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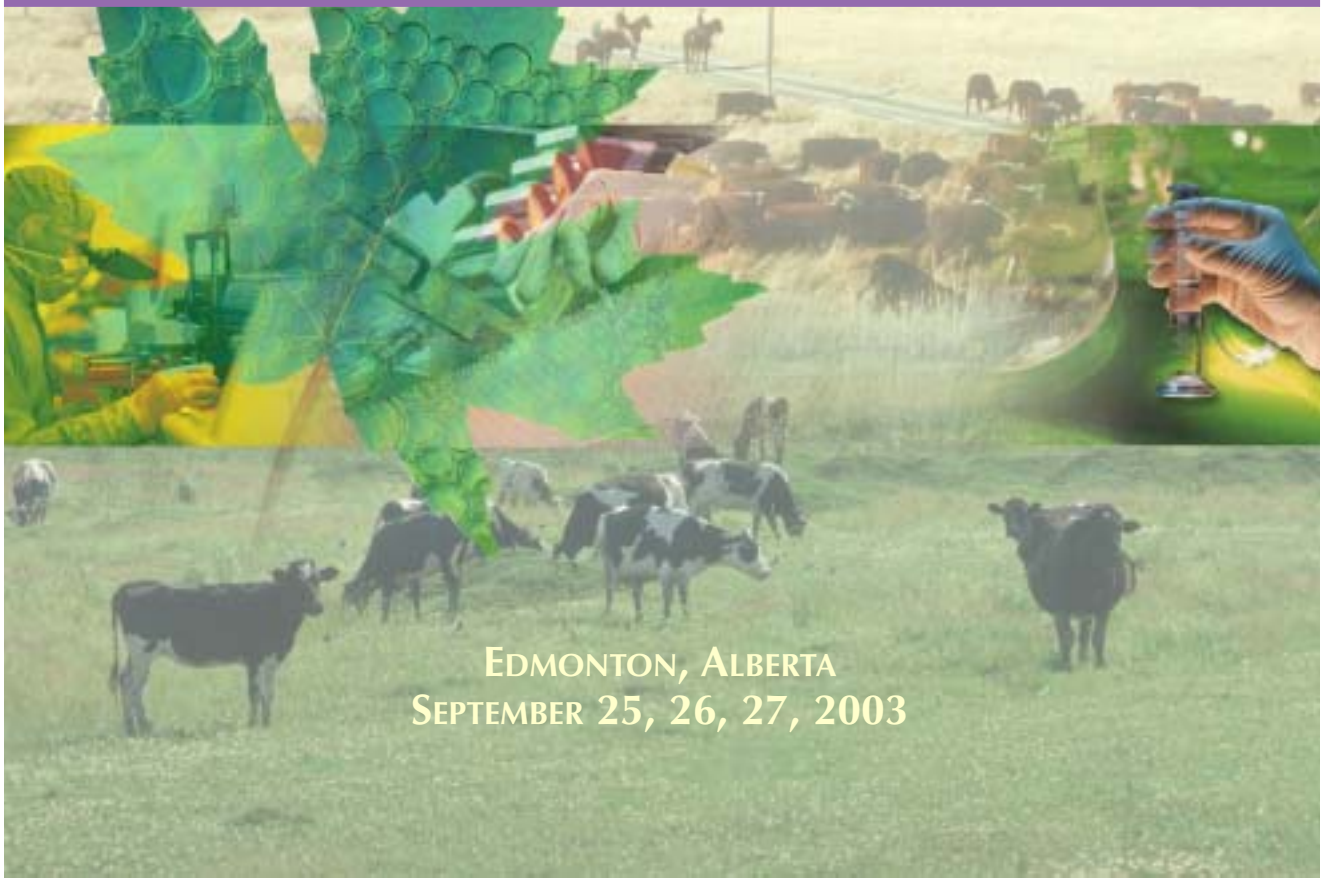
Meeting the Challenge of PRION DISEASES

CONFERENCE PROCEEDINGS AND INVITATIONAL RESEARCH PLANNING WORKSHOP REPORT



EDMONTON, ALBERTA
SEPTEMBER 25, 26, 27, 2003

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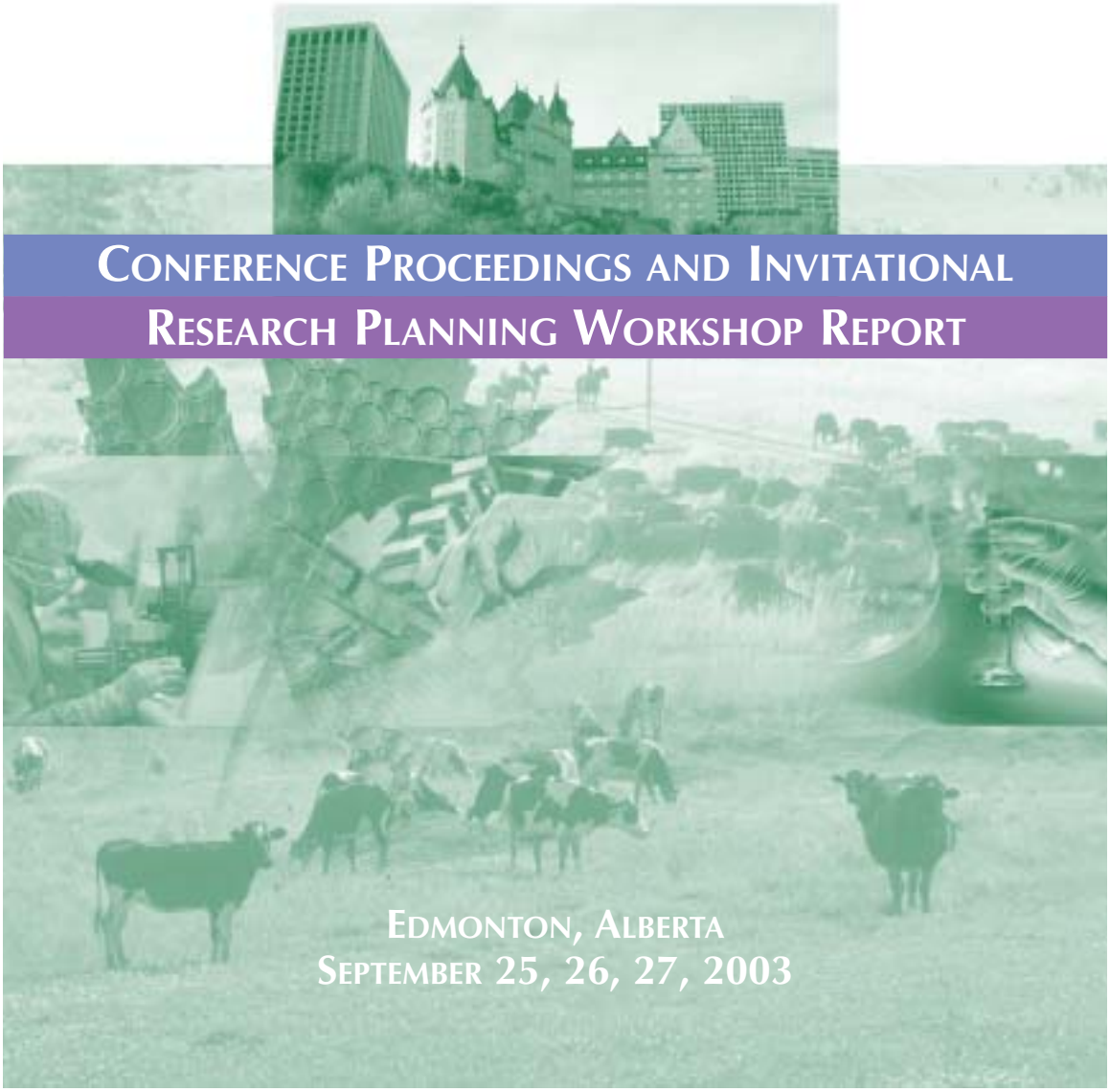

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CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute, Suite 214
The University of Western Ontario
1400 Western Road
London, ON N6G 2V4
Fax (519) 661-4226
www.cihr-irsc.gc.ca

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Preface

In the last two decades of the twentieth century, the staggering impact of the prion disease bovine spongiform encephalopathy (BSE) on human and animal health and economics was felt in the United Kingdom. Recognizing that the potential implications of BSE were a concern to Canadian health and economics as well, Health Canada held several meetings to discuss prion diseases. The meetings underscored the necessity of developing a long-term plan in Canada to address the health, economic, and research challenges posed by these diseases. This conference was born out of that necessity.

Meeting the Challenge of Prion Diseases was initially planned for the fall of 2001. The attacks on the World Trade Center and Pentagon, and the subsequent anthrax poisonings in the United States, however, had the conference organizers scrambling to address what had suddenly become a more pressing issue: bioterrorism and the diseases it potentially could unleash. Rescheduled for April 2003 in Toronto, the conference next fell victim to Nature's own brand of bioterrorism as the SARS epidemic struck the Greater Toronto Area, and the World Health Organization issued a travel advisory against the city. The conference was once again postponed; yet the urgent need to address prion diseases and their impact was dramatically emphasized just one month later in May 2003, when Canada's first case of BSE was identified. Unfortunately, these delays meant that when the first BSE cow was identified in Alberta, we still had no long-term plan in place to deal with it.

Bringing together scientists, students and health workers from universities, institutes and governments in Canada, the United States and Europe, the conference was finally held in Edmonton, Alberta, on Thursday, September 25 and Friday, September 26, 2003.

Following the research conference, a working group met on Saturday, September 27, to determine how to enhance Canadian research opportunities and results related to prions and prion diseases. The conference program was planned to address research across four themes: biomedical, clinical, health services and systems, and the health of populations as it is affected by societal, cultural and environmental influences.

The results of the conference and working group are contained in this report. Important areas of research and capacity building have been identified, and plans to address them have been put in place. The need remains to follow up on these plans; yet the current ability to do so is minimal, as we still do not have a Canadian capacity to address prion disease in terms of diagnostics, surveillance, monitoring therapy, and treatment. With only one biocontainment level four facility in Winnipeg and relatively few level three facilities across the country, we lack sufficient infrastructure to do the work. We need to build capacity and bring people into it, but we also need to build the facilities. We cannot do it without the people, and we cannot do it without the facilities. It remains to be decided how we will sustain such facilities once the immediate threat is diminished.

While prion disease and its implications fall within the mandate of the CIHR, they are also within the Canadian government's mandate regarding human health, economic development, and innovation. Indeed, all stakeholders and policy makers should consider this an area of urgent need to address. Both public and private sectors should be working hand in hand to give the financial support and to do the research. We must put policies in place so we are ready for the future, and these policies should be based on scientific evidence. The purpose of the conference and its ensuing report, therefore, is to inform how that policy can be developed and implemented based on science. The federal and provincial governments plus the private sector all share the responsibility to put this together.

Fortunately, our policy makers have been listening to our needs. In the time it has taken to prepare this report since the conference was held in September 2003, the federal government tabled its new budget, and based on information made available through this meeting and other sources, has committed an additional $5 million a year through the Networks of Centres of Excellence program to support research on BSE and other TSEs. It is a step in the right direction to follow up on our plans, build the capacity and infrastructure we need, and secure a position for Canada as a forerunner in prions research.

The success of any enterprise depends on the efforts of the people involved in its planning, implementation and follow-up. I would like to thank the following groups and individuals for their contributions to the Meeting the Challenge of Prion Diseases Conference and Invitational Planning Workshop, and the preparation of this report. We are extremely grateful for their expertise and assistance.

- Dr. Neil Cashman, Professor, Centre for Research in Neurodegenerative Diseases, University of Toronto and head of the Organizing Committee
- The Organizing Committee, comprised of Dr. Arumaga Balachandran, Dr. Michael Coulthart, Dr. Antonio Giulivi, Ms. Carol Richardson, Dr. Ron Rogers, and Ms. Francine Villeneuve
- Dr. Alan Bernstein, President, CIHR
- Dr. Judy Bray, Assistant Director, Special Projects, CIHR Institute of Infection and Immunity
- Mr. Bruce Moor, Assistant Director, CIHR Institute of Infection and Immunity
- Dr. Kevin Keough, Chief Scientist, Health Canada
- Ms. Janet Weichel McKenzie, Media Specialist, CIHR
- Strachan•Tomlinson and Associates: Mr. Peter Ashley, Project Management and Ms. Dorothy Strachan, Process Design and Facilitation
- Ms. Nikki Kelvin, Professional Writer

EXECUTIVE SUMMARY

The **Canadian Institutes of Health Research Institute of Infection and Immunity (CIHR-III)**, in partnership with the CIHR Institute of Population and Public Health and Health Canada, sponsored Meeting the Challenge of Prion Diseases, an international research conference, in Edmonton, Alberta, at the Fairmont Hotel Macdonald on Thursday, September 25 and Friday, September 26, 2003. The conference brought together scientists, students, and health workers from universities, institutes, and governments in Canada, the United States, and Europe. Following the research conference, a working group met on Saturday, September 27, to determine how to enhance Canadian research opportunities and results related to prions and prion diseases.

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are a group of fatal neurological diseases of humans and animals characterized by deterioration of the central nervous system which causes vacuoles (sponge-like holes) in the brain. Human variants include Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), Gerstmann-Sträussler-Scheinker disease (GSS), and Kuru. Prion diseases in animals consist of bovine spongiform encephalopathy (BSE), chronic wasting disease in deer and elk, feline spongiform encephalopathy, scrapie in sheep, and transmissible mink encephalopathy (TME).

