Strange Bedfellows: Infection & Chronic Disease

Conference Report

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GREETINGS AND WELCOME

Mr. Gerald Dafoe, Chief Executive Officer, Canadian Public Health Association

Mr. Dafoe welcomed participants, mentioning the origins of the conference in the Communicable Disease Conference held in April 1997, and thanked the planning committee. He placed the meeting in the context of the role of CPHA in promoting public health, and outlined the objectives of the conference as follows:

First, to raise awareness, especially among public health decision-makers, about associations between infections and chronic diseases.

Second, to identify and discuss critical issues in areas such as:

- Implications for public health policy and health economics
- Questions of how to measure public health effects and outcomes
- Options for surveillance, intervention, diagnosis and treatment
- Optimal choices of areas for investment in research
- Future impact of integrative trends in the biomedical sciences (e.g., human and pathogen genomics)
- Appropriate causal models and research approaches for diseases of complex etiology
- Ethical concerns and dilemmas (e.g. long-term prophylactic anti-microbial therapy; tests for host susceptibility)

Third, to summarize the proceedings in such a way that they may be developed and published as a document.

Mr. Dafoe concluded by stating that the conference was intended to stimulate discussion and interchange of ideas and information, not necessarily to achieve consensus on specific recommendations.

On behalf of the Canadian Public Health Association, Mr. Dafoe thanked the following sponsors for their enthusiasm and support:

- The Canadian Institutes of Health Research, formerly known as the Medical Research Council
- Hoffmann-LaRoche Ltd.
- Aventis Pasteur
- The Laboratory Centre for Disease Control (LCDC)

Dr. Paul Gully, Associate Director General, LCDC, Health Canada

Dr. Gully welcomed the participants and recognized the conference as an example of cooperation between the Laboratory Centre for Disease Control and the Canadian Public Health Association. He reminded participants that, as of July 1, the Laboratory Centre for Disease Control would be merged with elements of the Health Promotion and Programs Branch at Health Canada, a merger he felt would be of benefit to both. He commented that this meeting would help public health professionals and other health care providers develop knowledge on these issues and would contribute to setting the agenda for a future consensus conference in this area.

Dr. Gully noted a number of examples of well-known associations between infection and chronic disease and expressed the belief that the meeting would provide a step toward developing the firm ground needed to take action on the new and complex associations with chronic disease.

SETTING THE STAGE

Searching for Microbial "Fingerprints" in Chronic Idiopathic Diseases

Dr. David Fredricks, Division of Infectious Diseases, Stanford University Medical Center & VA Palo Health Care System

Dr. Fredricks pointed out that there are numerous chronic diseases that remain unexplained, despite advances in medicine. Currently, there are cases in which the epidemiology, pathology and clinical characteristics of some chronic diseases suggest a role for infectious agents, but conventional diagnostic techniques have not allowed clear identification of these agents. Molecular diagnostics have identified microbial causes for a number of diseases and have the potential for doing so for a number of others. Dr. Fredricks urged an approach integrating microbiology, epidemiology, public health and clinical medicine.

Dr. Fredricks noted that studies of microbial diversity in environmental niches reveal that most microbes have not been described using cultivation technology. Several recent studies looking at microbial diversity in human-associated niches have also found a surprising number of novel microbes. This raises the issue of whether there are novel pathogens that might cause some idiopathic diseases.

Citing the examples of Whipple's Disease, Peptic Ulcer Disease, Kaposi's Sarcoma and other disorders, Dr. Fredricks showed how epidemiological data combined with serology and highly sensitive nucleic acid sequence-based microbial detection combine to provide definitive diagnoses. Consideration of these cases illustrates that, for a number of reasons, diagnosis and identification of infections causing chronic disease have historically been difficult. For example, in some cases chronic diseases can be infectious but culture negative; in others microbes may initiate pathogenesis but be absent at the onset of clinical disease – the so-called "hit and run" hypothesis. Sequence-based microbial detection proved invaluable in final identification of microbial pathogens in a number of these cases.

Dr. Fredricks characterized sequence-based pathogen discovery to be analogous to finding a fingerprint at a crime scene. Evidence of a microbial sequence provides valuable information, but to be definitive it must be part of a more comprehensive approach requiring integration of molecular diagnostics with epidemiology, pathology and clinical data. To facilitate use of sequence-based techniques, he provided an adaptation of Hill's Epidemiological Criteria for Causal Association that provides guidelines for sequence-based proof of microbial causation.

In his concluding remarks, Dr. Fredricks stressed that the focus should initially be placed on diseases with high incidence and high burden of disease costs. This implies

coordinated involvement of epidemiologists, public health and clinicians. The "hit and run" phenomenon in particular highlights the desirability of a bank of tissues and serum from patients with chronic diseases in order to identify microbial causes.

Helicobacter pylori: Public Health Perspectives

Dr. Richard Schabas, Head of Preventive Oncology, Cancer Care Ontario

Dr. Schabas began by noting the re-emergence of infectious diseases as an issue in the past twenty years. He cautioned that, while it is important, it is not apocalyptic and should be kept in perspective. In his presentation, Dr. Schabas reviewed the history and current knowledge of *Helicobacter pylori (H. pylori),* elaborated its chronic disease associations and analyzed potential opportunities for public health interventions.

H. pylori is known to be associated with chronic gastric inflammation and idiopathic peptic ulcers. In 1994, it was designated by International Association of Research in Cancer (IARC) as a Group 1 carcinogen, due to its association with adenocarcinoma of the stomach. The reservoir of this organism is human and transmission appears to include waterborne transmission. Its effects follow a strong socio-economic gradient and it is more prevalent in the developing world.

H. pylori's significance as a health issue is particularly related to its association with adenocarcinoma of the stomach which is the 7th most common cancer in Canada, resulting in approximately 2,000 deaths per year and carrying a case fatality rate close to 90%. There are varying estimates of relative risk of adenocarcinoma from *H. pylori* infection, estimates being from 2-9.

