient number of experts among physicians other health professionals, it is clear that a significant proportion of

Canadians with HCV are getting sub-optimal care. In order to ensure access to high quality care, responsive to new developments and responsible for the creation of new therapeutic strategies, a trans-Canada network of closely linked-treatment centres should be created.

This network should be anchored in Canadian Academic Health Sciences Centres in order to benefit from the generation and application of new knowledge by multi-and inter-disciplinary research teams.

The HCV centres should be part of a Clinical Trials Network responsible for prospective studies on new treatments. Clinical trials on children with HCV, adults with HCV and normal ALT, the aboriginal population, relapsers and post-transplant HCV should be undertaken. In transplant patients, a unique pattern of HCV is seen. A high level of viremia is associated with profound hepatocellular damage suggesting direct viral cytopathic injury of liver cells. In this context, new potent antiviral agents need to be tested. Clinician investigators, in close collaboration with the private sector, should be involved in phase I and II studies and in the design of phase III clinical trials. In view of the enormous burden associated with the progression of HCV, the feasibility of "fast track" studies, like in HIV/AIDS, should be examined.

## LABORATORY TESTING FOR SCREENING, DIAGNOSIS AND FOLLOW UP:

### CURRENT PROBLEMS WITH LAB TESTING

A variety of tests are available for the diagnosis of HCV. Tests that detect antibody against the virus include the enzyme immuno-assays (EIAs) which contain HCV antigens from the core and non structural genes, and the recombinant immunoblot assays (RIBAs) which contain the same HCV antigens as EIAs but in an immunoblot format.

In addition, several polymerase chain reaction (RT-PCR) assays for HCV RNA have been developed to detect the RNA virus directly in the serum. Liver biopsies are commonly done to assess the severity of the disease before treatment, but there are no readily available tests for detection of HCV antigens in the liver.

There are a number of unresolved questions regarding these laboratory tests:

EIAs: The second and third generation EIAs have a high sensitivity (95% to 99%) and positive predictive value in high prevalence populations such as patients with clinical hepatitis ( >95%). However, in populations with a low HCV infection prevalence (<5%) assay specificity is problematic and supplemental testing is often necessary. All positive EIA results should be rechecked either by repeat testing using another manufacturer's EIA, or by a supplemental immunoblot assay and/or nucleic acid amplification assay. It has been shown that dual testing with two different EIAs can reduce the need for supplemental immunoblot testing by approximately 85%.

RIBAs: Supplemental testing of EIA positive results by immunoblot assays is used to demonstrate specific antibody reactivity. However, it must be realized that indeterminant or negative EIA and immunoblot results can be seen early during seroconversion, in immuno-suppressed individuals as well as in patients who may be resolving their clinical infection.

RT-PCR: While typically 85% - 95% of EIA and immunoblot positive individuals are actively viremic, immunological reactivity cannot differentiate active from resolved infection. Hence, there is a clear need to use nucleic acid based testing to accurately assess whether an individual is actively infected.

Furthermore, RT-PCR technology is the only means of detecting HCV within one to three weeks following exposure and in immunocompromised individuals, and depending on how soon after infection and how immunocompromised the tested individual is (the overall negativity of current anti-HCV assays probably occurs in less than 2% of cases). Quantitative HCV RNA levels in serum have been used to demonstrate the intense replicative capability of HCV (approximately 10 $^{10\text{-}13}$ virions per day in infected individuals) to prognosticate therapeutic response as well as to assess anti-viral therapy treatment response. The currently available commercial RT-PCR assays (AMPLICOR) have a lower limit of detection of 100 copies/ml.

The quantitative assays are approximately 5-10 fold less sensitive and differ in standardization. This means that quantitative results from the same specimen tested on the different assays (AMPLICOR vs Chiron bDNA) may differ 10-fold or more. To minimize false negative or inaccurate quantification results, serum must be rapidly separated from cellular components following collection. Once separated, serum is stable at 4°C for at least 4 days and may be frozen. Freeze thawing up to 8 times does not affect stability. In house PCR assays have a reputation for poor reproducibility. Both for in-house and commercial assays, rigorous quality assurance and control should be in place in laboratories performing the assay.

GENOTYPES: At least six genotypes and >90 subtypes of HCV exist. Unfortunately, genotypes I, the predominant genotype is relatively resistant to interferon compared to genotype 2 and 3. Treatment regimens may be guided to some extent on the basis of genotypes.

QUASI-SPECIES: Identification of quasispecies remains a research tool. However, it promises to be useful as failure of IFN treatment has been associated not only with a high viral load but also with a large quasispecies diversity.

**INTEGRATED APPROACH TO LAB TESTING FOR DIAGNOSIS AND MONITORING:**

This requires the collection and tracking over time of data on clinical problems; services; interventions/adverse effects; as well as appropriate definitions and outcome measurements. These data must undergo analysis to assess the impact of intervention(s) and the healthcare infrastructure should include mechanisms to change practice to optimize the care of individuals and populations. Fundamentally this would require an integrated Hepatitis Network which would assess intervention outcomes and strive to continuously use the most appropriate algorithms for screening, diagnosis, prognosis and monitoring of HCV infections as well as assess populations which could benefit from additional prevention and/or treatment interventions. This can only be achieved through a national infrastructure with very strong information technology components to facilitate data collection from multiple sources and allow the data to be transformed into useful information to update clinical and public health guidelines policies.