Dr. Bhagirath Singh, Scientific Director for the CIHR Institute of Infection and Immunity, related CIHR's mandate—to identify and study diseases and their impact on human health—to the conference's four main goals: **1) to identify research questions and health challenges of prions, 2) to determine key areas for interdisciplinary prion research, 3) to foster new research efforts and opportunities in prion diseases in Canada and internationally, and 4) to lay the background for a working group to discuss possible courses to establish a Canadian research agenda for prion diseases.**

CONFERENCE PROCEEDINGS

SESSION I: PRIONS AND PRION DISEASES

Chair: Dr. Neil Cashman, Centre for Research in Neurodegenerative Diseases, Toronto, Canada

The speakers in Session I provided a compendium of Prions and Prion Diseases, looking at their history and development, phenotypes and phenomenology, pathology, and genetics in human and animal populations. **Dr. Paul Brown** from the National

Institutes of Health, USA, presented the keynote address, Prions and Prion Diseases: An Overview. He explained the history of prion studies beginning with scrapie, which was well established and identifiable as an infectious disease in Europe by 1756, up to the present. **Dr. Richard Knight,** of the CJD Surveillance Unit, Edinburgh, United Kingdom, spoke on Prion Diseases: Phenotypes and Phenomenology, describing the phenotypes and phenomenology of prion diseases, focusing mainly on the four types of CJD, sporadic, genetic, iatrogenic and variant. **Dr. Herbert Budka,** University of Vienna, Vienna, Austria, discussed the Pathology of Human Prion Diseases, noting the importance of neuropathology in both the surveillance and research on prion diseases**. Dr. Maura Ricketts,** Health Canada, chaired the final presentation in Session I, in which **Dr. Michael Coulthart,** also from Health Canada, presented Genetics of Prion Diseases: Overview and Comparative Perspectives. He gave a summary of the genetics of human prion diseases and presented the results from the Canadian BSE case.

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SESSION II: PRIONS AND PUBLIC HEALTH

Chair: Dr. Michael Coulthart, Chief, National Laboratory for Prion Diseases, Health Canada

In Session II, the speakers focused on Prions and their relationship to Public Health, investigating such issues as emerging animal prion diseases, the epidemiology, transmission, and immunobiology of prion diseases, and the Canadian BSE case and the policy framework surrounding it. **Dr. Ray Bradley,** CBE, BSE Consultant, United Kingdom, discussed Emerging Animal Prion Diseases. Dr. Bradley defined the term *emerging disease*, and applied his definition against the major animal TSEs in chronological order of their discovery and appraised the risk to humans for each of the diseases. **Dr. Maura Ricketts,** Health Canada, spoke about the Epidemiology and Risk Factors of Prion Diseases, discussing the epidemiology of BSE from the perspective of public health policy, focusing on two important routes of transmission, food and vaccines, to illustrate the complexity of the problems that they present. **Dr. Paul Brown,** National Institutes of Health, USA, addressed issues surrounding the Iatrogenic Transmission of Prion Diseases, Including Blood, noting that the iatrogenic potential of blood is minimized by the fact that it is an inefficient route. No cases of CJD in a recipient of a blood product or a blood component have yet been identified. **Dr. Ron Rogers** of Health Canada presented information on The Canadian BSE Case and Public Health, outlining the steps taken in the identification of Canada's 2003 BSE case and government response to it. The Policy Framework and Transparency in Relation to Human TSEs was presented by **Dr. Paul Gully** from Health Canada. Dr. Gully described Health Canada's purpose and strategic plan, noting that its decision-making framework is a collaborative process by decision makers involving all interested and affected parties.

SESSION III: NEW CHALLENGES OF A PROTEIN-ONLY AGENT

Chair: Dr. Maura Ricketts, Senior Medical Advisor, Blood Safety Surveillance and Health Care Acquired Infections Division, Health Canada

Session III gave consideration to New Challenges of a Protein-Only Agent, examining the possibilities for rapid diagnosis of BSE, prion decontamination, and prion research infrastructure. **Dr. Jean-Philippe Deslys** of the Atomic Energy Commission, France, spoke about Rapid Diagnosis of BSE. His studies evaluating the "Biorad" BSE assay found that this test was 10 to 30 times more sensitive than the other three BSE assays. **Dr. David Taylor,** Institute for Animal Health Neuropathogenesis Unit, Edinburgh, United Kingdom, discussed Prion Decontamination, addressing the inherent problems in finding effective means to inactivate the infectious agents that cause transmissible spongiform encephalopathies. **Dr. Robert Rohwer** from the Veterans Administration Medical Center, Maryland, USA, presented issues surrounding Prion Research Infrastructure, noting that TSE research requires biocontainment level 3 (BL3) facilities designed for animal studies equipped with state-of-the-art instrumentation, access to reagents and materials, and researchers and staff with TSE expertise.

SESSION IV: PRION SCIENCE AND HEALTH

Chair: Dr. Antonio Giulivi, Director, Blood Safety and Health Care Acquired Infections Division, Health Canada

In Session IV, Prion Science and Health was discussed. The morning session consisted of four presentations. **Dr. Inga Zerr,** CJD Surveillance, Neurologische Klinik, Universitatskilikum Gottingen, Germany, provided information on the Diagnosis of Prion Diseases, explaining the differences in clinical features between variant and sporadic CJD. **Dr. Byron Caughey,** National Institutes of Health, USA, spoke about the Treatment of Prion Diseases, describing studies in which he performed high throughput screening of a library of 2,000 small molecular weight compounds for inhibitory properties of PrP conversion from a protease sensitive to a protease resistant state using the RML and 22L strains. **Dr. Neil Mabbott,** Institute for Animal Health, Edinburgh, United Kingdom, presented Immunobiology of Prions 1: Cells. Dr. Mabbott has demonstrated that follicular dendritic cells are important for the early accumulation of prions in lymphatic tissue in a mouse model of scrapie disease. **Dr. Neil Cashman,** University of Toronto, Canada, continued the discussion of the Immunobiology of Prions with a related presentation on Antibodies. Dr. Cashman's studies indicate that YYR motifs may be ideal therapeutic and diagnostic targets, and antibodies directed against this motif may be an ideal therapeutic.

In the afternoon, five talks were presented. **Dr. David Westaway,** University of Toronto, Canada, discussed The Prion Protein Homolog Doppel. The results of his studies question some of the currently held views that Dpl and PrP interact with

proteins outside of the cell. **Dr. Andrea Leblanc** from McGill University, Canada, addressed issues surrounding Prions and Apoptosis. Dr. Leblanc showed that the normal PrP protein provides a protective effect to neurons when they come under oxidative stress or when the cell death inducing protein Bax is present. **Dr. Witold K. Surewicz,** Case Western Reserve University, Ohio, USA, discussed the Biophysics of Prion Proteins and explained the folding properties of prion proteins. **Dr. Catherine Bergeron,** from the University of Toronto, presented on Lesion Profiling, noting that examination of the lesions in various sections of the brain showed that lesion profiling alone cannot predict the molecular phenotype of CJD though four groups could be recognized, Type 1, Type 2, MM2, and vCJD, and lesion profiling could reliably identify new prion strains. In the last presentation of the conference, **Dr. Surachai Supattapone,** Dartmouth Medical School, Hanover, New Hampshire, USA, discussed Host Factors Required for Amplification of Protease-resistant PrP Molecules *in vitro*. Dr. Supattapone was able to amplify PrP^{Sc} greater than 10 fold from a mixture of PrP^{Sc} and PrP^{C} proteins. He further showed that the amplification is prion strain specific and is dependent on time, temperature and free thiol groups. Interestingly, Dr. Supattapone identified that the process of amplification requires additional cell factors, namely RNA.

INVITATIONAL RESEARCH PLANNING WORKSHOP

Following the research conference, a working group met on Saturday, September 27, to determine how to enhance Canadian research opportunities and results related to prions and prion diseases. The consultation's objectives were to summarize key learnings and implications of the conference for future Canadian research; develop draft recommendations on five or six priority strategic research themes for Canadian researchers over the next 10 years; identify opportunities to build capacity through supportive infrastructures; and enhance linkages and interactions among participants.

For the purpose of this workshop, strategic research themes were defined as prions-related research areas and applications central to the reduction of the burden of these diseases in Canada. Research themes were required to meet the following criteria:

- Have population/public health significance
- Focus on strategic knowledge and health gaps
- Build on and develop Canadian strengths
- Involve multidisciplinary, integrated approaches
- Provide an opportunity for international collaboration and impact
- Contain defined questions focused on achievable endpoints

Volunteer leaders each focused on one of four questions to stimulate the plenary session. **Dr. Kumanan Wilson** led a discussion based on the question, *What international research priorities are currently in place?* Replies included the need for biomedical research into prion diseases, capacity building, knowledge translation and communication, agricultural and wildlife research and economic impact of prion diseases. **Dr. Paul Gully**'s presentation focused on the question, *What are the major health challenges of prion diseases?* He emphasized that the overall challenge is to educate politicians and the public that although epidemics may occur that we cannot prevent, the expertise must be in place to respond when they happen. Prion stakeholders need to be where policy is being made to have an impact on decision making. Investigating the question, *What are the major unanswered questions in the basic science of prion diseases,* **Dr. Neil Cashman**'s presentation elicited a lively discussion on a number of contentious issues that are related to prion basic science, including the nature of the prion hypothesis in general, whether there is a need to continue research into defining the infectious protein, and whether focusing on prions may be too narrow an approach as they may be part of a broader range of misfolding proteins or connected to viral agents. Consideration of the final question, *What are Canada's strengths and gaps (opportunities) in relation to research on prion diseases,* was led by **Dr. Michael Coulthart**, who opened discussion in this area with his description of a three-part focus on approach, issues and assets.

From these discussions, priority research themes and capacity building priorities, as well as strategies with which to deal with them, were established. The participants agreed that the following research themes (alphabetical order) merited investigation: applied CWD pathogenesis; ecology (the relationship of humans to prions and the environment); testing methods; infectivity, prevention and treatment of prion diseases; rendering and decontamination research in various settings such as hospitals and farms; and risk assessment, communication and socio-economic impact, including public health policy and impact. Identified capacity building priorities included the creation of a national virtual network or institute for laboratories or people; the development of a Canadian Prions Institute that contains a common P3 facility or training centre; support for recruiting and maintaining highly qualified personnel for lab support; and the creation of a virtual interdisciplinary forum to facilitate comprehensive and integrated approaches to issues such as policy. The participants suggested the following strategies for implementing these research themes and capacity building: i) build on Canada's neuroscience capacity; ii) create funded exchange programs with other countries; iii) provide more longer-term funding for basic research; and iv) develop a mechanism for applying for peer-reviewed funding and infrastructure.

INTRODUCTION

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of fatal neurological diseases of humans and animals. They are characterized by deterioration of the central nervous system which causes vacuoles (sponge-like holes) in the brain. Human variants include Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), Gerstmann-Sträussler-Scheinker disease (GSS), and Kuru. Prion diseases in animals consist of bovine spongiform encephalopathy (BSE), chronic wasting disease in deer and elk, feline spongiform encephalopathy, scrapie in sheep, and transmissible mink encephalopathy (TME). Although some of these diseases, such as scrapie, have been recognized since the middle of the eighteenth century, the recent emergence of BSE worldwide, particularly in North America, has caused great concern for their economic impact as well as their possible effects on public health.

In response to these concerns, the **Canadian Institutes of Health Research Institute of Infection and Immunity (CIHR-III)** in partnership with the **Institute of Population and Public Health** and **Health Canada** sponsored **Meeting the Challenge of Prion Diseases**, an international research conference. Held in Edmonton, Alberta, at the Fairmont Hotel Macdonald on Thursday, September 25 and Friday, September 26, 2003, the conference brought together scientists, students, and health workers from universities, institutes, and government in Canada, the United States, and Europe.

The conference was opened by **Dr. Bhagirath Singh, Scientific Director for the CIHR Institute of Infection and Immunity**. After welcoming the speakers, participants, and organizers, Dr. Singh observed that the conference was necessary to answer both scientific questions as well as public concerns about prion diseases. Dr. Singh noted that the meeting was about more than just prion disease itself. He emphasized that it was also about gaining a better understanding of what prions are and what they do, as well as recognizing the individuals engaged in prion research in Canada and across the globe. He stressed that there is still much to learn about the science of prion diseases and that it is important for Canada to do its share in this work.

Dr. Singh reiterated CIHR's mandate to identify and study diseases and their impact on human health. In keeping with these objectives, the purpose of the conference was to address four main issues: **1) to identify research questions and health challenges of prions, 2) to determine key areas for interdisciplinary prion research, 3) to foster new research efforts and opportunities in prion diseases in Canada and internationally, and 4) to lay the background for a working group to discuss possible courses to establish a Canadian research agenda for prion diseases.**

The conference began with a head start in meeting objective number three as the Institute hosted eight new researchers who received awards to attend the symposium and meet with world experts in the field.

A working group that included Canadian clinicians, researchers, decision makers and an expert from the USA met following the research conference. Focusing on the following four key questions, this group sought to determine how to enhance Canadian research opportunities and results related to prions and prion diseases:

- *What international research priorities are currently in place?*
- *What are the major health challenges of prion diseases?*
- *What are the major unanswered questions in the basic science of prion diseases?*
- *What are Canada's strengths and gaps (opportunities) in relation to research on prion diseases?*

To furnish the background to address these questions, the conference was structured around four important areas in prion research. In Session I, the speakers provided an overview of **Prions and Prion Diseases**, looking at their history and development, phenotypes and phenomenology, pathology, and genetics in human and animal populations. The speakers in Session II focused on **Prions and Their Relationship to Public Health**, investigating such issues as emerging animal prion diseases; the epidemiology, transmission, and immunobiology of prion diseases; and BSE in Canada and the policy framework surrounding it. Session III gave consideration to **New Challenges of a Protein-Only Agent**, examining the possibilities for rapid diagnosis of BSE, prion decontamination, and prion research infrastructure. In Session IV, **Prion Science and Health** was discussed. Diagnosis and treatment of prion diseases, the immunobiology of prions, and the prion protein homolog doppel made up the morning sessions. In the afternoon, talks on the biophysics of prion proteins, lesion profiling in CJD, and host factors required for amplification of protease-resistant PrP molecules *in vitro* were presented. The program agenda, presentation abstracts, and speaker biographies appear in Appendices II, III, and IV of this report.