Discussing public health perspectives, Dr. Schabas referred to the "epidemiologic triangle" of host, agent and environment and commented that, from a population standpoint, host and environment factors are key. Sanitation, both at individual and public levels, is an important controlling factor, as is general improvement of living conditions. One area of intervention Dr. Schabas suggested for public health consideration is agent screening for *H. pylori*. This would require determining whether the disease associations represent an important health problem and whether screening would reduce mortality. Dr. Schabas suggested increased public surveillance and the possibility of trials in the area of screening.

Retroviruses and Chronic Diseases

Dr. Paul Sandstrom, Associate Director, Bureau of HIV/AIDS, STD and TB, LCDC, Health Canada

Dr. Sandstrom outlined the fundamentals of retrovirus evolution, genetics, replication and pathogenesis, highlighting the associations between endogenous retroviruses and chronic disease and indicated significant questions to be addressed. He noted that knowledge in this area has increased dramatically over the past 20 years, citing as major discoveries:

- the retroviral origins (HIV) of acquired immunodeficiency syndrome (AIDS)
- the process of reverse transcription, in which the retroviral RNA genome is converted to a DNA form.

By carefully examining the genetics of animal and human retroviruses, it is now apparent that cross-species transmission of *exogenous* retroviruses has been occurring for eons, and that all known human retroviruses have arisen from closely related retroviruses endemic to Old World primates.

As part of the normal replication cycle, exogenous retroviruses will insert a copy of their DNA genome into the genome of the infected host. However in a phenomenon unique to retroviruses, the genomes of all mammals so far examined contain multiple germline-fixed *endogenous* retrovirus (ERV) sequences that are inherited from parent to offspring in a Mendelian fashion. Undoubtedly, some ERVs represent the accidental germline fixation of infectious exogenous agents. It has been postulated that this process provided some evolutionary advantage to the animal: perhaps in surviving an ongoing epidemic of the exogenous form of the virus. Once a permanent part of the host genome, endogenous viruses accumulate random mutations at the same frequency as cellular genes. Over time, and in the absence of any ongoing selective advantage provided by viral expression, this accumulation may result in defective and, in most situations, dormant virus. Retroviruses, therefore, are unique in that they have the potential to leave a record of themselves in the genome of their host in the form of these viral remnants. The presence of integrated ERVs may have a number of important health implications for humans with regard to chronic diseases. Dr. Sandstrom outlined the following associations between several families of endogenous retroviruses and chronic diseases:

- HERV-E: association with interstitial lung disease
- HERV-R: mothers of children with congenital heart disease have increased levels of antibodies to HERV-R
- HERV-H: possible role in tumour development
- HERV-K: possible role in development of mammary tumours

CARDIOVASCULAR PANEL

Evidence of Association Between *Chlamydia pneumoniae* and Atherosclerosis

Dr. Lee Ann Campbell, Professor and Associate Chair, Pathobiology, University of Washington

Dr. Campbell examined the association between *Chlamydia pneumoniae (C. pneumoniae*) and atherosclerosis. Referring to known risk factors for atherosclerosis (i.e., genetic background, untreated hypertension and diabetes), Dr. Campbell asked the question, "Is infection also a risk factor?" In order to allow consideration of the data addressing this question, she briefly outlined the events that occur in the progression of atherosclerosis, illustrating how initial endothelial injury results in a cascade of events that lead to plaque formation and atherosclerosis.

Dr. Campbell then pointed out that to recognize the potential public health impact if *C. pneumoniae* plays a role in atherosclerosis, it is necessary to understand the epidemiological patterns of infection associated with the disease. Antibodies to *C. pneumoniae* are commonly found; everyone gets infected between the ages of five and fourteen. Overall, the antibody prevalence in adults is approximately 50% and may reach 70-80% in elderly individuals. The risk of atherosclerosis is increased by a factor of two if the individual has *C. pneumoniae* infection. This relative risk is similar to that of untreated hypertension.

A summary of histopathological findings showed that a variety of methods found *C. pneumoniae* to be present in atherosclerotic lesions, but the organism is rarely found in normal arterial tissue. Accepting that *C. pneumoniae* appears incontrovertibly to be present in atherosclerotic lesions, Dr. Campbell addressed the evidence supporting the notion that the organism may play a role in atherosclerosis. Data from animal studies strongly indicate that infection with *C. pneumoniae* accelerated the progression of atherosclerosis in mice that had genetic or diet-induced hyperlipidemia.

Dr. Campbell concluded by stating that persistent infection with *C. pneumoniae* has biological plausibility as a contributor to atherosclerosis. She suggested a number of possible mechanisms through which it could influence the progression from endothelial injury to atherosclerosis. Commenting that persistent chlamydial infection can cause immunopathology and that atherosclerosis is essentially a chronic inflammatory disease, Dr. Campbell concluded that the burden of proof lies in two areas: human intervention studies and the development of a vaccine that delays disease development or decreases its incidence.

"Is Infection a Cause of Atherosclerosis?"

Dr. William Fong, Director, Infectious Diseases, St. Michael's Hospital

Dr. Fong reviewed the evidence concerning the relationship between atherosclerosis and infection by *C. pneumoniae, cytomegalovirus (CMV), herpes simplex* and *H. pylori* as well as periodontal disease. The question, "Is infection a cause of atherosclerosis?" is raised by data that show that lipid-lowering agents reduce heart attack in only 20-30% of cases and that in approximately 40% of cases, there is an absence of known risk factors.

Referring to Dr. Campbell's presentation, Dr. Fong noted that the strongest evidence implicating infection as being involved in atherosclerosis is that for *C. pneumoniae*. Evidence is less strong for *CMV*. One study found it almost equally in diseased and non-diseased blood vessels, suggesting it may be an "innocent bystander". When *CMV* is implicated, it appears to be associated not with naturally occurring atherosclerosis, but with restenosis following angioplasty or heart transplant. There are conflicting data concerning *H. pylori*. With respect to periodontal disease, the evidence is also inconclusive, with the strongest association being in 40 to50-year-old males. One study showed a correlation between periodontal disease and subsequent development of atherosclerosis in this group.