In the context of laboratory testing issues: focused studies to enhance the convenience, cost effectiveness and improving the accuracy of current testing methods are clearly necessary. Examples include: the use of dried blood and saliva testing, optimizing screening of at risk populations including pregnant women. Ethical concerns raised by patient registries and serum banks will need to be addressed.

Reliable, easily accessible and effective lab testing is the foundation for the broad network of research necessary to decrease the burden of HCV. The entire spectrum of basic, clinical, epidemiological and evaluative research is dependent upon an integrated, closely linked and accessible national patient database and a serum repository.

## EPIDEMIOLOGY

No single discipline will be effective in reducing the burden of HCV. In an area where research questions are complex and on their own have wide ramifications, productive research teams and centres will increasingly be those which can bring together the full range of disciplines. Opportunities for advance in knowledge and for its application have never been greater. Over the past two decades, epidemiology has made significant progress. There is significant strength in Canada but human resources and facilities are problematic. These need to be addressed if epidemiology is to follow progress on the biomedical aspects of HCV.

**URGENT EPIDEMIOLOGICAL ISSUES:** Early assessments of the total number of infected individuals and rates of infection have been greatly underestimated. A number of factors, each of which , can be the object of study, must be taken into consideration:

1) The disease is not generally recognized by the public so levels of concern and testing are low. The incidence of the disease is unknown.

2) The medical community is not well educated about HCV. Many cases go unrecognized, untreated or poorly treated.

3) The true burden of the disease is still a matter of speculation since it is based on fragmentary data.

4) Epidemiological studies are regional and cross sectional instead of being national and prospective. There are no ongoing studies on the annual incidence of HCV.

5) Study samples should not only be targeted to high-risk populations such as drug users, prisoners, Aboriginals, immigrants, and persons with multiple sexual partners but also to low-risk populations other than the ones which regularly donate blood.

6) HCV has an inherent ability to mutate rapidly (quasi-species) and produce diverse genotypes. This requires the use of different assays which may introduce confounding variables in current epidemiological studies.

7) Between 10% to 40% of currently infected individuals contracted the disease by a mode of transmission which either cannot be positively identified, or which is unknown altogether, epidemiological studies are needed on transmission modes other than those already recognized.

8) The relative importance of exposures associated with the transmission of HCV haschanged over time. In the past, blood and blood products accounted for 15% to 20% or more of all infections. It is now a negligible contributor while the proportion accounted for by intravenous drug use now contributes 60% to 90% of new cases. Thus it is evident that most epidemiological and prevention studies should be directed to this group. The prevalence associated with high-risk sexual behaviour and with household contacts is not well studied, neither is the incident associated with sporadic percutaneous blood to blood contact. (e.g. sharing straws for cocaine snorting) Growing attention has been given to vertical transmission as the risk of an HCV positive mother infecting her infant is now estimated to be 5% with an increase to 20% if the mother is also infected with HIV.

9) In view of the fact that most infected persons are asymptomatic for decades there is inaccurate and under reporting of HCV.

10) Surveillance is not up to par. It needs to be national in scope brining the federal government (LCDC) and the provincial governments as well as local public health authorities together.

11) As pointed out in the section on the burden of HCV infection, the burgeoning incidence of complication (cirrhosis, HCC, endstage liver disease) calls for reliable models on which allocations of resources for care and facilities will be made.

**CREATION OF AN EPIDEMIOLOGY ON HCV:** Incidence studies, surveillance, case control studies, cross-sectional surveys of population groups demonstration projects, as well as the monitoring of modes of transmission and of sequelae of HCV would be best addressed by the creation of a multi-centred epidemiology network involving academics, not-for-profit foundations, governmental public health authorities and the private sector. This network could not only carry out high quality research to fulfill national needs but also could collaborate at the international level.

**INCREASING THE EPIDEMIOLOGY RESEARCH CAPACITY:** It is quite clear that the HCV research strategy needs to take into consideration the fact that human resource limitations is a serious problem. The creation of appropriate infrastructures and access to new research resources have the potential to attract qualified epidemiologists to the field. Notwithstanding this type of recruitment, attention needs to be given to attracting young talent. Within the next one to four years and given the appropriate infrastructure and resources, it may be possible to build the capacity for HCV epidemiology research from existing programs. On a long term (five to ten years) basis, one should reasonably envisage the need for 30 to 40 new hepatitis C epidemiologists in Canada.

## PRIMARY AND SECONDARY PREVENTION

Reducing the burden of HCV infection and HCV-related disease requires the implementation of primary prevention activities aimed at reducing the risks for contracting HCV, and secondary prevention strategies targeted to reduce the risk for liver disease, its complications and other HCV-related diseases in infected persons. In devising primary and secondary prevention policies, social and political aspects need to be taken into consideration. (e.g. drug abuse harm reduction policy and correctional services policy).

Effective strategies cannot be devised without the acquisition of new clinical and epidemiological knowledge. Their implementation will need to be the object of research in order to evaluate their effectiveness to reduce the incidence of disease, to identify persons infected, to provide appropriate care and follow up as well as to promote healthy lifestyles and behaviours.