CONFERENCE PROCEEDINGS

Panel Presentations
Thursday, September 25, 2003

SESSION I: PRIONS AND PRION DISEASES

Chair: Dr. Neil Cashman Centre for Research in Neurodegenerative Diseases, Toronto, Canada

Session I provided the background on prions and prion diseases upon which to build a foundation for the rest of the conference. After noting the coincidence of the timing of the conference with recent news reports of cases of prion disease in both humans and animals, **Dr. Neil Cashman** from the **Centre for Research in Neurodegenerative Diseases, Toronto, Canada,** introduced the keynote speaker, **Dr. Paul Brown.** At the conclusion to Dr. Brown's talk, Dr. Cashman presented him with a commemorative plaque acknowledging both his keynote address at the conference as well as his contribution to prion research over the years.

Prions and Prion Diseases: An Overview

Dr. Paul Brown, Senior Investigator, Laboratory of Central Nervous System Studies, National Institutes of Health, USA

Dr. Brown's keynote address provided an overview of the history of prion research. Today's BSE studies began with early research on scrapie, which was well established and identifiable by the middle of eighteenth century in Europe. It was mentioned in both the English parliament and a German manual on veterinarian medicine in the 1750's, which gave a good clinical description of the disease, including the observation that it is contagious in sheep).

During the mid-nineteenth century most literature on scrapie came from France where veterinarians made extensive studies of the disease. Benoit, for example, recognized spongiform change in the spinal cord. By the early nineteenth century, two other French investigators, Cuille and Chelle (1936) built on Benoit's work and determined that scrapie had an incubation period that could be as long as two years.

In the 1920s Jakob and Creutzfeldt described what is now called Creutzfeldt-Jakob Disease. Through the 1950s-1960s, a gap existed between clinicians studying CJD and veterinarians studying scrapie since neither group was aware of the other. This situation changed when Gajdusek introduced Kuru, a disease isolated to the Fore natives of New Guinea, to the Western world, and the veterinarian Hadlow saw the connection between CJD and Kuru in 1959.

Early scrapie researchers thought the disease was host-specific to sheep and goats, but experiments by Chandler (1961) adapted sheep scrapie to laboratory mice, opening the floodgates to research on the transmissibility of TSEs. Between 1966 and 1968, Kuru was experimentally transmitted to primates, as was CJD.

In the early 1980s Merz identified the scrapie associated fibril, or prion rod as it was later termed by Prusiner. Proceeding from the idea that the infectious agent may not include a nucleic acid (based on Alper's studies of radiation resistance), Prusiner worked to purify the prion rod to obtain a preparation that was almost pure protein, which permitted identification of its encoding gene in 1985, which to everyone's surprise turned out to reside in the host and not a foreign invader. In 1990 the first mutation was described and today more than 30 mutations that cause a variety of disease phenotypes are recognized.

In 1986, BSE was first recognized in the UK. Cases of BSE peaked around 1992 and are now falling off to the point that the disease could possibly disappear altogether. Ten years after the first case of BSE was identified, vCJD was recognized in humans, and it, too, now looks to be on its way out. Although these forms of TSE are declining, one other TSE seems to be on the rise. In 1970, chronic wasting disease (CWD) was found in mule deer in only one American state but by 1980 it had spread to a second state and from domestic to wild herds. As the only spongiform encephalopathy existent in the wild, it is a troubling issue because wild roaming animals cannot be controlled. By 2000 CWD appeared in three more states and Saskatchewan in both captive and wild herds, and in elk and white-tail deer as well as mule deer. By 2003 it was found to have spread to Alberta and three more states.

Prions research in the 21st century should focus on three major goals:

To find an ante-mortem diagnostic screening test for infected people and animals
To identify the infectious agent, and if a protein, the mechanism of replication
To develop preventative or curative therapy

Prion Diseases: Phenotypes and Phenomenology

Dr. Richard Knight, Clinical Neurologist, CJD Surveillance Unit, Edinburgh, United Kingdom

Dr. Knight described the phenotypes and phenomenology of prion diseases, focusing mainly on CJD. He noted that the four separate types of CJD—sporadic, genetic, iatrogenic and variant—share a core feature in that their underlying pathology is similar and there is an underlying core transformation of the prion protein to an abnormal form. Although disease is confined to the central nervous system in all cases, the deposition of the abnormal protein may not be.

Prion diseases are always progressive and fatal. Because they affect the central nervous system, most human diseases present with the following symptoms in some combination: memory and cognitive disturbances; neuropsychiatric features; cerebella features and including involuntary movements. Despite sharing a common underlying mechanism there are variations in the clinical pictures of the four types of CJD. Method of disease acquisition, prion agent strain, and host genotype have been suggested as factors in explaining the differences. Dr. Knight examined each of these factors as they relate to the four types of CJD. He also described the differences in symptoms and other main features such as onset and duration of disease for each of the four types of CJD. Dr. Knight concluded that a firm molecular classification of cases requires greater understanding of pathogenesis, protein typing, and the nature of the prion agent.

Pathology of Human Prion Diseases

Dr. Herbert Budka, Professor, Institute of Neurology (Obersteiner Institute), University of Vienna, Vienna, Austria

Dr. Budka began by noting the importance of neuropathology in both the surveillance and research on prion diseases. Keeping these two features in mind, he divided his talk into two parts: the first part gave a short overview of pathological features encountered in patients, and the second part presented information on research which has contributed to our pathological understanding of prion disorders.

Surveillance contributes diagnostic confirmation as well as potential identification of new disease (sub)types, which is important in view of the wide and steadily growing spectrum of clinical and pathological phenotypes and prion protein (PrP) gene (*PRNP*) genotypes. Although the hallmark of histopathology in CJD is spongiform change—which may be light, moderately pronounced, or highly changed—neuropathologists prefer not to make diagnosis based on this change alone since holes due to loss of tissue for other possible reasons must also be ruled out. Along with spongiform change, neuronal loss and astro-and microgliosis are also indicators of prion disease in humans. As well, the presence of the prion protein PrP (PrP^{Sc}) is essential for disease identification, especially when histological changes are uncharacteristic, and can be detected by a variety of methods.

In the second part of his talk, Dr. Budka presented information on his major research interests: the pathogenesis of TSEs, in particular disease evolution in the brain, including identification of early and selective neuronal vulnerability; oxidative stress and complement activation as important pathogenetic avenues; and potential transport of PrP/infectivity by mobile cells.

Dr. Budka concluded by presenting a recent exciting observation his group shared with collaborators in Brazil. In analyzing a peculiar case of a patient with CJD who had suffered for ten years from a muscle disorder that is characterized by abnormal protein deposits, they were able to observe abundant disease-associated prion protein and vacuoles in muscle tissue.

Dr. Maura Ricketts, Senior Medical Advisor, Blood Safety Surveillance and Health Care Acquired Infections Division, Health Canada, chaired the final speaker in Session I.

Genetics of Prion Diseases: Overview and Comparative Perspectives

Dr. Michael Coulthart, Chief, National Laboratory for Prion Diseases, Health Canada

Dr. Coulthart reviewed the field of prion genetics. The first part of his presentation dealt with the basics of genetics; the second part provided an overview of the genetics of human prion diseases; and the third part discussed the results from the Canadian BSE case. Throughout the presentation, he provided a comparative perspective on the genetics of the diseases.

The gene, PRNP, which encodes the human prion protein, is located on the short arm of chromosome 20. The prion gene locus consists of a family of at least two genes, PRNP and PRND, which encodes for the Doppel protein. PRNP and PRND have similar gene structures and share similarities within functional domains of the protein. The two proteins, however, apparently have different functions. A third gene, PRNT, found within the chromosomal region may also be related. The PRNP genes and PrP^{C} proteins from other species including sheep and mouse show a high degree of relatedness to the human PRNP gene and PrP protein.

Ten to fifteen percent of all human prion diseases are related to genetic mutations. Most mutations fall within the C terminal region of the protein causing amino acid substitutions. Fourteen different mutations are associated with CJD, ten with GSS and one with FFI. The CJD and some GSS mutations are found within the alpha 2 and 3 domains of PrP, while additional GSS mutations are found in the octapeptide repeats.

The human genetic information and comparative animal genetics can be used to determine if the Canadian bovine BSE case of 2003 is the result of a genetic mutation. Sequencing of the affected cow's PRNP gene shows that differences in the coding region of PrP are also observed in other bovine sequences from healthy animals. Similarly, differences in the non-coding promoter region of the PRNP gene are consistent within the bovine population. None of the observed differences cause amino

acid changes that are found within human prion diseases associated with genetic mutations. Thus there is no supporting evidence for a genetic cause for BSE in the case of 2003, strengthening the conjecture that the case was infectious in nature.

SESSION II: PRIONS AND PUBLIC HEALTH

Chair: Dr. Michael Coulthart, Chief, National Laboratory for Prion Diseases, Health Canada

The goal of Session II was to emphasize the importance of acknowledging the relationship between prion diseases and human health. Human fear, human and animal health, and economic loss are all concerns, and we must ensure that the ongoing collaboration between veterinary schools and human health enterprise continues.

Emerging Animal Prion Diseases

Dr. Ray Bradley, CBE, Veterinary Surgeon (retired), BSE Consultant, United Kingdom

In his presentation, Dr. Bradley examined animal TSEs to determine if they are emerging diseases and identify those posing a risk to human health. He also discussed the origin of BSE, and provided an update of experimental transmission of scrapie to cattle.

According to the literature, an emerging disease is defined as "a disease that has appeared recently in a population or one that has existed previously but is rapidly increasing in prevalence or geographic range" (Morse, 1995; Williams, 2002). To these two criteria, Dr. Bradley added one of his own, that an emerging disease is also "one that is assuming importance now by application of emerging technology."

To determine if they are emerging diseases, Dr. Bradley examined the major animal TSEs in chronological order of their discovery, noting the milestones for each disease, and applying the three criteria of his definition of emerging diseases against them. He also appraised the risk to humans for each of the diseases, namely scrapie, TME, CWD, BSE and TSE in nyala and other captive wild ruminants, and feline spongiform encephalopathy (FSE). Due to their historical occurrence, none of the diseases can be regarded as "emerging" according to the first criterion of Dr. Bradley's definitions, and only CWD can be identified as an emerging disease according to the second. When the third criterion is applied, however, scrapie, CWD, and BSE can be defined as emerging diseases because the emerging technologies have enabled us to find out more about the prevalence of the diseases and how to control them.

The BSE agent poses a definite risk to humans and causes vCJD. Effective exposure is presumed to be from consumption of meat products from cattle contaminated with BSE-infected central nervous tissue. There appears to be no risk to humans from scrapie or TME agents, and no positive evidence for risk from the CWD agent. The biological and molecular properties of the agent isolated from domestic cats with FSE, and nyala and greater kudu with TSE, are indistinguishable from those of the BSE agent. There is thus a presumed risk to humans from the agents that cause disease in these three species and possibly all the captive wild species affected with TSE. None of these diseases, however, appears to be contagious and no human cases of vCJD have been attributed to exposure to them. A test to detect BSE infection in live cattle is urgently needed.

Epidemiology and Risk Factors of Prion Diseases

Dr. Maura Ricketts, Senior Medical Advisor, Blood Safety Surveillance and Health Care Acquired Infections Division, Health Canada

Dr. Ricketts discussed the epidemiology of BSE from the perspective of public health policy, focusing on two important issues, food and vaccines, to illustrate the complexity of the problems that these particular routes of exposure present. The major prion diseases causing concern in Canada are scrapie, CWD, and BSE. At present only BSE can be positively identified as zoonotic, to which humans are likely exposed through bovine based food products. However, due to the lack of certainty, we are obligated to undertake public health interventions that control the risk of exposing humans and animals to BSE even if the route of exposure is not known to cause infection and disease.

The problems encountered when dealing with prion diseases from a public health perspective are complex. Although prion disease in humans is rare, vCJD is an emerging human prion disease unreported before 1996. In addition, the incidence of prion diseases in animals, such as BSE and CWD, is increasing. Furthermore, even though the increased reports of prion disease in both humans and animals may be explained, in part, by improved technology and better diagnostic capacity, the fact remains that there is no diagnostic test that works before the onset of symptoms, and prion diseases remain uniformly untreatable and fatal. The public health management of BSE and human prion diseases is complicated by the long incubation period. Experience from other countries indicates that BSE infections in cattle are more numerous than illness because illness rarely appears before 30 months of age, while exposure and infection generally occurred in the first months of life. Finally, although most cases of BSE have been found in Europe, we cannot exclude ourselves from being at risk due to potential exposure through international trade.

While some exposures (e.g., through the food chain and iatrogenic risks such as exposure through dura mater) are recognized routes of infection, other exposures are considered to be theoretical risks. A theoretical risk can be said to be one where the exposure has been confirmed, but infection and illness are not known to have occurred in human populations. Risks may be described as theoretical in humans because they have been reported in animal models. Blood and blood products, vaccines, biological products, organ and tissue transplantation, and even cosmetics are possible routes of exposure for human populations. Each requires a policy that controls or eliminates human exposure. Theoretical risks present profound ethical and logistical problems. For example, even though we have never seen a transmission of any form of human TSE via blood, it has been necessary to develop policies to prevent human exposures, costing millions of dollars a year.

Dr. Ricketts also outlined the difficulty of dealing with public health policy regarding TSEs and vaccines. The major issues for vaccines include problems regarding their highly complex production, their importance in public health policy and the fact that so many people receive vaccines. Additionally, since the majority of vaccines are received during childhood, there is always the concern that if the incubation period is long, then exposure in childhood might be the worst case scenario. However, the failure to use vaccines to avoid a theoretical risk would undoubtedly lead to outbreaks of known fatal infectious diseases. It is important to remember that vaccines prevent infection, illness, disability and death and that in countries lacking the public health infrastructure and financing to conduct vaccine programs, vaccine preventable diseases account for a very large proportion of childhood deaths.