Dr. Fong also discussed the efficacy of antibiotics in reducing atherosclerosis. Such an effect would both be supportive of the hypothesis that infection does play a role in atherogenesis and would provide an avenue of treatment. In Dr. Fong's view, although preliminary results indicate that antibiotics may be of some use, more data are needed. He stated that in order to answer the questions regarding the effectiveness of antibiotics, results from large studies are needed to find the subgroup it would work for and how to effectively test for this subgroup.

Dr. Fong concluded by stating that, while an association has been well established between *C. pneumoniae* and atherosclerosis, cause and effect have not been established. Further evidence of causation will be available if those studies currently in progress show improvement with the use of antibiotics.

Public Health Implications of Infectious Etiologies of Ischemic Heart Disease

Dr. Andreas Wielgosz, Head, Division of Cardiology, Ottawa Hospital - General Campus

Dr. Wielgosz began by summarizing the public health implications of infectious etiologies of ischemic heart disease. He opened by saying that an appropriate public health response depends on the pathophysiologic relationship between the infectious agent and acute ischemic episodes (AIE). He argued further that current and projected rises in the rates of acute myocardial infarction make this a compelling item for a public health response.

Dr. Wielgosz pointed out, however, that current understanding of this relationship is not sufficient to support enlightened public health intervention since public health response would differ according to the form of transmission of the infection. Factors requiring increased understanding include method of transmission, inoculation period, virulence of the infection and host susceptibility. He then provided the following examples of infectious etiological relationships with heart disease:

- Streptococcus and rheumatic heart disease
- Enterococcus and endocarditis
- Rickettsia and Lyme myocarditis
- Coxsackie B and heart failure
- Influenza and increased mortality from heart disease, particularly ischemic heart disease
- Chlamydia's association with heart disease

Dr. Wielgosz pointed out that, of these, the relationship between influenza and ischemic heart disease was the most serious in public health terms since influenza transmits so quickly. He added that some experts predict an influenza pandemic within five to ten years.

One challenge to public health will be to identify populations at risk since it is unlikely that the entire general public will be at risk. Those likely to be most at risk are the young, the elderly, specific subsets of cardiac patients and those genetically predisposed. Each group may require a different public health response.

Dr. Wielgosz outlined the strategies that he felt should be included in a public health approach. These were:

- Surveillance to record the spread of infection-related heart disease
- A registry of at-risk populations

- A stockpile of antibiotics, antivirals, vaccines, especially in the context of a risk of an influenza pandemic
- A response plan and preparedness including communication networks

After noting that public health policy should be based on absolute rather than relative risk, Dr. Wielgosz added that prevention of ischemic heart disease should continue to be based on a hygienic lifestyle that includes no smoking, a low fat diet, exercise and stress management, including adequate sleep.

Discussion:

Following their presentations, panel members responded to questions from the floor.

The question was raised as to whether immunization against Chlamydia is an option in the foreseeable future. Participants were told that attempts have been made unsuccessfully for the past thirty years, and that three companies are actively working in this area. A participant added that, in his opinion, it is too early to tell whether immunization would be either possible or useful. It was also indicated in discussion that there are currently no laboratory-based markers for chronic infection, making it difficult to know towards whom prospective vaccines would be targeted.

In this context, a participant commented that the most powerful tool to identify causal agents of chronic disease has been epidemiological studies. He cited the most notable findings in the epidemiology of ischemic heart disease to be the international differences (a finding which led to the cholesterol hypothesis) and the rise and fall of ischemic heart disease in the west, particularly in Canada. The question was asked whether there was a correlation between these epidemiological patterns and those of *C. pneumoniae* as a possible explanation for these trends.

In response, it was noted that the strongest epidemiological correlation was with influenza, and studies were cited to support this. It was added that although mortality due to ischemic heart disease was waning, its incidence was not and that mortality, in the participant's opinion, could very well climb following another influenza pandemic.

With respect to delineating pathophysiology, it was proposed from the floor that, if there is a strong association and a low-risk intervention, it is arguably better to proceed before causality is definitively established. It was noted that, in fact, in the case of *C. pneumoniae* there are too many unknowns and there is no clear intervention to deal with the infection.

There was a suggestion that cardiovascular disease may involve a succession of different infections. The responding participant said that since cardiovascular disease is

multifactorial, causation is difficult to establish, however there were some data to support the suggestion.

The view was expressed that greater knowledge of the immunology of *C. pneumoniae* is needed. Changing patterns of infection may very well change the immunological consequences of the disease. In response to this observation, it was agreed that this was an area for study and interest, an example being current research on so-called "hot lesions". Other participants supported the need for greater knowledge of the immunology of *C. pneumoniae*.

When asked to comment on the best interventions possible, it was repeated that, while lifestyle priorities remain important, not enough is known about infectious etiology to propose a public health response in that area at this time.

It was asked whether the panel felt there should be more aggressive pro-active approaches to treatment of Chlamydia. There was a reponse that the prime need at this time is more long-term natural histories to better plan strategies in light of more complete knowledge of infectious etiology mechanisms.

Another question raised was the issue of the safety of blood transfusion and transplant, however it was felt there was no definitive answer to the question at this time.

GENITOURINARY DISEASE PANEL

Human Papillomaviruses are Causative Agents of Cervical Cancer

Dr. François Coutlée, Microbiologiste, Hôpital Notre-Dame du Centre hospitalier de l'Université de Montréal

Cancer of the cervix is the third most common cancer among women worldwide, with 80% of the incidence occurring in women from developing countries. The association between sexual behaviour and genital cancers has long been observed and a number of STDs have been investigated as possible causative agents. Dr. Coutlée illustrated that a preponderance of evidence links cervical cancer with human papillomavirus (HPV), and noted that in 1995 the International Association for Research in Cancer (IARC) accepted HPV as a causative agent in this disease. He cited data gathered from approximately 2,000 women worldwide, in which 99.7% of cervical cancer samples assayed were found to contain HPV.