### PRIMARY PREVENTION

The final solution to HCV is the development of a vaccine. However, it is not a “be-all-end-all” as it cannot be expected to be available in the foreseeable future. Efforts should be made to develop the vaccine but not at the expense of prevention.

RESEARCH INTO UNDISCOVERED MODES OF TRANSMISSION: Current practices that screen blood, plasma, organ, tissue or semen donors determined to be at increased risk for HCV by history or who have serologic markers for HCV infection must be maintained to prevent HCV transmission. Viral inactivation of all blood products must also be continued. Little is known about virus viability on needles, toothbrushes, astroturf etc. and about the most efficient cleanup methods.

Data with regard to sexual transmission are incomplete. Studies on discordant couples (only one partner infected with HCV) and on vertical transmission are needed. The magnitude of risk from female to male and vice versa is unknown. The biological factors influencing the risk of sexual transmission, such as host susceptibility and viral load of sexual secretions, require clarification. Information is also lacking on percutaneous exposure in health care settings (e.g. EEG, endoscopy equipment, dialysis, healthcare personnel). Reliable data on other potential risk factors include tattooing, body piercing etc., would be helpful because they could have an impact on present primary prevention strategies. Finally, the risk of intra-familial transmission should be the object of ongoing surveillance.

IV DRUG USE (IVDU): Healthcare professionals in all patient care settings should routinely obtain a history about the use of drugs. As IV drug use now accounts for the large majority of new cases, it is appropriate to concentrate research efforts and primary prevention activities on this mode of transmission.

Research questions which should be addressed include the following:

**Initiation into injection drug use**: What factors predict the risk of initiation? What factors predict the cessation of needle use? What factors predict relapse?

Actions needed include:

1) the design of epidemiological surveys involving diverse sites and cultures;
2) an alliance with other drug use prevention research in order to work out combined methodological approaches.

**New Intravenous Drug Users**: How can HCV transmission be prevented? What is the effectiveness of new innovative strategies to reduce harm? What are the determinants of initial IVDU? Can we identify groups at risk and prevent initiation of drug injection?

**Post-Exposure Prophylaxis**: What is the risk inherent to different types of exposure? What is wrong with current prophylactic programs? How can we increase compliance with those programs? Longitudinal studies should be performed in order to adopt a national strategy along with nested case control studies.

It would be appropriate to combine HCV and HIV research efforts. However HCV research should not be piggy-backed to HIV, as there are many specific aspects which justify specific prevention activities namely:

1) Transmission of HCV is mainly due to blood exposure;
2) The HCV epidemic is essentially driven by IVDU;
3) Among IV drug users, HCV is acquired more rapidly after initiation than HIV.

## SECONDARY PREVENTION

A number of secondary prevention activities aimed at preventing and decreasing the consequences of HCV infection are already in place. However, they deserve to be revisited as some are not based on solid information and represent isolated efforts. In view of the rapidly increasing burden of HCV, the research background for innovative secondary prevention activities need to be laid down.

TESTING OF HIGH RISK GROUPS: Persons most likely to be infected with HCV should be identified, counselled and treated in order to prevent complications and transmission to others. Routine testing should

be offered along with counselling and appropriate follow-up. Much remains to be learnt about the epidemiological relationships between a risk factor and acquiring HCV as well as on the prevalence of infection among persons with a risk behaviour.

At this time, the appropriate infrastructure and resources ought to be in place to test routinely the following:

1) Recipients of blood, blood products and organ transplants prior to 1992. Systematic nation-wide "look back, trace back" programs should be made a priority.

   They include the counselling, testing and follow-up of the following:
   - Persons who received blood/blood products before 1992;
   - Persons who received blood/blood products from donors who later tested positive for HCV;
   - Persons who received an organ transplant prior to 1992;
   - Repeat blood donors subsequently found to be responsible for cases of post-transfusion hepatitis.

2) Individuals who ever injected drugs including those who injected once or a few times many years ago and do not consider themselves as drug users.

3) Patients with selected medical conditions including:
   - Children and adults with hemophilia, thalassaemia, sickle cell anemia and other hematologic disorders;
   - Persons on chronic hemodialysis;
   - Persons with abnormal ALT levels.

4) Persons who have had a recognized exposure to HCV:
   - Infants born to an infected mother;
   - Sex partners of infected persons;
   - Healthcare workers following needle sticks or mucosal exposure to infected blood.

There is a need for new knowledge on the efficiency and cost effectiveness of policies and practices on testing. So far, targeted notification programs have been used. Their efficiency is variable in view of poor record-keeping, change of address and unreliable testing. A general education program should be launched following scientifically sound pilot studies.

Routine screening of HCV in persons with multiple sex partners, men who have sex with men, pregnant women, healthcare workers, prisoners, persons with tattoos, pierced body parts and household contacts is not recommended at this time. However, the recommendation is based on fragmentary information. Research is needed as 10% of HCV victims have no known risk factor nor exposure.

PREVENTION MESSAGES AND COUNSELLING/FOLLOW-UP OF INFECTED PERSONS: HCV specific information and prevention messages should be provided along with information about community resources available for management and social support. Research is needed so that the education programs targeted to the persons with positive test results will:

1) prevent further harm to their liver i.e. abstinence from alcohol, vaccination against HAV and HBV;

2) reduce the risk for transmitting HCV to others and,

3) advocate the need for medical evaluation and treatment.