In dealing with public health matters regarding BSE, we must employ interventions that are commensurate with the risk. As Dr. Ricketts noted, there is no sense in choosing interventions if they do not actually lead to reduced risk. She likes to keep in mind the expression that "the perfect is the enemy of the good." The expense of control measures plus the lack of certainty about the efficacy of interventions contributed to the WHO declaration that the eradication of BSE should remain the principal public health objective of national and international animal health control authorities.

Iatrogenic Transmission of Prion Diseases, Including Blood

Dr. Paul Brown, Senior Investigator, Laboratory of Central Nervous System Studies, National Institutes of Health, USA

Dr. Brown spoke about the iatrogenic transmission of prion diseases, particularly through blood and/or blood components. He began by presenting the distribution of cases of iatrogenic CJD identified throughout the world, grouped by surgical procedure

route of transmission. The great majority of cases, occurring in France, Japan, the United Kingdom and the United States, resulted from either contaminated human growth hormone or dura mater grafts from cadavers. He noted that all the new cases that are now being identified stem from old infections that occurred in the 1980s. A very small number of cases, none of which is recent, resulted from contaminated surgical instruments, EEG needles, corneal transplants, or gonadotropin, and the few anecdotal reports of CJD with speculative iatrogenic causality from other kinds of tissues or surgical procedures remain unauthenticated and unduplicated. Dr. Brown therefore feels that the situation regarding vCJD is improving because we have a very good understanding of the causes of iatrogenic CJD, we have identified the high-risk tissues, and we have put into place the proper precautions to minimize the risk of exposure to humans. He is confident that the problem of BSE is going to diminish in the next several years, and therefore so, too, will vCJD.

Dr. Brown next examined the potential risk of iatrogenic CJD transmitted by blood, focusing particularly on secondary transmissions of vCJD from patients with vCJD. He noted that transmission of disease is both route and dose dependent. In experiments in which human cases of CJD and Kuru have been inoculated into primates, large doses given intra-cerebrally, intra-durally, and subcutaneously caused disease with a short incubation period, while small doses through inefficient routes did not necessarily cause disease at all. The iatrogenic potential of blood, therefore, is minimized by the fact that it is an inefficient route. The reality is that a single case of CJD in a recipient of a blood product or a blood component has not yet been identified.

Although there is an unknown number of people still incubating vCJD, recent projections predict the number of cases will decrease in the future because now we have more information to work with. A comparison of the risks—such as misdiagnosis of sporadic CJD, infectivity levels in blood, and lymphoreticular tissue infectivity—that surround variant and non-variant forms of TSE lead to the conclusion that risk from variant disease has not been shown to be any greater than that from non-variant disease. However, low infectivity levels by peripheral routes result in very long incubation periods, so precautions must still be taken. Dr. Brown recommends, however, that these precautions should be reviewed at least once a year because he suspects that secondary iatrogenic transmissions from blood are unlikely and precautions and concerns may well be relaxed rather than tightened in the next few years.

The Canadian BSE Case and Public Health

Dr. Ron Rogers, Senior Scientific Advisor, Bureau of Microbial Hazards, Health Canada

Dr. Rogers gave a historical perspective on Canadian policy regarding TSEs and then outlined the steps taken in the identification of Canada's 2003 BSE case and government response to it.

On January 31, 2003, a beef cow from northern Alberta was sent for slaughter to a provincially licensed meat facility, where it was condemned as unsuitable for human consumption. The head was collected and submitted as part of a federal/provincial surveillance program for BSE, and the carcass was sent to inedible rendering. On May 16, 2003, Alberta Agriculture made a tentative diagnosis of BSE, which was confirmed on May 20. The World Organization for Animal Health general session was immediately notified. An animal trace back investigation showed that the positive animal was moved to the Alberta farm from Saskatchewan. All tests of the index herd proved negative, and DNA testing did not return a definitive finding for the Saskatchewan line of inquiry. As a result of the investigation, 15 premises were quarantined, and an additional 25 herds were scrutinized. The trace out included the identification and notification of the export of five animals to the US in 1997. In the end, 2,000 animals 24 months of age or older were tested and all were found negative, and more than 2,700 cattle were culled. The feed investigation confirmed that the BSE positive cow did not enter the human food chain. Potential exposure was also considered during the feed investigation, and three additional farms were quarantined when investigation could not preclude the exposure of 63 head of cattle to feed destined for poultry feed. The animals were culled and all tested negative. The investigators concluded that the discovery of BSE proves that Canada's active surveillance and BSE diagnostic programs are working. After ruling out maternal transmission, TSEs resident in other animals (CWS, scrapie), and spontaneous BSE, the investigators also concluded that contaminated meat and bone meal used in feed products at some point early in the life of the animal was the most probable source for infection.

After the investigation was completed, an international team report was compiled. The panel concurred with the findings of the investigators and made further recommendations including the prohibition of Specified Risk Materials (SRMs), as well as increased efforts to improve awareness among producers, veterinarians and the general public. They also recommended tighter controls on non-ruminant feed, enhanced disease testing and surveillance, and the strengthening of existing cattle identification, tracking and tracing systems. The elimination of SRMs has already been acted on. Ninety-five percent of beef cattle is being slaughtered in federally registered

establishments, and the other five percent in provincial abattoirs. Only animals slaughtered at federally registered establishments can be exported.

The next steps for Canada to take include expanding the animal feed ban, BSE surveillance, the cattle identification program, and food and safety plans. Canada must also review national standards and approaches regarding risk assessment and research links to policy on tissue infectivity, susceptibility and transmissibility, species barriers, agent removal and inactivation, surveillance, and environmental issues.

The Policy Framework and Transparency in Relation to Human TSEs

Dr. Antonio Giulivi, Director, Blood Safety and Health Care Acquired Infections Division, Health Canada

Dr. Paul Gully, Senior Director General of the Population and Public Health Division, Health Canada

Dr. Paul Gully delivered the presentation for Dr. Giulivi. Dr. Gully first provided background on Health Canada's purpose and strategic plan. Health Canada is responsible for helping the people of Canada maintain and improve their health. Preventing illness by protecting and promoting health is more efficient, effective, and sustainable than treating diseases and injuries afterward. The entire health continuum—including health care and public health systems—help deliver on this mission. Public health interventions can take place in many different settings such as clinics, schools, doctors' offices, hospitals, etc. The enabling functions within Health Canada's structure that allow a promotion, prevention, and protection approach to population health include Health Surveillance; Policy, Legislation, Regulation and Planning; Research, Evaluation and Knowledge Translation; and Human Resources Planning, Development and Training.

Dr. Gully next explained the framework surrounding Health Canada's approach to policy formation and related the discussion to current concerns with BSE. Prion related diseases are a classic example of the complexity of a population health issue in how they touch many determinants of health including biologic, environmental, and even behavioural factors. The topic of TSEs covers issues dealing with blood and risk in the health system; climate and ecological change that may make a difference in terms of the rising population of deer that relates to CWD; and globalization of food, food delivery, and transportation of food. Discussions about improving capacity in public health, therefore, require involvement at all government levels, including the animal health care system and research.

Dr. Gully noted that Health Canada has a structure in place for deciding how to use science and incorporate it into decision and policy making. This decision-making

framework involves a risk assessment framework, risk assessment structure and overview, and multi-organization collaborations. The process of the decision making is actually common sense in terms of identifying the issue and its context, assessing risks and benefits, identifying and analyzing options, selecting a strategy, implementing the strategy, and monitoring and evaluating results, which is especially important in terms of policies relating to blood, organs, tissues and transplants because these policies have to be continually evaluated due to the potential consequences they pose for the health care system. Dr. Gully presented an organizational chart showing how various branches of government and Health Canada—including but not limited to the Provinces and Territories Chief Medical Officers of Health; Canadian Food Inspection Agency; Population and Public Health Branch; Centre for Infectious Disease Prevention and Control; Food Directorate; Blood Safety Surveillance and Health Care Acquired Infections Division; and the TSE Secretariat Science and Policy Teams—interact to build policy. It is a collaborative process by decision makers involving all interested and affected parties.

SESSION III: NEW CHALLENGES OF A PROTEIN-ONLY AGENT

Chair: Dr. Maura Ricketts, Senior Medical Advisor, Blood Safety Surveillance and Health Care Acquired Infections Division, Health Canada

Although the number of human deaths worldwide due to infections from prion diseases is small when compared with other diseases, they still present a threat not only because they are untreatable, fatal illnesses, but because their incubation period is so long and the infectious prion agents are resistant to traditional decontamination methods. Procedures for rapid diagnosis in cattle to prevent infectious agents from entering the food chain, effective decontamination methods, and the infrastructure necessary to carry out ongoing and future studies were therefore the focus of the third session as speakers examined the new challenges of a prion-only protein.

Rapid Diagnosis of BSE

Dr. Jean-Philippe Deslys, Head, Prions Research Group, Atomic Energy Commission, France

A rapid test for diagnosing BSE should have the capacity to recognize the pathogenic form of PrP but the sensitivity to distinguish the pathogenic form from the normal PrP. While bioassays are recognized as gold standards for pathogenic PrP these assays are not rapid enough to screen large numbers of animals in a short period of time. Ideally, the results of a rapid test on animals with clinical symptoms should be obtained within 12 hours before slaughtered animals are butchered. Four rapid tests have been evaluated in Europe. Dr. Deslys's institute evaluated the "Biorad" BSE assay and found that this test was 10 to 30 times more sensitive than the other three BSE assays. It

showed 100% specificity in laboratory tests and 100% specificity when tested on animals showing clinical signs of disease. In both cases no false positives were observed. In field trials the test was conducted on 400,000 specimens. The test identified 32 animals of 35 showing clinical signs of disease, indicating an extremely low rate of false positives. The future of diagnostic testing for BSE will likely be done on biofluids such as blood or urine though the current tests available for BSE in these fluids need further refinement.

Prion Decontamination

Dr. David Taylor, MBE, Principal Research Scientist (retired), Institute for Animal Health Neuropathogenesis Unit, Edinburgh, United Kingdom

Dr. Taylor addressed the inherent problems in finding effective means to inactivate the infectious agents that cause transmissible spongiform encephalopathies. It has been known for some time that many methodologies which would inactivate conventional microorganisms are ineffective when dealing with the agents that cause TSEs. Furthermore, some procedures such as exposure to 1M sodium hydroxide for an hour at room temperature, gravity-displacement autoclaving at 132° C for an hour, and porous-load autoclaving at 134-138° C for 18-60 minutes, which were previously thought to be completely effective, are now known to provide a high degree of, but not complete, inactivation. The strong resistance of TSE agents to inactivation has resulted in accidental transmissions of disease in spite of the use of various methods to sterilize instruments or other devices after they had been used in situations where CJD was a risk. Iatrogenic transmission of vCJD is particularly worrisome since a greater range of tissues appear to become infected than in other forms of the disease, and the disease-specific protein can be present in these tissues before the clinical onset of the disease itself, which increases the possibility of cross-contamination during surgery.

Recent studies indicate that combining sodium hydroxide treatment, either consecutively or simultaneously, with autoclaving appears to result in complete inactivation at autoclaving temperatures as low as 121° C. In addition, these conditions have achieved complete inactivation even in studies using the 301V strain of mouse-passaged BSE agent, which replicates to relatively high titres in mouse brain and is the most thermostable mouse-passaged agent yet known.

Prion Research Infrastructure

Dr. Robert Rohwer, Director, Molecular Neurovirology Unit, Veterans Administration Medical Center, Maryland, USA

Dr. Rohwer stated that his talk was about how TSE research is conducted and how in his opinion it can be improved. He noted that although his topic was not directly related to the session's theme of new challenges of a protein-only agent, it furnished

an appropriate note on which to end the afternoon because it provided a perspective on reorganizing BSE research in Canada if changes are to be made in the future as a result of the 2003 BSE case.

Apart from sufficient funding and a responsive, supportive environment, TSE research requires biocontainment level 3 (BL3) facilities designed for animal studies equipped with state-of-the-art instrumentation, access to reagents and materials, and researchers and staff with TSE expertise. For these reasons, Dr. Rohwer proposes establishing a private commercial or nonprofit facility specifically for TSE research. A national core facility of this type would enhance TSE research by facilitating participation among a larger community of investigators. In the same way that astronomers and particle physicists share telescopes and accelerators, TSE researchers would be able to set up their preliminary work at their own institutions and then have access to the specialized facility to collect their data. As a result, both career investigators whose institutions cannot supply the funding for necessary expensive equipment and long-term animal studies, as well as immunologists who do not necessarily make a career out of TSE research but have some good ideas that need to be tested, would benefit.

Besides serving researchers from government, academic and industry sectors, a core facility would provide the further benefit of being staffed with people who are knowledgeable in working with TSE agents which would help prevent cross-contamination between experiments. Furthermore, the scale of investigation would be increased as costs could be consolidated because necessary equipment, reagents and other resources would be readily available, and unnecessary duplication of expensive instruments subject to contamination would be limited. Problems surrounding disinfection and disposal of contaminated materials would also be lessened.

Dr. Rowher estimates that funding a core facility of 40,000 square feet that included 10,000 square feet of BL3 laboratory space and housed 25,000 rodents would cost approximately $14 million (US), not including lab equipment. Although loan guarantees or long-term contracts would be required to obtain commercial funding, Dr. Rohwer further estimates that such a facility would pay its own way even if it operated at only 70% capacity.