At least thirty genotypes of HPV that infect the genital tract have been described. These have been categorized as high or low risk types according to their oncogenic potential. Dr. Coutlée reported that HPV genotypes 16 and 18 are the most commonly encountered that pose a high risk for oncogenesis, and therefore should be included in any vaccines that may be developed.

Dr. Coutlée provided a wealth of evidence, both epidemiological and molecular, that implicates HPV as the cause of cervical cancer. HPV meets all but one of Hill's epidemiological criteria for causal inference. The sole exception is interruption of the infection leading to the elimination of the disease, since there is currently no treatment available. Both *in vivo* and *in vitro* studies provide molecular evidence of oncogenicity, with the apparent molecular mechanism having been elucidated. Of importance is the finding that oncogenesis appears dependent on persistent HPV infection, with transient infection not being linked to carcinogenesis. Co-factors, such as smoking and other STDs (possibly *Chlamydia trachomatis*), are possible contributors.

Dr. Coutlée concluded by restating that HPV causes genital cancer. He stressed that persistent infection is necessary. He noted that the implication of this for identification of at-risk women is that one-time screening may be inadequate and misleading, especially in young women. The future development of vaccine is plausible, as is the development of screening methods, making significant reduction of cervical cancer possible in the foreseeable future.

HPV and Anogenital Tract Cancers: Public Health Implications

Dr. David Patrick, Director, Epidemiology Services, B.C. Centre for Disease Control

Dr. Patrick focused on the public health issues raised by the human papillomavirus (HPV) cancer connection. He characterized the evidence for HPV as a causal agent as being compelling enough to suggest that removal of oncogenic HPV could possibly prevent anogenital cancer. Also contributing to the importance of HPV is the epidemiological evidence showing its high rate of transmission between partners. An interesting finding, he noted, is that there seems to be a dynamic interaction involving a number of infections, indicating that there is not necessarily a lifetime infection as is the case with HIV. This has implications for screening, since what appears to be persistent infection may, in fact, be re-infection with a new strain.

Pap screening in Canada has reduced the incidence of cervical cancer by half in the past four decades, so that cervical cancer has decreased to become the tenth most common cancer among Canadian women. It does, however, represent a higher burden among select groups. Dr. Patrick raised the possibility that a recent flattening of the mortality curve for cervical cancer may indicate that the limit of the effectiveness of Pap screening has been reached.

Dr. Patrick listed the following problems facing public health with respect to HPV:

- HPV is a high prevalence infection, broadly distributed among the population, making isolation of target populations difficult
- HPV has very efficient transmission
- HPV infects the squamous epithelium including surfaces of the vulva and scrotum, limiting the effectiveness of condoms
- Treatment of visible warts has little impact on subclinical disease

On the positive side, Dr. Patrick noted that spontaneous resolution of infection is common and that the low-risk types of HPV are common and are of largely cosmetic concern. Also mentioned were a number of challenges to vaccine makers. One key fact is that research indicates that protection is type-specific. This implies vaccination should focus on the two most common high-risk genotypes, HPV 16 and 18. In fact, two companies are currently studying the prophylactic use of HPV 16/18 vaccines with young women.

Dr. Patrick then discussed new technologies that might address conventional Pap limitations. Pap screening, while a highly effective and important method, has limits to its accuracy. This is complicated further by the interpretation of the presence of abnormal squamous cells of undetermined significance (ASCUS). New developments

include the use of thin layer, liquid-based Pap smears, automated re-screening devices and specific testing for oncogenic HPV. Testing for HPV has not been suggested for primary screening, with proposed future uses of these technologies suggesting a combination of Pap testing from liquid media and HPV testing.

Dr. Patrick concluded by suggesting the need for more complete epidemiologic assessments. Careful decision analyses and economic analyses should be done to discern how current knowledge of the importance of HPV could improve diagnostic algorithms. A question remains as to whether the use of new technologies will reduce cancers further. Second, he strongly urged vaccine preparedness including the identification of initial target groups should vaccine become available. Finally, he urged that the lessons learned from prevention of cervical cancer be applied in the treatment of anal cancer. Incidence rates of anal cancer in gay male populations resemble those of cervical cancer in women before the introduction of Pap screening. Dr. Patrick argued for exploring male Pap testing and colposcopy of high-grade anal lesions.

Discussion:

A participant noted increased rates and earlier onset of cervical cancer among First Nations women and asked whether this could be due to vertical transmission, given the early age of onset. It was suggested that earlier rates of exposure are more plausible and added that there may be host factors involved. A participant added that there may be different strains of the virus involved in Northern populations. Both respondents agreed that there is a need for study in this area.

The question was raised as to whether factors other than Pap testing have contributed to the decrease in mortality from cervical cancer over the last decades and the participant asked if there were any temporal effects noted about HPV over this period. In response, it was indicated that the techniques used to identify variance in HPV DNA are relatively new, and consequently this question remains unanswered.

A participant referred to the foreseeable development of screening for *Chlamydia trachomatis* among young people and asked whether the panel felt this would impact HPV prevalence in terms of length of infection and time for oncogenicity. A couple of participants agreed that any interpretation of this would require more study, since at the present time there are a number of confounding factors.

The panel was then asked if there would be a benefit to sequential HPV screening, given that the technology exists. The response indicated that there have been trials in situations where cytology is unreliable. At this time there are studies in progress comparing the efficiency of HPV detection versus conventional Pap screening. If increases in cost proved large, HPV testing would have to show significantly greater effectiveness than

current screening techniques, which have proven quite effective. It was agreed that some form of HPV testing may be available in the future for certain groups.

A final comment was made that, either with current techniques or in light of future technologies, routine screening of patients is central to any attempt to reduce cervical cancer and the limiting factor often remains the actual application of testing.

GASTROINTESTINAL PANEL

"Who Would Have Thought That Such a Small Virus Could Cause Such Havoc?" Hepatitis C and Chronic Disease

Dr. Kelly Kaita, Director of Viral Hepatitis Investigation Unit, Manitoba Health Sciences Centre, University of Manitoba

Dr. Kaita reviewed the link between Hepatitis C (HCV) infection, liver cirrhosis, hepatocellular carcinoma, and liver failure requiring liver transplantation. He also explored links to other risk factors. Since 1992, 80,000 HCV cases have been reported to the LCDC, making Hepatitis C the second most reported disease in Canada. It presents a serious challenge for public health interventions, particularly with regard to those who use intravenous drugs.