## QUALITY OF LIFE ISSUES

HCV has become an important issue for public health as biomedical, clinical and epidemiological evidence have emerged. Those disciplines have highlighted the prevalence of the infection and its complications. Governments at both the federal and provincial levels are sifting through the evidence and attempting to create structures to deal with the epidemic. Policies and implementation policies have unfortunately largely been based on the medical and scientific models of disease and have undervalued the psychosocial and quality of life issues facing patients infected with HCV.

**HEALTH-RELATED QUALITY OF LIFE (HRQOL):** Significant progress has been made in the creation of instruments which attempt to define the characteristics of a given health state. These instruments attempt to gauge the impact of a disease state upon an individuals' perception of their overall health well-being. Very few studies of HRQOL have been done in HCV. The studies which have been performed consistently demonstrate that HCV patients have a significantly reduced HRQOL. However, HRQOL scores do not correlate with the degree of hepatic inflammation and fibrosis nor with ALT levels or the presence or absence of HCV viremia. Of interest is the observation that HRQOL scores are lower in IVDU patients that in other groups. The impact of treatment of HCV patients with interferon upon their HRQOL is controversial. Studies to date have described either similar improvement in HRQOL scores in interferon treated responders and nonresponders or greater improvement in HRQOL scores in responders compared to nonresponders. Therefore, the impact of viral clearance versus the impact of undertaking treatment alone in HCV infected patients upon changes in their HRQOL are unknown.

In an excellent report published in April 1999 on the health and socio-economic status of Hepatitis C positive transfusion recipients, 1986 - 1990, Robert Hogg and a Team of investigators from the B.C. Centre for Excellence in HIV/AIDS conclude that "the study's results will never be able to show us the personal hardships people with Hepatitis C have faced or how their poor health status has affected their lifestyle and personal well being".

**HRQOL RESEARCH ISSUES**: There is an urgent need for studies in the area of quality of life. Ongoing issues which require attention in HCV patients include:

- Need for better HRQOL assessment techniques specific for HCV infected patients
- Does the mode of transmission affect HRQOL?
- Do patients in trials fare better in terms of quality of life?
- What is the prevalence and the impact of co-morbid conditions (e.g. anxiety and depression)?
- Is fatigue related to depression and anxiety or to the disease itself?
- What are the consequences of HCV on education, employment, insurance, personal relationships, child bearing?
- What are the direct and indirect costs of the disease (e.g. drugs, absenteeism, disability)?

As disease labelling alone effects HRQOL, screening policies should not only consider the benefits (i.e. early treatment, reduction of risk of contamination and social impact of complications) but also the drawbacks. Areas for research include:

- Will aggressive, early patient education programs in HCV infected individuals improve their long term HRQOL?
- Is the perception of the public for the disease changing in response to education programs?
- What are the iatrogenic consequences of screening and the consequences of a positive test result?

**QUALITY OF LIFE ISSUES AND CLINICAL RESEARCH**: It is clear that HRQOL assessments should be incorporated into all patient-based research where appropriate. The exclusion or marginalisation of disciplines such as sociology, psychology and philosophy from the equation can lead to difficulties in interpreting knowledge, viewpoints and problems as well as in policies and infrastructures unresponsive to the day-to-day experience of living with the virus.

**ASSESSMENT OF PATIENT NEEDS**: Few attempts at needs assessment of affected communities have been done. A renewed commitment is needed to obtain this information and to incorporate it for the formulation of policies and for the allocation of resources. The workshop was careful in giving due attention to quality of life an socio-economic issues of affected communities. In order to develop a research agenda with a maximum impact on the burden of HCV, these issues should be articulated with all patient and population-oriented research. Otherwise, there is a risk that programs will be too narrowly conceived and too poorly implemented to help those people in need. Finally, quality of life research must be heard as an independent and separate voice for a better understanding of the problems of every day life with HCV. It is also important to remember that these problems are compounded by representation of the disease as resulting solely from IVDU and by stigmatisation and discrimination.

## HEPATITIS C RESEARCH IN CANADA: INVENTORY AND SOURCES OF FUNDING

### INVENTORY OF HCV RESEARCH

During the 1970s and 1980s, Non-A, Non-B (NANB) hepatitis was the most frequent infection transmitted by blood transfusions. Its epidemiology was studied with indirect diagnostic tools such as elevation of transaminases weeks after a transfusion in the absence of positive tests for hepatitis A and B and for hepatitis secondary to the Eptein-Barr virus and to cytomegalovirus. Following cloning of HCV and the development of specific tests for anti-HCV antibodies in 1989, there has been an exponential increase in new knowledge covering the full spectrum of research indicative of the growing importance of this major global public health problem.

A bibliometric analysis of Canada's contribution to the world literature in biomedical and health sciences places Canada ahead of several large countries with a percentage of 4.9%. However, this does not hold true for HCV research. A mail questionnaire of 59 hepatologists and scientists as well as a Medline search reveal that Canadian researchers published only 23 papers on HCV during the 1991-1995 period and 26 between 1996 and 1998. This is a disappointing performance since Canadian productivity accounts for less than 0.6% of the world literature on hepatitis C during these last two periods. The mail survey revealed that 37 studies were ongoing and 16 were proposed for 1999. The table below illustrates the research areas and themes.