Friday, September 26, 2003

SESSION IV: PRION SCIENCE AND HEALTH

Chair: Dr. Antonio Giulivi, Director, Blood Safety and Health Care Acquired Infections Division, Health Canada

Chair: Dr. Neil Cashman Centre for Research in Neurodegenerative Diseases, Toronto, Canada

Dr. Neil Cashman, Centre for Research in Neurodegenerative Diseases, Toronto, Canada, chaired Session IV in Dr. Giulivi's absence**.** While it is clear that the pathogenic form of the cellular PrP protein can cause prion disease, little is known about the normal function of this protein. The following presentations examine possible functions of this protein in regulating cellular apoptosis by blocking the toxic effects of related PrP proteins, as well as the biochemical and biophysical properties of the normal PrP and pathogenic forms. Session IV begins, however, with the diagnostic features of prion disease and possible therapeutic interventions and the role that the immune system plays in the pathogenesis of prion disease.

Diagnosis of Prion Diseases

Dr. Inga Zerr, Neurologist, CJD Surveillance, Neurologische Klinik, Universitatskilikum Gottingen, Germany

Human transmissible spongiform encephalopathies (TSE) may be acquired as infectious diseases, inherited as autosomal dominant diseases, or occur sporadically. Creutzfeldt-Jakob disease (CJD) is the most common TSE in humans, with sporadic CJD being the most common type. Diagnosis of sporadic CJD is based on the presence of progressive dementia and at least two of four clinical features: myoclonus, visual or cerebellar signs, pyramidal or extrapyramidal signs, and akinetic mutism. Probable CJD shows periodic sharp and slow wave complexes (PSWC) in EEG, or 14-3-3 proteins in CS with a duration of less than two years, whereas possible CJD shows no PSWC in EEG or the presence of 14-3-3 in cerebrospinal fluid (CSF). Six phenotypes have been described: MM1**,** MM2, MV1, MV2**,** VV1, and VV2. They are characterized by clinical syndrome, neuropathological lesion profile, the genotype of codon 129 in the Prp gene, and the type of abnormal prion protein (PrPscp).

Of the six molecular classifications of CJD, MM-1/MV-1 is clinically characterized by a median duration of five months, with dementia and anopsia at onset. MM-1/MV-1 also shows a positive test for periodic sharp and slow wave complexes in EEG, and hyperintense signals in the basal ganglia on MRI and the presence of neuronal proteins, such as 14-3-3 in the CSF. VV-2 has a median duration of eight months and is characterized by ataxia. VV2 also shows hyperintense signals in the basal ganglia on MRI and increases in 14-3-3 in CFS, but PSWC in the EEG rarely occur at early stages of the disease.

MV-2, on the on the other hand, is characterized by symptoms including ataxia, dementia, and extrapyramidal, and has no remarkable features in EEGs and no elevation in 14-3-3 but shows hyperintense signals in MRI. The use of 14-3-3 in the CFS has a greater than 90% sensitivity and specificity in diagnosing CJD and increases in concentration during the course of CJD but usually decreases in amount in other

neurological diseases. In elderly patients the differential diagnosis for sporadic CJD is Alzheimer's disease and Lewy body dementia; however, in younger patients inflammatory disorders of the central nervous system must be considered.

Treatment of Prion Diseases

Dr. Byron Caughey, Senior Investigator, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA

At the present time there is no known practical treatment for human TSEs. The prognosis is bleak, resulting in a fatal outcome for those who are affected by prion diseases. Potential target areas for developing therapeutics or prophylactics are at the initial stages of infection, the spread of the agent to the brain, the formation of abnormal PrP, and neutralization of the toxic effects of abnormal PrP in the brain. Polyanions/sulfated glycans, Congo red and related sulfonated dyes, and Tetrapyrroles have previously been identified as potential inhibitors of prion disease through their effects in preventing prion accumulation, the conversion of PrP to abnormal PrP, or disease progression. While several drugs have prophylactic activity, only two inhibitors, quinacrine and curcumin have been tested as therapeutics and shown to have either transient or limited value.

In an attempt to discover other prophylactic or therapeutic drugs, Dr. Caughey performed high throughput screening of a library of 2,000 small molecular weight compounds for inhibitory properties of PrP conversion from a protease sensitive to a protease resistant state using the RML and 22L strains. The protease sensitive state is indicative of the prion form of PrP. He was able to identify 17 inhibitors with an IC50 of less than 1 µM versus both the RML and 22L scrapie strains. Most of these inhibitors are well characterized and are known either to cross the blood brain barrier or to have properties similar to other compounds that cross the blood brain barrier, thus making these molecules good therapeutic candidates.

Immunobiology of Prions 1: Cells

Dr. Neil Mabbott, Senior Research Scientist, Institute for Animal Health, Edinburgh, United Kingdom

Transmissible spongiform encephalopathies (TSEs) or prion diseases are usually acquired through peripheral exposure such as ingestion of prion infected food. Following ingestion TSEs usually accumulate in lymphoid tissues including the spleen long before spreading to the central nervous system. Dr. Mabbott has demonstrated that follicular dendritic cells are important for the early accumulation of prions in lymphatic tissue in a mouse model of scrapie disease. Blocking of follicular dendritic cell (FDC) differentiation and function reduces the accumulation of prions in

lymphatic tissue and prevents neural transmission and pathogenesis. Additional experiments using mutant strains of mice showed that the immune molecules, complement components C1q and C3, are critical for the early steps in neuroinvasion of scrapie prions. Dr. Mabbott proposed a model of TSE pathogenesis where dendritic cells in the gut take up TSEs and possibly transmit the infectious prions to peripheral neurons which in turn transmit the infectious agents to the central nervous system.

Immunobiology of Prions 2: Antibodies

Dr. Neil Cashman, Professor, Department of Medicine (Neurology), University of Toronto, Canada

The immune system is inadequate at recognizing infectious prions and mounting an immune response sufficient to neutralize these infectious particles. There is an absence of anti-prion neutralizing antibodies, anti-prion antibodies in natural infections, or the development of immune complexes even though the humoral responses in infected individuals in general appear to be normal. Several laboratories have demonstrated that antibodies against the normal PrP^{C} protein can interfere with prion propagation *in vivo* and *in vitro*, indicating that antibodies against PrP may be a useful therapeutic strategy. The major drawback with this strategy is that PrP is a ubiquitously expressed protein found on many cell types and treatment with anti-PrP antibodies will cause deleterious side effects.

To circumvent these problems, Dr. Cashman hypothesized that the transition of PrP^{C} into PrP^{Scp} will reveal novel sites which could be recognized by antibodies that reacted with PrP^{Scp} but not PrP. He was able to define a tripeptide region in the PrP^{Scp} protein, Tyr-Tyr-Arg (YYR) that was exposed in the PrP^{Scp} form but not in the PrP form. The YYR peptide was used as an immunogen to create a series of monoclonal antibodies that reacted specifically with the PrP^{Sc} or PrP^{vCJD} proteins but not normal PrP^{C} protein. Furthermore, one of the monoclonal antibodies was able to recognize follicular dendritic cells with PrP^{Sc} on the surface but could not recognize normal follicular dendritic cells. Dr. Cashman's studies indicate that YYR motifs may be ideal therapeutic and diagnostic targets, and antibodies directed against this motif may be an ideal therapeutic.

The Prion Protein Homolog Doppel

Dr. David Westaway, Associate Professor, Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada

Dr. Westaway presented a cell based experimental system for measuring the effects of the PrP protein and a prion-like protein called Doppel (Dpl). With this system he was able to introduce the PrP or Dpl genes by transfection into brain derived granule cells. When the Dpl gene alone was introduced into granule cells lacking the gene for *Prnp*,

a large percentage of the cells underwent cell death. The toxic effect caused by the introduction of the Dpl gene could be prevented if the PrP gene was introduced into the cells at the same time as the Dpl gene. Using this system Dr. Westaway was able to determine specific regions of PrP and Dpl proteins that were involved in Dpl toxicity or the toxic blocking ability of PrP. He introduced specific mutations in the PrP and Dpl genes and transfected these genes into granule cells and measured cell death. He showed that the copper binding octarepeats of the PrP^{C} protein were important for the Dpl toxic blocking activity. These results question some of the currently held views that Dpl and PrP interact with proteins outside of the cell.

Prions and Apoptosis

Dr. Andrea LeBlanc, Associate Professor, Department of Neurology and Neurosurgery, McGill University, Canada

Even though the cellular prion protein PrPc is abundantly expressed in the adult brain, the normal function of this protein is not clearly defined. The normal protein contains several regions that are conserved in normal prion proteins from several species including human, mice, and cow. The conservation of these regions throughout evolution suggests that the normal prion protein has an important function in the central nervous system. Ironically when the PrP gene is removed or knocked out in mice, the animals appear healthy and develop normally. However, when brain cells come under stress in mutant mice lacking the PrP gene they develop a neuropathology. Dr. LeBlanc showed that the normal PrP protein completely protects neurons from cell death-inducing protein Bax. Furthermore, investigations were performed in human primary neurons on the potential cytotoxicity of the cytosolic form of PrP suggested previously as a potential initiator of neuronal apoptosis. LeBlanc's group demonstrated that part of the newly synthesised PrP is effectively sent to the cytosol in human neurons. In contrast to previous observations, this cytosolic PrP does not cause cell death nor does it convert to the proteinase resistant form of the disease-causing protein. However, it can still rescue cells completely from Bax-mediated cell death. These results indicate that the normal form of prion protein can have beneficial actions in neurons and guards against procedures aimed at eliminating prion protein completely from brains in order to prevent its conversion to the disease-causing form of the prion protein.

Biophysics of Prion Proteins

Dr. Witold K. Surewicz, Professor, Department of Physiology and Biophysics, Case Western Reserve University, Ohio, USA

To define the folding properties of prion proteins, Dr. Surewicz reported on the use of highly pure genetically engineered human prion proteins produced in bacteria to study the effect of specific mutations on the folding and oligomeric properties of prion

proteins. Even though bacterial produced human prion proteins have some limitations, Dr. Surewicz demonstrated that these limitations do not affect the folding properties of normal prion proteins. He further showed that under very specific conditions the normal PrP protein could be converted from its normal alpha-helical state to a beta-sheet oligomeric state characteristic of the brain scrapie PrP^{Sc} protein. PrP appears to fold in a three-step fashion, from an unfolded state to an intermediate partially folded state, followed by the fully folded protein. In addition to its role in normal PrP folding, the intermediate step may be a crucial monomeric precursor of the pathogenic PrP^{Sc} form. The conversion from the normal to scrapie-like state of PrP could be greatly enhanced if the PrP protein contained familial mutations associated with prion disease. Dr. Surewicz also showed isolation of a mutant region of PrP, known as huPrP145Stop, which acts as a nucleation site, starting the oligmerization process of mutant and normal PrP resulting in prion disease.

Lesion Profiling

Dr. Catherine Bergeron, Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto; Principal Investigator, Centre for Research in Neurodegenerative Diseases, University of Toronto; Staff Neuropathologist, University Health Network Canada

Even though the multiple forms of CJD are all prion based diseases, many forms display different lesions and different distribution of PrP proteins within the lesions. To determine if quantitative profiling of the lesions could be used to predict the molecular phenotype of CJD cases or identify different prion strains, Dr. Bergeron and her colleagues profiled lesions in 30 sporatic CJD, 4 variant CJD, and 5 control cases using quantitative criteria such as PrP distribution and burden. Examination of the lesions in the cortex (frontal, temporal, parietal, occipital), hippocampus (H1 and subiculum) globus pallidus, putamen, thalamus (medial and lateral), nigra, pons, olive, and cerebellum showed that lesion profiling alone cannot predict the molecular phenotype of CJD though four groups could be recognized, Type 1, Type 2, MM2, and vCJD. Type 1 contained low PrP burdens and uneven PrP distribution, Type 2 contained high PrP burdens and more even and widespread PrP distribution, MM2 had a unique profile (strain), and vCJD displayed a unique and very consistent profile. Lesion profiling could reliably identify new prion strains. This approach also demonstrated that PrP conformation as reflected by the banding pattern determines the amount and distribution of PrP in lesions and the banding pattern is more critical than the allelic status at codon 129 of the PrP gene for determining lesion profile.

Host Factors required for Amplification of Protease-Resistant PrP Molecules *in vitro*

Dr. Surachai Supattapone, Assistant Professor of Biochemistry and Medicine, Dartmouth Medical School, Hanover, New Hampshire, USA

Infection of neurons with PrP^{Sc} generates additional PrP^{Sc} molecules through the induced conformational change of the normal cell PrP^{C} protein into PrP^{Sc} molecules. Dr. Supattapone utilized and modified the Protein Misfolding Cyclic Amplification (PMCA) method of Saborio and Soto to investigate the mechanism of PrP^{Sc} induced protein conformational change and determine the biochemical factors needed for the change from PrP^{C} to PrP^{Sc}. In a test tube, Dr. Supattapone was able to amplify PrP^{Sc} greater than 10 fold from a mixture of PrP^{Sc} and PrP^{C} proteins. He further showed that the amplification is prion strain specific and is dependent on time, temperature and free thiol groups. Interestingly, Dr. Supattapone identified that the process of amplification requires additional cell factors, namely RNA.

Saturday, September 27, 2003

INVITATIONAL RESEARCH PLANNING WORKSHOP

Introduction

This Prions Research Planning Workshop was held on September 27, 2003, following the international research conference. The purpose of this session was to consult with stakeholders on how to enhance Canadian research opportunities and results related to prions and prion diseases. Participants included Canadian clinicians, researchers and decision makers, and an expert from the USA.