Hepatitis C is largely asymptomatic in the acute phase, but progresses to chronic disease in 60-80% of cases. Best models predict that, even given an apparent 85% drop in incidence between 1989 and 1994, a reduction in the rate of those affected for twenty years or more is not expected until 2015. Since most health problems do not occur until twenty years after infection, this indicates that Hepatitis C will pose a serious burden on health care in the decades to come.

The mechanism of pathogenesis in hepatocellular carcinoma is not clear at this time. What appears to be clear is that a key factor in the development of carcinoma is the concurrent presence of Hepatitis C infection and liver cirrhosis. Data indicate that in the absence of cirrhosis, the risk of developing cancer is low. However with cirrhosis present, the rate approaches 20%. Co-infection with Hepatitis B is also a significant risk factor.

Dr. Kaita reported that data indicate that alpha-interferon treatment of patients with chronic Hepatitis C infection may prevent the development of hepatocellular carcinoma and Hepatitis C-related cirrhosis. Data have shown sustained remission with this therapy.

Discussion:

A key theme of the discussion that followed was the efficacy of current public health approaches to reduction of Hepatitis C among intravenous drug users. A participant commented that the force of transmission of the virus renders current harm reduction strategies, specifically needle exchange programs, ineffective in limiting infection among intravenous drug users. A participant added his concerns. Both proposed that primary prevention of intravenous drug use may be the only effective approach at this time.

Primary prevention programs for Hepatitis B were also discussed, specifically universal infant vaccination as a prevention of cancer and other chronic sequelae of Hepatitis B. There was support for this, particularly since infected infants are known to have a 90% probability of developing chronic infection. A question was raised as to the cost effectiveness of adult vaccination, given low levels of chronicity in adult infection.

It was noted that recent Canadian data showed that, of 100 cases of acute HCV infection, 60% were injection drug users. The number two risk factor was drug snorting, followed by blood transfusion. There were no known risk factors in 30% of cases. There was a coment on the need for research to identify new risk factors in that 30%. Some behaviours possibly implicated are body piercing and tattooing.

A participant agreed with the desirability, from a public health perspective, for the reduction of these behaviours but questioned its feasibility. Another participant, citing that widespread treatment of HIV in gay men appears to have reduced the force of transmission in this population, suggested treatment as a possible approach to HCV infection, given the reference to sustained remission of HCV infection with anti-viral therapy. However, it was noted that 75% of those infected have multiple contra-indications for therapy and such an approach would place an extreme burden on current staffing resources, thereby limiting its practicality at this point.

"Is There a Microbial Etiology for Inflammatory Bowel Disease?"

Dr. Jamie Blanchard, Provincial Epidemiologist, Manitoba Health

Dr. Blanchard provided an overview of the current findings with respect to the possible microbial etiology of Inflammatory Bowel Disease (IBD) – both Crohn's Disease and Ulcerative Colitis – stating that at this time such an etiology remains speculative. Epidemiological and animal data do, however, suggest that there is an exogenous agent involved in the development of IBD.

IBD was uncommon in the early 20th century, with incidence increasing in the middle decades and reaching a plateau or decreasing subsequently. There is high variability of incidence with a North/South gradient and strong birth cohort effects. Such epidemiological dynamism, which is supported by animal studies, is suggestive of an external etiological agent.

Proposed microbial agents include measles and mumps viruses, *Mycobacterium avium paratuberculosis* (MAP), and rubella. Of these, measles has received the most interest and study. Dr. Blanchard characterized the epidemiological data on measles as intriguing but inconclusive and limited by methodological weakness. The strongest association

shown was with dual measles/mumps infection. One researcher has suggested a role for measles vaccination of young children. Dr. Blanchard noted that this has not been strongly supported by research.

Dr. Blanchard concluded by suggesting that the incompleteness and inconclusivity of the data argue the need for:

- expanded epidemiological data bases to explore associations with both viral exposure and measles vaccination
- use of newer technologies to look for microbes in tissue
- formation of multi-disciplinary teams to research the disease

Discussion:

The discussion raised two interesting points. First, that an observed lower incidence rate among First Nations people is seen both on and off reserves. Second, that a reported variability from area to area in Manitoba correlates with socioeconomic situation, higher socioeconomic status being associated with higher risk. The significance of this correlation is unknown, but bears further research.

NEUROLOGIC AND NEUROPSYCHIATRIC PANEL

Corona Viruses and the Development of Multiple Sclerosis

Dr. Pierre Talbot, Professor and Director, Human Health Research Centre, INRS-Institut Armand Frappier, Université du Québec, Laval & Pointe-Claire

Dr. Talbot opened by noting the difficulty in discerning definitive links between ubiquitous viruses and non-ubiquitous diseases, a challenge presented in the case of corona virus and multiple sclerosis (MS). He reported that, although associations have been noted between viruses and a number of neurological diseases, such links remain anecdotal at this time.

Corona virus is a respiratory virus responsible for 10-35% of common colds. It has been shown that by age 5, all individuals are seropositive for this pathogen, making causation difficult to prove and epidemiological evidence linking corona virus to MS inconclusive. Currently the etiology of MS is considered to be multifactorial. Research indicates a genetic susceptibility to MS. However, the concordance rate in monozygotic twins is only 25%, suggesting the existence of an exogenous environmental agent. This is supported by the existence of geographic high-risk areas, specifically a North/South gradient.

Dr. Talbot presented extensive data, from both animal research and molecular biological investigations of human neural cell cultures and tissues, that strongly implicate corona virus as a potential agent in MS. Molecular research is consistent with a probable mechanism being molecular mimicry. The T-lymphocytes of MS patients, for genetic reasons, may have a predisposition to be activated by both corona virus and myelin antigens. The data suggest that viral antigens in the periphery activate T-cells, which migrate to the CNS and there react with myelin antigen – a so-called "hit and run" mechanism. As recently proven, this can be exacerbated by viral persistence in the brain. This also provides a unifying mechanism explaining the anecdotal association of a variety of pathogens with MS.