**DOMAINS OF ONGOING RESEARCH ON HCV IN CANADA**

| BASIC | EPIDEMIOLOGICAL | CLINICAL | QUALITY OF LIFE |
|---|---|---|---|
| MOL BIOL: 2 | PREVALENCE: 4 | NATURAL HIST: 1 | FATIGUE AND QUOL:1 |
| IMMUNOLOGY:1 | TRANSMISSION: 6 | LIVER DISEASE: 2 | |
| PATHOGENESIS: 1 | OUTCOMES: 1 | TREATMENT: 15 | |
| DIAGNOSTICS: 2 | | | |
| DRUG DESIGN: 1 | | | |

(Unpublished data from Morris Sherman)

There are glaring deficiencies not only in terms of the number of studies but also in terms of coverage. It is clear that there is an urgent need for an increased research effort in all areas. In laboratory-based research more effort is needed for the creation of in vitro and animal models to study replication, transcription and translation.

A better understanding of the host immune response and of the mechanisms of persistence will also require more attention in order to fuel more applied research. The same comment applies to the design of new drugs. In the clinical arena, information is needed to identify factors affecting progression and means of evaluating it. As HCC is a fatal complication, it is disconcerting that no studies are in place to improve on the crude methods of screening for cancer.

Given Canadian strength and word class excellence epidemiology, it is imperative that studies be initiated on the incidence of HCV in populations at risk, as a function of modes of transmission to complement those on prevalence. Research on the natural history has yielded fragmentary and often vulnerable information. Research on long-term population-based natural history, age-specific progression rates, in children particularly, and on the risk of cirrhosis and HCC, are necessary, Finally, policies and the allocation of resources cannot be guided properly until the burden of disease in terms of quality of life and of current future health care costs is more throughly evaluated in Canada.

## FUNDING: PRESENT AND FUTURE SOURCES

### PRESENT SOURCES:

Current funding of research other than from the private sector is very modest.

- **The MRC** supports only three grants directly concerned with HCV. However, funding is provided for four others dealing with the liver and are therefore relevant to HCV. Furthermore, 47 projects in very basic research have been identified as indirectly related to liver research since they will impact on our understanding of how the liver is injured and repairs itself.

- **The Canadian Liver Foundation (CLF)** IS celebrating its 30th anniversary this year. It has done a remarkable job at raising the awareness of Canadians for liver disease. Unfortunately, a difficult budget situation has prevented CLF from funding research during the past three years.

- **The National Cancer Institute of Canada** is a distinguished funding agency with a 52-year history of support for cancer research. Only two of 675 ongoing research grants deal with liver cancer.

- **The National Health Research Development Program** supported important projects between the years 1990-1996 totalling close to 1.8 million dollars. With the recent reorientation of its programs, NHRDP has not funded any disease-related research. However, since it is funding HIV research, perhaps it would be receptive to the larger epidemic represented by HCV.

- **The Canadian Health Services Research Foundation** was created in 1997 as a five-year partnership program. Although proposals should not include disease-related projects, the Foundation would perhaps be receptive to research in innovative approaches to integrated care proposed for HCV.

- **The Canada Foundation for Innovation** has recently completed its first round of funding for research infrastructure. It provides a unique opportunity for partnership with hospitals research

institutes, foundations and with the private sector for the renovation of laboratories, equipment and the creation of research networks.

- **The Hepatitis C Society of Canada** was created in 1994 to improve the lives of Canadians infected with HCV. Its mission is four-fold:
  1) Support to patients and comfort
  2) Awareness and education
  3) Research into prevention and cure
  4) Seeking social justice

The Society headquartered in Toronto has chapters across the country. It is committed to the creation of Centres of Excellence for early, timely and state-of-the-art health care services as well as for research. Its budget is very modest but the commitment to research is there.

- **The Thalassemia Foundation** was created in 1982 for disease awareness, the support of patients and of research. Three research projects are funded in 1999 but none are on HCV research. The commitment is to use 90% of the Foundation's budget for research.

- **The Canadian Hemophilia Society** is committed to education, patient care and research. Its 1998 Annual Report reveals that about 11.5% of its expenditures on programs went for support of research. However, none of the funded projects were directed to HCV.

- **Pharmaceutical and Biotechnology Industries** have funded over the past few years basic research, research into diagnostic tests and clinical trials. They are playing a key role in HCV research with an approximate amount of $25M having been invested in 1997 and 1998.

The private sector is playing an increasing role in health research in Canada where 32 drugs on the market were discovered and/or developed in Canada. However, policy makers and stakeholders need to be made aware of the fact that a healthy, vibrant, innovative publicly funded research enterprise is paramount to the success of targeted private sector efforts. In the words of John Clement of Biochem Pharma, it is clear that..."more pressing public health issues will require additional funding to mobilize and focus the Canadian research expertise on HCV."

**FUTURE SOURCES:**

**Hepatitis C Disease Prevention, Research and Community-Based Support Program of Health Canada**: Of the $10M/year available through the Minister Rock's proposal over five years for community support, prevention and research, it would be appropriate for the Hepatitis C Disease Prevention, Research and Community-based Support Program to allocate a substantial proportion to the full spectrum of HCV research. As pointed out earlier, progress for the education, patient support, prevention and care programs are dependent on the acquisition and application of new knowledge. These resources could be used responsibly and efficiently from the very first year.