The consultation's objectives were as follows:

- Summarize key learnings and implications of the conference for future Canadian research
- Develop draft recommendations on five or six priority strategic research themes for Canadian researchers over the next 10 years
- Identify opportunities to build capacity through supportive infrastructures
- Enhance linkages and interactions among participants

In his opening remarks, Dr. Bhagirath Singh remarked that, given the breadth of infectious diseases and limited resources, it is especially important to determine Canadian research priorities based on current gaps and opportunities discussed during the prions conference and on unique Canadian strengths in this field. He noted that BSE was an animal disease with significant public health implications, which gives it

additional importance and profile. Dr. Singh emphasized the need to make a case for prion disease research with policy makers and the public, as well as to be realistic about existing resources, building on Canada's existing research base while recognizing the considerable potential of new partnerships in this complex and multi-faceted research challenge.

Planning Terms

For the purpose of this workshop, strategic research themes were defined as prions-related research areas and applications central to the reduction of the burden of these diseases in Canada. These themes may vary in scope but should be focused enough to enable identification of research questions.
Criteria for research themes:

- Have population/public health significance
- Focus on strategic knowledge and health gaps
- Build on and develop Canadian strengths
- Involve multidisciplinary, integrated approaches
- Provide an opportunity for international collaboration and impact
- Contain defined questions focused on achievable end points

Summative Discussion

During the two days of the conference prior to the consultation, volunteer discussion leaders focused on the following four questions:

1. What international research priorities are currently in place?
   Lead: Dr. Kumanan Wilson
2. What are the major health challenges of prion diseases?
   Lead: Dr. Paul Gully
3. What are the major unanswered questions in the basic science of prion diseases?
   Lead: Dr. Neil Cashman
4. What are Canada's strengths and gaps (opportunities) in relation to research on prion diseases?
   Lead: Dr. Michael Coulthart

Each leader then initiated discussion at this workshop in relation to his assigned topic with a preliminary overview of key points. A summary of these key points and others made by workshop participants follow. Points are generally listed in the order in which they arose during discussion.

Question #1: ***What international research priorities are currently in place?***

Using the following two charts, Dr. Kumanan Wilson provided a useful framework for initiating discussion. These charts were meant to be comparative rather than define where research should take place.

Chart 1. Relative Research Strengths by Research Themes

+ = Strength Ø = To a lesser extent ? = Uncertain

	Research Themes			
Disease	Biomedical	Clinical	Health Systems	Social, Cultural, Environmental
Creutzfeld-Jakob Disease (CJD)	++++	++++	+++	+
vCJD	++++	++++	+++	++
Scrapie	++++	++++	?++	Ø
Bovine Spongiform Encephalopathy (BSE)	++++	++++	+++	++
Chronic Wasting Disease (CWD)	?++	?++	?+	Ø

Chart 2. Key Features of Prion Disease Research by Research Theme

Research Themes			
Biomedical	Clinical	Health Systems	Social, Cultural, Environmental
• basic prion research • pathology of disease • genetic research • ?molecular phenotyping and strain typing	• iatrogenic transmission • infectivity • sterilization • testing • ?vaccine • ?treatment	• ?epidemiology • Øquality of care • Øcost-effectiveness	• Øethics • Ølegal • Øpolitical • Ørisk perception

Key Discussion Points

- Although comparatively speaking, more research is being done in the biomedical area than in several others, there is still a significant shortage of biomedical research being conducted on prion disease, particularly given the limited number of researchers. Continued research in this area is essential for the understanding of the disease.
- Capacity building is an important requirement in developing Canadian prion research capability. There is a need to recruit and invest in top quality researchers for all research areas. In addition, new partnerships are required (e.g., among health, veterinary, and agriculture, in government, academic, and industry) to provide integrated approaches to environmental stewardship and economic impact.
- Add communication and knowledge translation across all themes. Responsibility for these aspects of the field should not fall to the popular press.
- There is relatively little funding for agricultural and wildlife research, even though it has a much broader impact than understood. Most research in this area is applied and is funded depending on the use of results, and the group (generally industry) funding the research.
- The Canadian Food Inspection Agency (CFIA) research mandate is for applied research related to diagnosis and control of animal diseases. However, there is limited funding within CFIA for conducting research.
- CFIA manages the animal disease research agenda, including tissues. Researchers need to work with the agency to be able to do research.
- CWD is a significant gap because of its relative newness. Diagnostic tools are in development but at a very preliminary stage; it is important to remember the lead time needed to publish work that is currently in progress.
- The significant mental health aspects of prion diseases (e.g., the impact of BSE on farm families) should be reflected in research on the health of populations as it is affected by societal, cultural and environmental influences.
- Researchers need to think "outside the lab" and consider socioeconomic factors in their approaches.
- Agriculture Canada has its own priorities with approximately 600 researchers employed; they are now moving towards a core funding model. Agriculture Canada may have different priorities than Health Canada and CIHR, e.g., they do relatively little policy research.
- Involvement in political and legal areas is essential to effective policy development.
- Canada is in a unique position with respect to ecological stewardship, e.g., looking at CWD in the wild. This perspective broadens the potential partnership base and therefore the understanding of related social consequences.

- Scrapie and CWD are animal diseases that have enormous social and economic impacts. However, research funding only tends to become a priority when human health impacts are involved.
- Economic impact is one of the most common measures of the importance of a disease; ideally, 1% of projected costs of a disease should be directed into research.
- Diseases of the physical environment that affect sustainability have a higher profile because the environment is an important driver of economic resources. However, the public is not always willing to financially support environmental issues.

Question #2: ***What are the major health challenges of prion diseases?***

Dr. Paul Gully emphasized that the overall challenge is to educate politicians and the public that although epidemics may occur that we cannot prevent, the expertise must be in place to respond when they happen. Prion stakeholders need to be where policy is being made to have an impact on decision making.

Other challenges:

- Policy research for risk assessment and modeling, e.g., gathering information to formulate risk, risk communication and management.
- Transmission of CWD, e.g., being able to define and assess risk for affected populations, such as rural residents and hunters.
- Risk of BSE, e.g., development of capacity to assess risk related to issues such as presence in pet and human food and sterilization of equipment.
- Wildlife surveillance, e.g.
  - gathering data is difficult and limited by lack of resources.
  - there is concern in Canada about the spread of TSEs into caribou and moose; a long-range public health question is whether these food animals are subject to TSEs in their natural settings, e.g., one case among bison.
  - newly emergent diseases, e.g., it is possible that TSE diseases exist in nature that haven't been noticed; understanding the potential environmental load may help assess risk for other species.
- Socio-economic burden, e.g., understanding the effect on populations that can be achieved through cost impact analysis research.
- Ante-mortem diagnosis, e.g., identification of pre-symptomatic cases in animals and humans.
- Rendering and recycling, e.g., examination of recycled feed from a public health point of view; industry decisions in this area may sometimes be in conflict with public health concerns.
- More explicit surveillance of BSE, CWD and CJD, including identification of origins.

- Variability at the microbial level, e.g., strain variations and their impact on other aspects of the diseases.
- Treatment, e.g., of animal populations through vaccination or other methods.
- Disinfection, sterilization and environmental contamination, e.g., disposal of carcasses, particularly of older animals.
- Infrastructure (e.g., facilities for large animals and availability of qualified investigators) and whether we are making the best use of existing resources.
- Transmission of CJD by iatrogenic and other means.
- Relationship of other neurodegenerative diseases to prions, e.g., Amyotrophic Lateral Sclerosis.

Question #3: ***What are the major unanswered questions in the basic science of prion diseases?***

Dr. Neil Cashman's presentation elicited a lively discussion on a number of contentious issues that are related to prion basic science. While some researchers believe that there is a need to continue research into defining the infectious prion, others believe that this avenue of research may have been exhausted. There is some doubt about the prion hypothesis in general, although this issue may be resolved with the help of emerging tools. Other viewpoints hold that (a) focusing on prions may be too narrow an approach as they may be part of a broader range of misfolding proteins or connected to viral agents, and (b) it is not necessary to know everything about prions to develop treatments – detection and treatment are more important.

Further unanswered questions in the basic science area include:

- Prion to protein conversion (including links to treatment).
- How generalizable the prion concept is. Incorporation of more neurodegenerative diseases into prions research would change the field enormously. The extent of generalizability should be constrained by potential for transmissibility.
- How prions kill neurons and how quiescent prions function.
- Prion disease detection in biological samples; ante-mortem diagnostics.
- Prion disease prevention and treatment in humans and animals, e.g., immunotherapies, small molecules, other surrogate markers that could be more powerful than blood or peripheral prion fluids.
- The nature of the species barrier.
- Molecular epidemiology.
- *In vivo* models.
- Exploration of animal models other than the mouse.
- Preclinical vs. clinical risks, e.g., when infection becomes a risk in animals and humans.
- Answering as many questions as possible on the CWD model may provide the

opportunity to develop the whole area of TSE research. BSE and scrapie research is weak; knowledge of items such as structure, pathogenesis, treatment, and clinical application require development.

- Capacity would be greatly improved by
  - availability of reference materials and facilities to do the work; what are diagnostic tests; molecular mechanisms, etc.
  - tissue culture banks for these diseases.

Question #4: ***What are Canada's strengths and gaps (opportunities) in relation to research on prion diseases?***

Dr. Michael Coulthart opened discussion in this area with his description of a three-part focus on approach, issues and assets.

- **Approach**, e.g., networks, virtuality
  - We can't generalize international research to Canada. There is a need for Canadian studies to validate international research.
  - Networking needs to be enhanced with expanded involvement of researchers across the themes.
  - The National Animal Disease Laboratory Network is a good model, has already been established, and connects federal reference labs to provincial labs.
  - Both the agriculture and health sectors do risk assessment modeling, but there is little interaction between the sectors to help improve risk assessments, although Health Canada has some initiatives in this area.
  - It is difficult to bring all stakeholders, agencies and researchers to the table to explore synergies. Collaboration is required across research themes in both animal and human health in prion diseases.
  - Travel may not be the best way for people to network. We need to explore more efficient linkages, e.g., through more creative uses of information technology, e.g., the Alzheimer's Forum. Other options include a Biomed or Internet journal devoted to prions. The Canadian Health Services Research Foundation (CHSRF) has a net-based service for knowledge translation that could be useful for information dissemination.
- **Issues**, e.g., CWD, scrapie, blood, social responsibility, stewardship
  - Risk communication about issues is a key part of the health of populations and the health of populations as it is affected by societal, cultural and environmental influences.
  - More explicit guidelines need to be developed and disseminated related to safety and biocontainment issues, e.g., what types of clones, which level of facility, etc.

  - Canada is the only country currently dealing with all the transmissible spongiform encephalopathies (TSE) – how do we make this an opportunity?
- **Assets**, e.g., existing research, diagnostics, surveillance
  - Canada needs more qualified people, especially veterinary researchers.
  - Capacity should be extended, but weaknesses exist in how we network (e.g., among researchers, agencies and decision makers) in prion diseases in Canada. Many vital participants are silent because of lack of communication among prion organizations and isolation for geographical and other reasons. An important aspect of capacity building is interaction.
  - A central facility may be valuable, but it is not always practical for a researcher to move temporarily to a different site.
  - An animal model research facility/centre for prion research in one location (especially in Alberta for large animals) would facilitate collaborative research.
  - Central facilities would enable support for new researchers and cost efficiencies. Experiments are expensive; the maximum in yearly grants from CIHR for facilities is only $30k, whereas the real cost of running a facility is around $70k – or two or three times more with bioassays.

Priority Research Themes

Participants developed the following priority strategic research themes (alphabetical order) in plenary discussions following small group discussions:

i. Applied CWD pathogenesis, e.g., strain application, what is risk material, what is tissue distribution; developing science-based risk assessment

ii. Ecology (the relationship of humans to prions and the environment), e.g., basic research, ecology and epidemiology, integrated systems, species barriers, environmental protection, transmission, dose response, strain typing, unique environments such as identified Saskatchewan farms in SK

iii. Testing methods, e.g., development of improved laboratory models

iv. Infectivity, e.g., molecular nature

v. Prevention and treatment of prion diseases, e.g., vaccines

vi. Rendering and decontamination research in various settings, e.g., hospitals, farms

vii. Risk assessment, communication and socio-economic impact, including public health policy and impact

Capacity Building Priorities

During the first part of the workshop, when participants were discussing their responses to the four questions, frequent mention was made of the urgent need to build capacity in support of strategic research themes. Following are their suggestions to address this challenge:

- Create a national virtual network, e.g., a virtual institute or centre for laboratories and people. The National TSE Veterinary Diagnostic Laboratory Network is already in place and has made a big difference in enabling communication among researchers and agencies.
- Develop a Canadian Prions Institute, e.g., a common P3 facility or training centre. Begin with an inventory of current facilities to determine whether current facilities are available and are being used to full potential. Develop a business case including upgrading possibilities and a focus on approaches that will link specialized facilities across the country. Consider a National Centres of Excellence proposal that includes an organized bio-repository system for transgenic materials, strains, tissues, etc.
- Provide support for recruiting and maintaining highly qualified personnel, e.g., financial and lab support, opportunities through the Canadian Foundation for Innovation (CFI).
- Create an ongoing virtual interdisciplinary forum (cross-cutting themes) to facilitate comprehensive and integrated approaches, e.g., to policy. The existing Health Canada TSE Web site could be improved through the addition of a discussion forum and resources, educational materials and a mechanism for knowledge translation.