Dr. Talbot concluded by pointing to the need for a large-scale sero-epidemiological study that links the immune response to a variety of pathogens with MS in a prospective way.

Discussion:

In the discussion, it was agreed that public health, in collaboration with clinical medicine and molecular biology, has an important role to play in the surveillance of this and other viruses. It was also agreed that vaccination could play a key role in the prevention of

chronic disease, including vaccination against viruses not currently linked to serious acute disease.

POTPOURRI OF CHRONIC DISEASES PANEL

Infections and Cancer

Dr. Sherri O. Stuver, Assistant Professor of Cancer Epidemiology, Harvard School of Public Health

Dr. Stuver provided a comprehensive summary of the current understanding of oncogenic infections, focusing on those that have been established as human carcinogens by the World Health Organization's International Agency for Research on Cancer (IARC). She set out the established infection-malignancy relationships, providing the evidence supporting these relationships.

Infection-related malignancies have been estimated by researchers at IARC to contribute significantly to the total incidence of cancer, representing 14.8% of cancer worldwide, 6.8% in developed countries. Dr. Stuver noted that the contribution of oncogenic infections to the total cancer burden is most pronounced in developing countries. However, infection remains a significant causative agent in the developed world. Of particular note in this context were the following relationships, which show the percentage of cancer cases attributable to a particular infection in developed countries:

- Human papillomavirus and cervical cancer (81%)
- Hepatitis B virus and liver cancer (23%)
- Hepatitis C virus and liver cancer (21%)
- *Helicobacter pylori* and stomach cancer (35%)

Central to the natural history of oncogenic infections is the ability of these organisms to establish latent or persistent infection. Many of the oncogenic viruses can integrate into the host genome; some also produce proteins that can disrupt the function of host genes/proteins that are important growth factors or tumour suppressors or that play a role in cell cycle control and apoptosis. In addition, persistent inflammation related to infection leads to continued cycles of cell destruction and replication, increasing the opportunity for mutations to occur, which transform cells into tumour cells.

Dr. Stuver pointed out that oncogenic infections are usually common infections, with oncogenesis a rare event. Risk of malignancy appears to be mediated by factors that affect the host immune response to the infection. These factors include age, severity and route of infection, host immune function, presence of co-infections and gender.

In conclusion, Dr. Stuver commented that prevention and control of oncogenic infections are worthwhile endeavors with respect to reducing cancer incidence, even in developed countries such as Canada and the United States.

Discussion:

In the discussion that followed, there was reference to the efficacy of programs of vaccination for HBV, and it was noted that vaccination for HPV would represent a major public health advance. It was also pointed out that there are technological difficulties in the development of vaccines, particularly for viruses such as HCV and HIV which mutate readily, thereby avoiding detection.

In conclusion, it was suggested that, with occurrence rates similar to those of cancers related to sedentary lifestyle and occupational factors, oncogenic infections are worthy of continued research. The efficacy of prevention programs such as protection of the blood supply in the cases of HIV and HCV, as well as HBV vaccination were also pointed out. Co-factors were referred to with respect to HPV/cervical cancer (multiple pregnancy, tobacco smoking, early age of first intercourse) that argue for the continued role of public education.

Infections and Arthritis

> **Dr. Robert Inman,** Director, Rheumatology Department, Toronto Hospital-Western Division

Dr. Inman discussed the relationship between gram negative infection and the development of chronic arthritis. Referring to epidemiologic data from a number of sources, Dr. Inman elucidated the current understanding of infection-induced arthritis as involving both infection and genetic susceptibility of the host. According to this model, infection by gram negative bacteria such as S*almonella typhimurium* and C*hlamydia trachomatis* results in chronic arthritis only in the presence of particular alleles at the HLA site.

The HLA site is involved in the interface between infection and the autoimmune response. Polymorphism exists at this site, with certain alleles conferring genetic susceptibility to arthritis. One suggestion is that these alleles result in a pathological response by recognizing an incorrect pathogen peptide, resulting in a different immune response pathway being activated.

Dr. Inman reported that, in those cases where chronic arthritis exists following infection, the joint structure itself appears to become a repository of microbial antigens thereby providing antigenic stimulation of the auto-immune response for a sustained period of time. Research on Chlamydia indicates the presence of bacterial proteins and lipopolysaccharides in the synovia of affected joints even when cultures are aseptic. This is of clinical importance in two ways. First, it implicates gram negative infection in what might be diagnosed as sero-negative, idiopathic arthritis. Second, it explains why the effectiveness of antibiotics such as tetracycline is dependent upon when they are administered, with effectiveness occurring only in the initial stages of infection.

Dr. Inman concluded by saying that we exist in a state of balance with a wide variety of microorganisms, with the autoimmune response being triggered when the combination of host susceptibility and presence of appropriate pathogens exists.

The Role of Viral Infection in Autoimmune Diabetes

> **Dr. Constantine Polychronakos,** Director, Paediatric Endocrinology & Metabolism, Montreal Children's Hospital

Dr. Polychronakos began by providing a compelling justification for diabetes being considered a major public health concern. Diabetes affects up to 5% of the population, is responsible for 8,000 deaths yearly and results in an annual cost of $9,000,000,000 in Canada. Autoimmune diabetes represents 5-10% of all diabetes but it contributes a disproportionately large proportion of serious morbidity.

Autoimmune diabetes is a multifactorial disorder with a strong genetic component, as shown by familial clustering and twin studies. That environmental factors also contribute is strongly supported by a relatively recent secular increase in incidence of diabetes in North America and Europe. In Finland, for example, a near doubling of incidence has occurred over the past two generations.