The HCV epidemic is a much larger epidemic than HIV and its complications are burgeoning. The research agenda necessary to deal with the most important public health problem of industrial nations will require considerable resources. In the HIV/AIDS federal program, out of a budget of $42.2M/year, close to 30% goes to research. HPB has access to $1M for directed epidemiological research, NHRDP is responsible for $5M made available for the HIV trials network, for community-based research and Aboriginal research. Finally, $7M is available for extramural research managed by MRC in collaboration with NHRDP for the proposals falling within its mandate.

**The Canadian Institutes of Health Research (CIHR)**: The creation of CIHR announced in the February 16, 1999 federal budget represents a landmark in the history of Canadian biomedical and health research. This initiative will not only increase the amount of public money available for research but will bring together diverse sources of funding. It will coordinate isolated research efforts and link them more closely to health care and to the health care system. Doctor Henry Friesen, who chaired the Task Force on CIHR and who also chairs the Interim Governing Council of CIHR, challenged all HCV stakeholders to seize the opportunity. Thought should be given to the creation of dedicated research program on HCV under the aegis of an Institute which could be dedicated to Microbiology and Infection.

As the MRC, which will soon be subsumed into CIHR, has a renewed commitment to partnerships, negotiations should be initiated to explore the possibility of matching funds from CIHR and from the Hepatitis C Disease Prevention, Research and Community - Based Support Program, as well as to put in place mechanisms by which MRC/CIHR would manage the greatly expanded research efforts on HCV in collaboration with that Program and with all stakeholders.

**The Canadian Blood Services (CBS)**. The new blood agency established at the end of 1998 is facing many challenges. Although its primary mission is to provide Canadians with an effective and safe supply of blood and blood products, there is a strong commitment to research and development. The principle that a substantial % of its budget should be dedicated to research has been accepted. In that context, it is appropriate to entertain the possibility that CBS would join the MRC/CIHR - Hepatitis C Program initiative as a third partner by contributing to the joint funding available for research, training and salary support.

## FRAMEWORK FOR A COORDINATED, AND INTEGRATED NETWORK FOR RESEARCH AND CARE

### NEW RESEARCH PARADIGM

The aims of Canadian research on HCV are: 1) to improve the outcome for the 240,000 individuals who have become infected and 2) to reduce the probability of infection among those who are not infected. This requires more than money and an expanded research capacity. A three-pronged knowledge strategy needs to be put in place:

- Knowledge generation to expand the stock of relevant knowledge:
- Knowledge transfer to assemble, package and deliver it to the right people including community people who have direct access to at-risk populations:
- Knowledge use so that best practices for prevention and care are adopted.

Integration of knowledge is key to the success of this undertaking and will not occur unless there is a profound transformation of the research landscape:

- Isolated research efforts should be integrated across the country;
- Disciplinary separation should be replaced by integration across disciplines, institutions and sectors;
- Lag between knowledge and its application in the health-care system should be shortened;
- Fragmented multi-agency funding should be coordinated through the Canadian Institutes of Health Research.

## STRATEGIC PLAN

Where would the HCV community of researchers, caregivers and affected patients like to be in five years? The strategic plan should be dictated by achievable goals and driven by principles, ensuring that:

1) coordinated multi and interdisciplinary research be fully integrated with public health activities;
2) exemplary patient care be accessible everywhere in the country; and
3) better outcomes result for those infected with hepatitis C.

There is time- and resource-limited funding available for research, prevention and community support through the Hepatitis C Disease Prevention, Research and Community-Based Support Program created following the Minister's proposal for the investment of $50M over 5 years.

Thus, it is imperative:

1) To prioritize certain research themes, and build on existing strengths;
2) To expand Canada's capacity for research and manpower for care;
3) To give undivided attention to the creation of a national network of HCV Centres of Excellence for education, prevention, care and research and;
4) To form a large consortium of diverse funding sources around the CIHR/Hepatitis C Disease Prevention, Research and Community-Based Support Program for a multi-pronged attack on HCV.

**PROGRAMMATIC APPROACH:** As borne out by the previous section of this report, there is virtually an unlimited amount of potential research which needs to be undertaken. However, there can be no prospect of substantial progress if there is not at the same time some degree of order.

The HCV research infrastructure should favour investigator-initiated projects but under well defined themes framed by multidisciplinary research programs which foster cross-disciplinary and inter-sectoral (academic, public health, private sector) collaboration. This is in keeping with recent orientation of research programs by the NHMRC Australia, the MRC-UK, as well as the strategic planning likely to be adopted by CIHR.

The creation of a national network for HCV research should rapidly increase both the quality and quantity of research. In doing so, it will contribute to increasing the research capacity. To start the ball rolling, a research committee of 8 to 10 representatives of all stakeholders should be formed.

**INCREASING THE RESEARCH CAPACITY AND HUMAN RESOURCES FOR CARE**: As pointed out above, the research performance of Canada in the field of HCV, although world-class in terms of quality, is quantitatively insufficient. HCV research needs to attract productive researchers from related field of inquiry. Given appropriate structures and dedicated funding, there is no doubt that the field would attract not only seasoned researchers but also new talent.