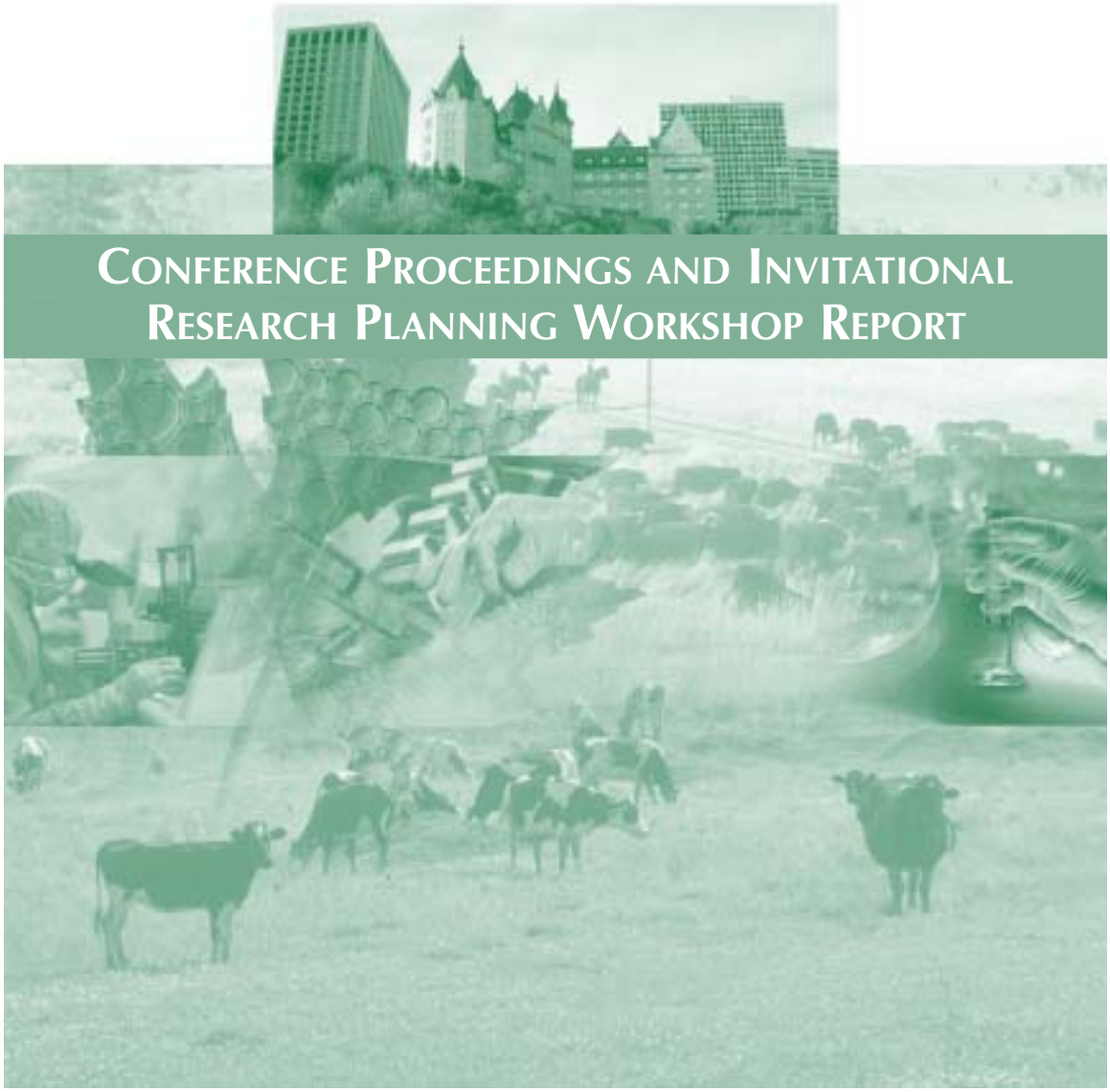
Potential Strategies

- Build on Canada's neuroscience capacity.
- Create funded exchange programs with other countries.
- Provide more longer-term funding for basic research, e.g., granting cycles equivalent to the lengths of experiments.
- Develop a mechanism for applying for peer-reviewed funding and for infrastructure.

Closing Remarks

Dr. Bhagirath Singh delivered the closing remarks to the research conference and planning workshop. After thanking the participants and organizers, he noted the importance of not losing the opportunity presented by the current attention being given to prion diseases and encouraged participants to support and promote the results of the workshop to ensure implementation once the political situation is clarified. He emphasized the stewardship role for all involved, the criticality of supportive policy development, and the need for accurate risk assessment.

Appendices


Conference Proceedings and Invitational
Research Planning Workshop Report

Appendix I

Meeting the Challenge of Prion Diseases

Organizing Committee, Young Investigator Awards and Research Planning Participants

Organizing Committee:

Dr. Neil Cashman, Professor, Centre for Research in Neurodegenerative Diseases, University of Toronto
Dr. Arumaga Balachandran, Veterinary Pathologist, Canadian Food Inspection Agency
Dr. Mike Coulthart, Chief, National Laboratory for Prion Diseases, Health Canada
Dr. Antonio Giulivi, Director, Blood Safety and Health Care Acquired Infections Division, Health Canada
Ms. Carol Richardson, Manager, Programs and Evaluation, CIHR Institute of Infection and Immunity
Dr. Ron Rogers, Senior Scientific Advisor, Bureau of Microbial Hazards, Health Canada
Dr. Bhagirath Singh, Scientific Director, CIHR Institute of Infection and Immunity
Ms. Francine Villeneuve, Senior Program Officer, Office of the Chief Scientist, Health Canada

Young Investigator Awards:

Mr. Harry Peery, University of Saskatchewan
Dr. Catherine Curtis, Canadian Food Inspection Agency, Alberta
Dr. Gerald Baron, NIAID, USA
Dr. Jennifer Griffin, Centre for Research in Neurodegenerative Diseases, University of Toronto
Dr. Marty Lehto, Centre for Research in Neurodegenerative Diseases, University of Toronto
Dr. Adbel Omri, Laurentian University
Dr. Xavier Roucou, Lady Davis Institute for Medical Research, Montreal
Dr. Luis Schang, University of Alberta

Invitational Research Planning Workshop Participants:

Dr. David R. C. Bailey, A/Director General, Food Safety Branch, Agriculture and Agri-Food Canada
Dr. Arumaga Balachandran, Veterinary Pathologist, Canadian Food Inspection Agency
Dr. Judith Bossé, Vice President, Science, Canadian Food Inspection Agency
Dr. Neil Cashman, Professor, Centre for Research in Neurodegenerative Diseases, University of Toronto

Dr. Avi Chakrabartty, Associate Professor, University of Toronto, Ontario Cancer Institute
Dr. Robert Clarke, Executive Director, McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health
Dr. Mike Coulthart, Chief, National Laboratory for Prion Diseases, Health Canada
Dr. Stephanie Czub, Canadian Food Inspection Agency
Dr. Paul Gully, Senior Director General, Population and Public Health Branch, Health Canada
Mr. Bob Hills, Manager, TSE Secretariat, Health Products and Food Branch, Health Canada
Dr. Gerard Jansen, Neuropathologist, BSSHCAID, Health Canada
Dr. Doug Kennedy, President, Icosahedron Consulting, Inc.
Dr. Brian Miller, Veterinarian, Alberta Agriculture
Dr. Chris Power, Professor, University of Calgary
Dr. Shane Renwick, Director, Animal Health Laboratory Services, Canadian Food Inspection Agency
Dr. Ron Rogers, Senior Scientific Advisor, Bureau of Microbial Hazards, Health Canada
Dr. Robert Rohwer, Director, Laboratory of Molecular Neurovirology and Associate Professor of Neurology at the University of Maryland, Baltimore
Dr. Bhagirath Singh, Scientific Director, CIHR Institute of Infection and Immunity
Ms. Francine Villeneuve, Senior Program Officer, Office of the Chief Scientist, Health Canada
Dr. Kumanan Wilson, University Health Network, Toronto General Hospital
Dr. Murray Woodbury, Chair, Specialized Livestock Research Program, Western College of Veterinary Medicine, University of Saskatchewan

Appendix II

MEETING THE CHALLENGE OF PRION DISEASES

Conference Agenda

Thursday, September 25, 2003

07:15 *Registration and Breakfast (Foyer of Empire Ballroom)*

08:00 **Welcome, Opening Remarks**
Dr. Bhagirath Singh, Scientific Director,
CIHR Institute of Infection and Immunity, Canada

08:10 **SESSION I: PRIONS AND PRION DISEASES**

Chair: Dr. Neil Cashman, Professor, Department of Medicine (Neurology), University of Toronto, Canada

08:15 **Keynote Address – Prions and Prion Diseases: An Overview**
Dr. Paul Brown, Senior Investigator, Laboratory of Central Nervous System Studies, National Institutes of Health, USA

09:00 **Prion Diseases: Phenotypes and Phenomenology**
Dr. Richard Knight, Clinical Neurologist, CJD Surveillance Unit, Edinburgh, United Kingdom

09:30 **Pathology of Human Prion Diseases**
Dr. Herbert Budka, Institute of Neurology (Obersteiner Institute), University of Vienna, Austria

10:00 **Genetics of Prion Diseases: Overview and Comparative Perspectives**
Dr. Michael Coulthart, Chief, National Laboratory for Prion Diseases, Health Canada

10:30 *Break*

10:55 **SESSION II: PRIONS AND PUBLIC HEALTH**

Chair: Dr. Michael Coulthart, Chief, National Laboratory for Prion Diseases, Health Canada

11:00 **Emerging Animal Prion Diseases**
Dr. Ray Bradley, CBE, Veterinary Surgeon (retired). BSE Consultant, United Kingdom

11:30 **Epidemiology and Risk Factors of Prion Diseases**
Dr. Maura Ricketts, Senior Medical Advisor, Blood Safety Surveillance and Health Care Acquired Infections Division, Health Canada

12:00 *Lunch*

13:30 **Iatrogenic Transmission of Prion Diseases, Including Blood**
Dr. Paul Brown, Senior Investigator, Laboratory of Central Nervous System Studies, National Institutes of Health, USA

14:00 **The Canadian BSE Case and Public Health**
Dr. Ron Rogers, Senior Scientific Advisor, Bureau of Microbial Hazards, Health Canada

14:30 **The Policy Framework and Transparency in Relation to Human TSEs**
Dr. Antonio Giulivi, Director, Blood Safety and Health Care Acquired Infections Division, Health Canada

15:00 *Break*

15:25 **SESSION III: NEW CHALLENGES OF A PROTEIN-ONLY AGENT**

Chair: Dr. Maura Ricketts, Senior Medical Advisor, Blood Safety Surveillance and Health Care Acquired Infections Division, Health Canada

15:30 **Rapid Diagnosis of BSE**
Dr. Jean-Philippe Deslys, Head, Prions Research Group, Atomic Energy Commission, France

16:00 **Prion Decontamination**
Dr. David M. Taylor, MBE, Principal Research Scientist (retired), Institute for Animal Health Neuropathogenesis Unit, Edinburgh, United Kingdom

16:30 **Prion Research Infrastructure**
Dr. Robert Rohwer, Director, Molecular Neurovirology Unit, Veterans Administration Medical Center, Baltimore, Maryland, USA

17:00 **Closing**

19:00 ***Group Dinner (Empire Ballroom)***

Friday, September 26, 2003

07:30 *Breakfast (Foyer of Empire Ballroom)*

08:15 *Agenda Overview*

08:25 **SESSION IV: PRION SCIENCE AND HEALTH**

Chair: Dr. Antonio Giulivi, Director, Blood Safety and Health Care Acquired Infections Division, Health Canada

08:30 **Diagnosis of Prion Diseases**
Dr. Inga Zerr, Neurologist, CJD Surveillance, Neurologische Klinik, Universitatsklinikum Gottingen, Germany

09:00 **Treatment of Prion Disease**s
Dr. Byron Caughey, Senior Investigator, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA

09:30 **Immunobiology of Prions 1: Cells**
Dr. Neil Mabbott, Senior Research Scientist, Institute for Animal Health, Edinburgh, United Kingdom

10:00 **Immunobiology of Prions 2: Antibodies**
Dr. Neil Cashman, Professor, Department of Medicine (Neurology), University of Toronto, Canada

10:30 *Break*

11:00	**The Prion Protein Homolog Doppel** Dr. David Westaway, Associate Professor, Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada
11:30	**Prions and Apoptosis** Dr. Andrea Leblanc, Associate Professor, Department of Neurology and Neurosurgery, McGill University, Canada
12:00	*Lunch*
13:30	**Biophysics of Prion Proteins** Dr. Witold K. Surewicz, Professor, Department of Physiology and Biophysics, Case Western Reserve University, Ohio, USA
14:30	**Lesion Profiling in CJD** Dr. Catherine Bergeron, Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto; Principal Investigator, Centre for Research in Neurodegenerative Diseases, University of Toronto; Staff Neuropathologist, University Health Network, Canada
15:00	**Host Factors Required for Amplification of Protease-Resistant PrP Molecules *in vitro*** Dr. Surachai Supattapone, Assistant Professor of Biochemistry and Medicine, Dartmouth Medical School, Hanover, New Hampshire, USA
15:30	Open plenary discussion with Session Chairs
16:00	Closing Remarks: Dr. Neil Cashman
18:00	*Dinner for speakers and young investigators* *The Edmonton Queen Riverboat*

Appendix III

MEETING THE CHALLENGE OF PRION DISEASES

Invitational Research Planning Workshop

7:00 am	*Breakfast*
7:45 am	**Welcome** Dr. Bhagirath Singh, Scientific Director, CIHR Institute of Infection and Immunity, Canada
7:50 am	Workshop Overview: Purpose, Agenda, Introductions Dorothy Strachan, Facilitator
8:10 am	**Question #1:** ***What are the major health challenges of prion diseases?*** Lead: Dr. Paul Gully (Summary 5 min; discussion 25 minutes)
	Question #2: ***What are the major unanswered questions in the basic science of prion diseases?*** Lead: Dr. Neil Cashman (Summary 5 min; discussion 25 minutes)
	Question #3: ***What international research priorities are currently in place?*** Lead: Dr. Kumanan Wilson (Summary 5 min; discussion 15 minutes)
	Question #4: ***What are Canada's strengths and gaps (opportunities) in relation to research on prion diseases?*** Lead: Dr. Michael Coulthart (Summary 5 min; discussion 25 minutes)
10:00 am	*Break*
10:30 am	**Criteria for Canadian Research Themes**
11:00 am	**Recommendations for Research Themes**
12:00 pm	**Next Steps / Concluding Remarks** Dr. Bhagirath Singh

Appendix IV

MEETING THE CHALLENGE OF PRION DISEASES

Speaker Presentation Abstracts and Biographies

Dr. Catherine Bergeron, *MD, FRCP(C), Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto; Principal Investigator, Centre for Research in Neurodegenerative Diseases, University of Toronto; Staff Neuropathologist, University Health Network.*

Lesion profiling in CJD

Abstract

Quantitative lesion profiling of sporadic (30 cases) and variant (4 cases) CJD was performed to determine the ability of this technique to predict the molecular phenotype of CJD cases (allelic status at codon 129, either M or V, and PrP^{res} banding pattern on Western blot, either type 1 or 2) and detect strain variation in humans. PrP^{res} immunodeposition was measured in 13 brain regions to generate a lesion profile. The profiles could not discriminate between MM1 and MV1 cases, or between MV2 and VV2. The two groups could be differentiated on the basis of the amount and distribution of PrP^{res}. MM1 and MV1 cases show low levels of PrP^{res} immunoreactivity in an uneven distribution while MV2 and VV2 cases have high PrP^{res} immunoreactivity in a more even and widespread distribution. VV1 cases showed a consistently low amount of immunoreactivity and could not be reliably profiled. Finally, MM2 cases showed a unique and distinctive pattern. All 4 cases of vCJD had identical lesion profiles and a distinctive PrP^{res} glycotype, thus supporting the hypothesis that vCJD is caused by a novel and unique prion strain. In conclusion, while lesion profiling cannot, in isolation, reliably predict the allelic status at codon 129, distinctive groupings emerge for the two PrP banding patterns. The lesion profiling technique may, however, play a significant role in the identification of new prion strains in emerging diseases.