Dr. Polychronakos summarized the literature regarding possible environmental causes, concluding that viruses are important environmental contributors to diabetes. He then cited a number of representative studies that provide strong sero-epidemiologic evidence of an association between diabetes and enteroviruses, the virus most likely implicated in autoimmune diabetes being *Coxsackie B*. The viruses appear to trigger the autoimmune destruction of pancreatic beta cells, in a manner not yet understood. Dr. Polychronakos cautioned that, while some studies have indicated molecular mimicry and others the presence of viral superantigens as causal agents, the data remain conflicting.

In his summary, Dr. Polychronakos concluded that, although association of seropositivity and the presence of viral genome with diabetes has been demonstrated, this does not constitute conclusive evidence. A question remains as to whether the association reflects

a causal role for enteroviruses or simply some characteristic of the immune systems of diabetic individuals that makes them susceptible to both diabetes and enterovirus. Currently, although the association of diabetes with enterovirus infection seems to be unquestionable, a causal relationship has yet to be established.

Discussion:

In the discussion following, a question was raised regarding evidence of clustering of diabetes after Coxsackie outbreaks. The response indicated that the delay in seeing any observable effects makes it impossible to make such an association at present. It was suggested that a vaccine for Coxsackie would be valuable, if it indeed resulted in a decrease in autoimmune diabetes.

WRAP UP

Dr. Ian Gemmill

Dr. Gemmill noted that this symposium was unique and predicted that public health will be challenged to develop interventions in new situations as more associations between infection and chronic disease become established.

Dr. Gemmill then thanked those whose ideas and initiatives made the meeting possible, specifically crediting Drs. Shannon, Gully and Tepper at the Laboratory Centre for Disease Control, Health Canada for putting forth the agenda, and Gerry Dafoe and Mary Ahearn at the Canadian Public Health Association for arranging the meeting. He also thanked the scientific planning committee for their hard work in bringing together an impressive group of experts, who brought cutting edge knowledge about the etiology of these chronic diseases.

"WHERE DO WE GO FROM HERE?"

Dr. Paul Gully

Dr. Gully began by noting that bringing together those interested in communicable diseases and those interested in chronic diseases was novel and would perhaps be a model for more dialogue between different areas of medicine. He referred to Dr. Schabas's triangle of host-agent-environment, emphasizing the need to remember that all points of the triangle must be considered.

Dr. Gully then stated his belief that public health would have to prioritize which idiopathic chronic diseases would be appropriate to pursue. Issues such as burden of illness and etiology will be important factors in this decision-making process. He argued that when risk factors are clarified, public health has a role to play in asking laboratory scientists and epidemiologists to seek answers that may improve prevention and control of these precipitating infectious diseases in the future.

In areas where there appear to be answers, Dr. Gully expressed the need to work on the availability of resources. He urged that care be taken when answers appear to be found, and that the implications of these answers need to be well understood. He specifically cited vaccination as an area in which the potential results of widespread use be well considered before application.

Dr. Gully urged public health professionals to keep abreast of new developments and expressed the hope that the Canadian Institutes of Health Research will contribute to strengthening this process. He proposed that the report of this conference may lead to

epidemiological research that would not only aid the public health professionals, but could aid in the discussion of health policy and public health policy.

Dr. Gully concluded by thanking the speakers, participants and the organizing committee, particularly Mary Ahearn for her energetic and productive efforts in organizing this conference.

Speakers

Dr. James Blanchard
Provincial Epidemiologist, Manitoba Health, 300 Carleton Street, Room 4058, Winnipeg, MB, R3B 3M9

Dr. James Blanchard has been the Provincial Epidemiologist at Manitoba Health since 1992, and Assistant Professor in the University of Manitoba's Department of Medical Microbiology since 1992, and in the Department of Community Health Sciences since 1998. He received his M.D. from the University of Manitoba in 1986 and his Ph.D. in Epidemiology from Johns Hopkins University in 1997. For the past five years, he has been collaborating on a study on the epidemiology and etiology of Inflammatory Bowel Disease.

Dr. Lee Ann Campbell
Associate Chair, Pathobiology, University of Washington, F161E Health Sciences Building, PO Box 357238, Seattle, WA, 98195-7238

Dr. Lee Ann Campbell is Professor and Associate Chair in the Department of Pathobiology at the University of Washington in Seattle. She received her Ph.D. in Microbiology from the Pennsylvania State University in 1982. She was a Postdoctoral Fellow at the University of Rochester where she investigated DNA repair and mutagenesis of *Neisseria gonorrhoeae*. Dr. Campbell is recognized as one of the pioneers in the study of *Chlamydia pneumoniae*, having studied this organism since she joined the University of Washington in 1985, and has published extensively in this field. Last year Dr. Campbell was a member of the U.S. delegation to a joint U.S.-Russian symposium on the basic biology of cardiovascular and pulmonary research.

Dr. François Coutlée
Microbiologiste, Centre hospitalier, Université de Montréal-Notre Dame, 1560, rue Sherbrooke est, Montréal, QC, H2L 4M1

Dr. François Coutlée is Adjunct Professor in the Department of Oncology in the Faculty of Medicine at McGill University, and Assistant Chief of Research at the Centre Hospitalier of the Université de Montréal, where he is Associate Professor in the Department of Microbiology and Immunology. He holds specialties in Internal Medicine and Infectious Disease in Canada, and is licensed by the Board of Examiners in the U.S. Dr. Coutlée's area of interest is the microbiology of infectious diseases and he is widely published in the area of microbiology and infectious disease.

Dr. I. William Fong
Director, Infectious Diseases, St. Michael's Hospital, 30 Bond Street, Toronto, ON, M5B 1W8

Dr. I. William Fong is Professor of Medicine at The University of Toronto and Director of the Division of Infectious Disease at St. Michael's Hospital in Toronto. He received his Doctorate in General Medicine in 1969 and his fellowship training and certification in Infectious Disease in Seattle in 1976. Dr. Fong's research activities have concentrated on the pathogenesis of vaginal candidiasis, AIDS-related complications, neuroendocrine response in HIV disease, and most recently the relationship of *Chlamydia pneumoniae* with atherosclerosis.