Salary and training programs will be necessary to increase the research capacity for hepatitis C. Education programs should also be available for the development of expertise amongst health care providers and public health professionals. The training programs should be targeted to physicians ie. family physicians, internists, gastroenterologists, and to nurses, public health personnel, counsellors in addiction centres, psychologists, social workers etc. who will be called upon to work in accredited HCV centres. Funds should be made available to train an increased number of specialist physicians in gastroenterology, hepatology and infectious diseases to meet the increasing demand.

This component of the strategic plan is particularly important because the promotion of HCV awareness is suboptimal. Disease prevention programs leave much to be desired and the majority of patients with HCV are getting sub-standard care because of an acute shortage of well trained health care professionals.

**NETWORKS OF CENTRES OF EXCELLENCE:** The case was made throughout this report for the urgent need for a well-orchestrated research effort in order to increase disease awareness, education of the public, training of health professionals, patient support, quality of care and prevention.

There is a wide consensus for the creation of a national network of Centres of Excellence. They should be closely linked by state-of-the-art information technology with access to a national patient registry and a repository for biological specimens. These Centres of Excellence anchored in Academic Health Sciences Centres would be the hubs for smaller satellite centres. Accreditation of these Hepatitis Treatment and Education Centres and the availability of Clinic incentive grants would ensure the quality of the programs and facilitate access to new therapeutic approaches and close monitoring.

In order to ensure a close linkage between the collaborative multi- and inter-disciplinary research activities and the diverse missions of the Centres of Excellence, individual researchers would be members of their own Centre of Excellence. They would participate in the strategic directions and would be encouraged to focus some of their research activities on its particular mission and needs for new knowledge and its application.

With expansion of Canada's research capacity over the wide spectrum of HCV research and maturation of productive interdisciplinary and intersectoral linkages, a long term goal would be to apply to the federally sponsored NCE program for a National Centre of Excellence dedicated to HCV research.

## CONCLUSIONS

Having taken stock of the burden of HCV and of the gaps in current knowledge, a broad-based research agenda was considered essential to achieve the following objectives:

1) to increase disease awareness, and public education;
2) to improve screening and diagnostic services;
3) to enhance the quality of care, patient support and prevention;
4) to accelerate the development of new strategies of intervention and of a vaccine, through a better understanding of the biology of the virus and of the pathogenesis of HCV.

An inventory of ongoing HCV research and of Canadian contributions to the world literature alerts us to a performance which, quantitatively, is unacceptable compared to those in other fields of biomedical and health research, and inappropriate given the dimension and the long-terms consequences of the epidemic. It is clear that the research capacity on HCV and the human resources for patient care and prevention are very limited and deserve immediate attention.

A survey of funding sources reveals that the overwhelming bulk of research funds for HCV comes from the private sector for targeted development of early discoveries in diagnostics and treatments. Access to increased public funding for laboratory and clinical research is deemed necessary to encourage an expansion of current research efforts by the pharmaceutical and biotechnology industries. Through the Hepatitis C Disease Prevention and Community-based Support Program, it is hoped that a substantial proportion of the $10M/year will be earmarked over the next five years for research targeted to the generation, transfer and use of new knowledge.

MRC whose operations are soon to be rolled into CIHR and Health Canada through its Hepatitis C Prevention, Research and Community-Based Support Program should be approached for partnership contributions. MRC/CIHR should be called upon to manage (peer review and administration) these funds in collaboration with that program, with other agencies, appropriate disease-related foundations as well as with the private sector.

Finally, the report proposes the creation of a Network of Hepatitis C Centres of Excellence anchored in Academic Health Sciences Centres which would be the hubs for smaller satellite regional centres. They would have a broad-based mission for research education, training and care. However, each centre would be called upon to develop a specific expertise, thereby contributing to the national effort.

The success of this daunting task and challenging undertaking will require unprecedented cooperation and closing of the ranks of all stakeholders. All partners (i.e researchers, health care providers, public health authorities and the HCV community) need to be actively involved in the analysis of the dimensions of the epidemic, the analysis of the health status and quality of life of victims, and in the strategic planning of research.

# APPENDIX

## HEPATITIS C:

## DEFINING A RESEARCH

## AGENDA FOR CANADA

WORKSHOP

JANUARY 15 - 16, 1999

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**SPONSORS:**

THE MEDICAL RESEARCH COUNCIL OF CANADA

HEALTH CANADA

CANADIAN BLOOD SERVICES

## BACKGROUND FOR THE WORKSHOP

On September 18, 1998 Health Minister *Allan Rock* announced a comprehensive Hepatitis C proposal to provide better HCV prevention and treatment, significantly strengthen blood safety and help Canadians infected with HCV through the blood system prior to 1986 and after 1990. The proposal had four components:

- A special transfer of $300 million over 20 years to be matched by provinces and designed to provide access to needed medical care not currently covered for people infected through blood.

- Half the cost ($25 to $50 million) of provincial and territorial look-back/trace-back initiatives designed to help identify people infected through blood or who have donated infected blood.

- A sum of $125 million over five years to strengthen blood regulation and disease surveillance following the recommendation of the Krever Commission.

- Up to $50 million over five years for community-based support and research programs.

Following an exchange of correspondence with Minister Rock, MRC and Health Canada decided to sponsor a HCV Workshop and asked Dr. Morris Sherman to strike a Steering Committee which met in Montreal on October 4, 1998, to plan the meeting.