Dr. David Fredricks
Division of Infectious Diseases, Stanford University Medical Center & VA Palo Health Care System, S-156, Stanford, CA, 94305-5107

Dr. David Fredricks is a Research Associate in the Division of Infectious Diseases at Stanford University. He received his M.S. from Stanford University in 1984 and his Doctorate in Medicine from Case Western Reserve University in 1990. He is certified in Internal Medicine and Infectious Diseases. Dr. Fredricks studies how nucleic acid sequences can be used to detect and identify microbial pathogens, particularly novel or uncultivated microbes.

Dr. Robert Inman
Director, Rheumatology Department, Toronto Hospital-Western Division, 399 Bathurst Street, Toronto, ON, M5T 2S8

Dr. Robert Inman is Professor of Medicine and Immunology at the University of Toronto, and Director of the University of Toronto Arthritis Centre of Excellence at the University Health Network. Dr. Inman did his Undergraduate Degree at Yale University and received his MD from McMaster University. He did his residency at Vanderbilt University and his fellowship in Rheumatology at Cornell University.

Dr. Kelly Kaita
Director of Viral Hepatitis Investigation Unit, Manitoba Health Sciences Centre, University of Manitoba, 820 Sherbrooke Street, Winnipeg, MB, R3A 1R9

Dr. Kaita is a graduate of Internal Medicine from the University of Manitoba. He completed his degree in Liver Diseases at the University of Manitoba and the University of Western Ontario. After completion of his training he joined the University of Manitoba Department of Medicine, Section of Gastroenterology. He is currently the Director of the Viral Hepatitis Investigative Unit of Manitoba. He is involved in many research-related activities relating to viral hepatitis.

Dr. David Patrick
Director, Epidemiology Services, B.C. Centre for Disease Control, 655 West 12th Avenue Rm. 2104, Vancouver, BC, V5Z 4R4

Dr. David Patrick is Assistant Professor of Medicine and Director of Communicable Diseases Epidemiology Services at the University of British Columbia Centre for Disease Control. He received his MD from the University of Ottawa in 1986 and specialized in Internal Medicine and Infectious Diseases at the University of Ottawa and the University of British Columbia. He completed a Masters in Health Sciences at the University of British Columbia in 1994. Between 1991 and 1999, Dr. Patrick was the Associate Director for STD/AIDS Control at the BC Centre for Disease Control.

Dr. Constantin Polychronakos
Director, Paediatric Endocrinology & Metabolism, Montreal Children's Hospital, 2300 Tupper Street, Room D371, Montreal, QC, H3H 1P4

Dr. Polychronakos is Professor in the Departments of Pediatrics and Human Genetics at McGill University, and Director of the Endocrinology Division at Montreal Children's Hospital where he also heads the Endocrine Genetics Laboratory. Dr. Polychronakos received his MD from Aristotelian University in Greece, and trained in Pediatrics at Dalhousie University and Pediatric Endocrinology at l'Université de Montréal. He trained in endocrine research at the McGill Polypeptide Hormone Laboratory. His major area of research is the genetics of autoimmune diabetes.

Dr. Paul Sandstrom
Associate Director of the Bureau of HIV/AIDS, STD and TB, LCDC, Health Canada - *detailed address not available.*

Dr. Sandstrom has been the Associate Director of the Bureau of HIV/AIDS, STD and TB with Health Canada since 1999. In this role, he has been responsible for planning, directing and managing laboratory research and surveillance programs as part of the National HIV/AIDS Strategy in Canada. He received his Ph.D. from the Department of Immunology at the University of Manitoba where he conducted research on the regulation of tumour progression by the immune system. He did post-doctoral research in North Carolina and was a Visiting Fellow at the HIV/AIDS and Retrovirology Branch of the Centers for Disease Control and Prevention in Atlanta, Georgia, where he worked as a staff scientist from 1996-1999.

Dr. Richard Schabas
Head of Preventive Oncology, Cancer Care Ontario, 256 Lytton Boulevard, Toronto, ON, M5N 1R6

Dr. Richard Schabas is the Head of the Division of Preventive Oncology at Cancer Care Ontario (CCO). His responsibilities include cancer surveillance, cancer prevention, screening and preventive oncology research. Prior to joining CCO, Dr. Schabas was Ontario's Chief Medical Officer of Health for ten years.

Dr. Sherri O. Stuver
Assistant Professor of Cancer Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, SPH3-826, Boston, MA, 02115

Dr. Sherri Stuver is Assistant Professor of Cancer Epidemiology in the Department of Epidemiology at the Harvard School of Public Health, where she has been on faculty since 1994. She received her doctoral degree in Epidemiology in 1991 from the Harvard School of Public Health. Her primary area of research is the study of oncogenic viruses and their related malignancies. She is the Principal Investigator of a community-based, prospective cohort study of the natural history of human T-lymphotropic virus type I and hepatitis virus infections in an endemic population in Japan.

Dr. Pierre Talbot
Professor and Director of Human Health Research Centre, INRS-Institut Armand Frappier, Université de Québec, Pointe Claire, 245 Hymus Blvd., QC, H9R 1G6

Dr. Pierre Talbot is a Professor in the Laboratory of Neuroimmunology and Director of the Human Health Research Centre, INRS-Institut Armand-Frappier at the University of Quebec, where he has been a member of the faculty since 1984. Dr. Talbot received his B.Sc. in Biochemistry at Laval University in 1977 and his Ph.D. from the University of British Columbia in 1981. He did post-doctoral studies in the Department of Immunology at Scripps Clinic and Research Foundation (now Scripps Research Institute) in La Jolla, California.

Dr. Andy Wielgosz
Head, Division of Cardiology, Ottawa Hospital, General Campus, Room 4128, 501 Smyth Road, Ottawa, ON, K1H 8L6

Dr. Andy Wielgosz is a Clinical Cardiologist at the Ottawa Hospital-General Campus and is Professor at the University of Ottawa. He serves as consultant for the Laboratory Centre for Disease Control, Health Canada, working on the Canadian Heart and Stroke Surveillance System. Dr. Wielgosz is also the Director of the World Health Organization Collaborating Centre on Global Cardiovascular Disease Surveillance.