## OBJECTIVES OF THE WORKSHOP

1) Review critically the full spectrum of HCV research, from the molecule to public health and psychosocial aspects carried out in Canada.

2) Identify knowledge gaps in our understanding of the pathogenesis, epidemiology, transmission, clinical and psychosocial aspects, complications, management and prevention of HCV.

3) Define a research agenda for Canada which takes into account the burden of the disease, the research capacity of the science community and financial resources.

4) Propose research, training and salary support programs which will have maximum impact on the acquisition of new knowledge and on the management and prevention of the disease.

# HEPATITIS C:
# DEFINING A RESEARCH AGENDA FOR CANADA

## FRIDAY, JANUARY 15, 1999

**08:15** **WORD OF WELCOME**
*Morris Sherman*

**08:30** **BURDEN OF HCV**
*Robert Remis*

**09:00** **WHAT ARE THE GAPS IN OUR KNOWLEDGE?** (Plenary session)
*Chair: Martin Tepper*

- Biology of the virus and pathogenesis of HCV
  *Raymond Tellier*

- Clinical manifestations, natural history of the disease and its complications
  *Averell Sherker*

- Laboratory testing for diagnosis and follow up
  *Mel Krajden*

**10:00** **HEALTH BREAK**

**10:30**
- Epidemiology of HCV including minority groups and non parenteral transmission
  *Jean Joly*

- Primary and Secondary prevention
  *Elise Roy*

- Treatment of HCV in the general population and in vulnerable populations
  *Sam Lee*
- Quality of life and socio-economic impact of the disease
  *Mark Swain*

**12:00** **LUNCH**

**13:00** **IDENTIFICATION OF RESEARCH PRIORITIES** (breakout groups)

• Biology of the virus and pathogenesis of HCV
*Robert Rando*

• Clinical manifestations and natural history of the disease and its complications
*Averell Sherker*

• Laboratory testing for diagnosis and follow up
*Mel Krajden*

• Epidemiology of HCV including minority groups and non parenteral transmission
*Jean Joly*

• Primary and Secondary prevention
*Elise Roy*

• Treatment of HCV in the general population and in vulnerable populations
*Sam Lee*

• Quality of life and socio-economic impact of the disease
*Mark Swain*

**14:30** **HEALTH BREAK**

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**15:00** **REPORT BACK SESSION OF THE SEVEN BREAKOUT GROUPS TO DEVELOP A CONSENSUS AROUND THEIR RECOMMENDATIONS**

**16:30** **SURVEY OF CANADA'S CONTRIBUTION TO HCV AND OF PRESENT AS WELL AS OF POTENTIAL SOURCES OF FUNDING**
*Chair: Claude Roy*

• Inventory of research either completed or underway in Canada
*Morris Sherman*

• Survey of present and potential sources of funding
*Mark Wheeler and Claude Roy*

**17:30** **ADJOURNMENT**

## SATURDAY, JANUARY 16, 1999

**08:30** **DEFINING AN HCV RESEARCH AGENDA FOR CANADA IN TERMS OF FEASIBILITY AND IMPACT (breakout groups)**

- Basic Science
  *Lorne Tyrrell*

- Clinical Research and treatment
  *Bernard Willems*

- Screening and Diagnosis of HCV in the blood supply
  *Jutta Preiksaitis*

- Epidemiology and outcome research
  *Robert Remis*

- Primary and secondary prevention
  *Paul Gully*

- Quality of life and socio - economic issues
  *Murray Krahn*

**10:00** **HEALTH BREAK**

**10:30** **REPORT BACK SESSION OF THE SIX BREAKOUT GROUPS TO DEVELOP A CONSENSUS AROUND THEIR RECOMMENDATIONS**

**12:00** **LUNCH**

**13:00** **WHAT SHOULD BE THE MECHANISMS IN PLACE FOR PERFORMING, EVALUATING AND ADMINISTERING THE HCV RESEARCH, SALARY SUPPORT AND TRAINING PROGRAMS?** (Plenary Session)
*Chair: Morris Sherman*

- How to deal with unlimited aspirations in the face of limited capability and resources?
  *Henry Friesen*

- Lessons from other constituencies:

  - The AIDS strategy, phases I and II
    *Allan Ronald*

  - The NCE model
    *Peter Macklem*

  - The increasing role of the private sector in health research
    *John Clement*

**14:30** **STRUCTURAL ISSUES FOR THE GRANTS AND AWARDS PROGRAMS**
*Chair: Mark Wheeler*

- A national network for HCV research
*Sam Lee*

- The balance between individual and group grants
*Mark Bisby*

- Salary and training programs to increase Canada's capability for patient care and research
*Jenny Heathcote*

**16:00** **WRAP UP AND CONCLUSIONS**
*Morris Sherman*

**16:30** **ADJOURNMENT**

## STEERING COMMITTEE

| | | |
|---|---|---|
| Chair: | Morris Sherman | |
| Members: | Fernando Alvarez | Jutta Pruksaitis |
| | Jeremy Beaty | Robert Rando |
| | John Clement | Robert Remis |
| | Francine Décary | Graham Sher |
| | Jenny Heathcote | Verna Skanes |
| | Sam Lee | Robert St-Pierre |
| | David Page | Martin Tepper |
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