Biography

Dr. Catherine Bergeron is a pathologist whose primary research interest is in the molecular neuropathology of degenerative diseases of the central nervous system.

Dr. Bergeron received her MD in 1973 from Laval University in Quebec. After completing residencies at St. Michael's Hospital, Hospital for Sick Children, Toronto General Hospital and Sunnybrook Medical Centre in Toronto, she went on to do post-doctoral training in the Department of Pathology at Albert Einstein College of Medicine, Yeshiva University (Bronx, NY), and then in the Department of Physiology at the University of Toronto under the supervision of Dr. D. R. C. McLachlan. She joined the CRND in 1990 as a Principal Investigator.· Currently, Dr. Bergeron is Staff Neuropathologist at the University Health Network, Toronto Western Hospital; Professor in the Department of Laboratory Medicine and Pathobiology, University of

Toronto; and Consultant Neuropathologist for Health Canada's CJD Surveillance System and for the Canadian Brain Tissue Bank.

Dr. Bergeron has a special interest in neurodegenerative diseases, in particular the pathogenesis of Lewy body diseases; the mechanisms of neurodegeneration and gene expression in ALS and Parkinson's disease; the classification of Lewy body disorders, non-Alzheimer dementias, corticobasal ganglionic degeneration, Pick's disease, and striato-nigral degeneration; and the pathological and molecular characterization of prion disorders.

Dr. Bergeron is the recipient of the RN Starr Medal in Medicine (University of Toronto), the National Certificate of Appreciation from the Huntington's Society of Canada, and the JB Walter Award for Teaching and Education (Department of Pathology, University of Toronto).

Dr. Ray Bradley, *CBE, MSc, BVetMed, FRCVS, FRCPath, CBiol, MIBiol*

Emerging Animal Prion Diseases

Abstract

Until 1947 only one animal transmissible spongiform encephalopathy (TSE) was known, scrapie of sheep and goats. Reports of scrapie preceded the discovery of Creutzfeldt-Jakob disease (CJD) of man by almost 200 years. We now know that the agents that cause these diseases are distinct from each other and are naturally species specific. From 1947, at approximately 20-year intervals, new animal TSEs have been discovered. Transmissible mink encephalopathy (TME) of farmed mink was first recognised in 1947 and chronic wasting disease (CWD) of mule deer and Rocky Mountain elk in 1967, both in North America. TME appears to be naturally species specific but CWD is known to naturally affect a number of CERVIDAE species. Due to the historical occurrence of these diseases they cannot be regarded as "emerging". Nevertheless, with advancing technical knowledge, it is now possible to appreciate better the biology of these diseases such that there are now prospects for detecting and eliminating scrapie from sheep flocks by genetic means and for understanding how CWD appears to be spreading in North America. Thus new concepts are "emerging". In 1986 bovine spongiform encephalopathy (BSE) of domestic cattle, especially dairy cattle, was discovered in the UK. More or less concurrently TSE in a small number of diverse ruminant species in captivity occurred and was traced to the same feed vehicle source responsible for BSE, namely mammalian meat-and-bone-meal (MBM). Shortly afterwards a new, naturally occurring disease (feline spongiform encephalopathy –

FSE) was identified in domestic cats and in captive wild FELIDAE. All these new diseases are proven or suspected to be caused by dietary exposure to the unique BSE agent. Fortunately new exposures of the feline and captive wild ruminant TSE appear to have been eliminated so these diseases cannot be regarded as "emerging". BSE of domestic cattle itself is an emerging disease and has been identified now in at least 21 countries in three continents. Eliminating the feed source of exposure is the key requisite to prevent the recycling of the BSE agent and to eliminate the disease. Importation of incubating cattle is a risk but is readily controlled. So long as affected cattle are detected and destroyed they present a negligible risk to the indigenous population. Importation of infected MBM is a higher risk and is most likely responsible for the initiation of at least some epidemics outside the UK. Recycling of infection will certainly fuel such epidemics. Measures to reduce the risk of exposure include feed bans, initiated in the UK in 1988, identification and appropriate safe disposal of TSE risk materials. In 1996 the first ten cases of variant CJD (vCJD) were reported in the UK. The agent that causes this new disease is biologically and molecularly indistinguishable from the BSE agent. Dietary exposure is the presumed route of exposure. Measures to eliminate such exposure (removal of clinically suspect cattle and specified bovine offals [SBO] from the food chain) were initiated in 1989 in the UK. Concern has been expressed that some scrapie cases might be caused by the BSE agent, though no such natural disease has to date been identified. This could theoretically expose the public to the BSE agent via sheep and goat products so, as a precaution, the SBO ban has been extended to include specified risk materials (SRM) from sheep and goats. To date, although tests are available to detect TSE-infected, live CERVIDAE, sheep and goats, none is available for cattle. "Rapid" post-mortem tests are available and used for active surveillance and for consumer confidence. A test to detect BSE infection in live cattle is urgently needed.

Biography

Dr. Ray Bradley is a veterinary surgeon who qualified from the Royal Veterinary College in London in 1959. He spent 10 years in mixed, mainly large animal practice in southern England and joined the Pathology Department of the Central Veterinary Laboratory, Weybridge (now the Veterinary Laboratories Agency) in 1969. He gained an MSc degree in veterinary pathology in 1972 and was appointed Head of Department in 1981. He was Head of Pathology when BSE was discovered in 1986. With colleagues he set up the primary research studies on BSE and was appointed BSE Co-ordinator for MAFF and Expert Adviser to the OIE on BSE and scrapie in 1991. He retired from the CVL in 1995 when he was appointed a Member of the SEAC (previously an Observer since 1990) though his extended term of office has now ceased. He is a Private BSE Consultant but retains membership of several important Committees including the Argentine Scientific Advisory Committee on BSE.

Dr. Paul Brown, *Senior Investigator, Laboratory of Central Nervous System Studies, National Institutes of Health*

Iatrogenic Transmission of Prion Diseases, Including Blood

Abstract

Iatrogenic Creutzfeldt-Jakob disease has caused somewhat more than 300 deaths since its first identification in the 1970s, the great majority having resulted from contaminated human growth hormone and dura mater grafts derived from human cadavers. Infrequent cases continue to occur on an irregular basis, following longer and longer incubation periods. The PRNP codon 129 genotype is influential but not determinant for both susceptibility and length of incubation period: homozygotes are over-represented, and at least for growth hormone recipients, have shorter incubation periods than do heterozygotes. No recent iatrogenic cases have resulted from neurosurgical instrumentation or corneal grafts, and the few anecdotal reports of CJD with speculative iatrogenic causality from other kinds of tissues or surgical procedures remain authenticated and unduplicated.

The issue of risk with regard to the blood of donors who have or are incubating sporadic Creutzfeldt-Jakob disease appears to have been put at rest, as systematic search for recipients of blood or blood products from such individuals continues to fail to uncover any cases. Current concern about blood instead focuses on possible risk from patients with the variant form of Creutzfeldt-Jakob disease. Although no cases of blood-borne disease have been identified, experimental observations have led to widespread precautionary measures. However, an inventory of the pros and cons on the comparative risks surrounding variant and non-variant forms of TSE leads to the conclusion that risk from variant disease has not been demonstrated to be any greater than that from non-variant disease, and precautions and concerns may well be relaxed rather than tightened in the next few years.

Biography

Dr. Paul Brown graduated from Harvard College and the Johns Hopkins School of Medicine, and obtained most of his training in internal medicine on the Osler Service of the Johns Hopkins Hospital. He has been a fixture in the Laboratory of Central Nervous System Studies at the National Institutes of Health for 40 years, where he currently holds the position of Senior Investigator. He is a Board Certified Internist and an apprentice Neuroscientist by virtue of having devoted almost his entire career to the study of various aspects of transmissible spongiform encephalopathy (TSE).

He is the author of nearly 350 publications, of which the most recent focus on the problem of iatrogenic Creutzfeldt-Jakob disease, and on the potential for disease

transmission through the administration of blood or blood products. In addition to his scientific research, he has served as Chairman of the TSE advisory committee to the FDA, and presently serves as consultant to the European Community CJD neuropathology and surveillance programs. His qualifications to speak today about iatrogenic Creutzfeldt-Jakob disease include a long history of handling CJD tissues, an increasing degree of forgetfulness, and occasional nocturnal muscle twitches.

Dr. Herbert Budka, *Professor, Institute of Neurology (Obersteiner Institute), University of Vienna, Vienna, Austria*

Pathology of Human Prion Diseases

Abstract

Neuropathology has a major role in surveillance and research on prion diseases. For surveillance, it contributes diagnostic confirmation as well as potential identification of new disease (sub)types. This is important in view of the wide and steadily growing spectrum of clinical and pathological phenotypes and prion protein (PrP) gene (*PRNP*) genotypes.

Human prion diseases classically feature a histological triad in brain of spongiform change, neuronal loss, and astro- and microgliosis. Another pivotal characteristic is accumulation of the disease-associated PrP (PrP^{sc}) that is detectable by a variety of methods and essential for diagnosis in particular when histological changes are uncharacteristic.

In research on prion diseases, neuropathology has essentially contributed to

- important transmission and infectivity studies
- development of immunocytochemistry for PrP^{sc} as standard diagnostic method
- identification and definition of distinct types of prion diseases, including variant Creutzfeld-Jakob disease (vCJD) and sporadic fatal insomnia (SFI) as new types of human TSE
- by going beyond the traditional morphological boundaries of pathology, elucidation of molecular factors determining the considerable phenotypic variation of human prion diseases, including the *PRNP* genotype, in particular at the polymorphic codon 129, and the "fingerprint" pattern of PrP^{sc} on Western blots from affected brains, allowing recognition of distinct phenotypes e.g. in sporadic CJD. However, the pathogenic action of these molecular factors has remained unclear
- disease modelling, including elucidation of peripheral and central pathogenesis of TSEs

Pathogenesis of TSEs, in particular disease evolution in the brain, has been one of Dr. Budka's major research interests that is presented in more detail, including identification of

- early and selective neuronal vulnerability
- oxidative stress and complement activation as important pathogenetic avenues
- potential transport of PrP/infectivity by mobile cells

Biography

Dr. Budka became Professor of Clinical Neuropathology, University of Vienna (UV) in 1992. In 1995, he was appointed Chairman, Board of Clinical Institutes (*Fachbereich*), Medical Faculty, UV and in 1999 became Director, Institute of Neurology, UV. Since 2000, he has been President of the European Confederation of Neuropathological Societies (EURO-CNS).

Dr. Budka's other activities include: Working Party on BSE, Austrian Health Ministry; Blood Bank Directorium, Austrian Red Cross; Project Leader, CEC Concerted Actions on Human Transmissible Spongiform Encephalopathies (Prion Diseases); Expert, WHO Consultations on Transmissible Spongiform Encephalopathies; Review Board and Steering Group, UK Department of Health CJD Surveillance Unit; Member, TSE/BSE ad hoc Group and Working Groups of the EU Scientific Steering Committee; Member, EU Framework Programme Expert Advisory Group on Control of Infectious Diseases; Member, International Expert Advisory Group on Risk Modeling of Rare and Emerging Diseases, Health Canada, and Science Advisory Board for Health Canada's Creutzfeldt-Jakob Disease Surveillance System and Research Program; Member, Permanent Monitoring Panel – Transmissible Spongiform Encephalopathies, World Federation of Scientists.

Dr. Neil R. Cashman, *Professor, Department of Medicine (Neurology), Centre for Research in Neurodegenerative Diseases, University of Toronto*

Immunobiology of Prions 2: Antibodies

Abstract

The immune system apparently does not recognize infectious prions, although cellular and perhaps humoral mechanisms participate in prion propagation. Even the normal cellular isoform of the prion protein (PrP^C) is poorly immunogenic. Successful strategies to achieve immune recognition of prion protein epitopes *in vivo* have included immunization across species barriers, immunization with PrP peptides, and immunization of *Prnp* null mice. Several laboratories have now reported that antibodies preferentially reactive against PrP^C can interfere with prion propagation *in*

vitro and *in vivo*, although immune recognition of this essentially ubiquitous cell surface protein could prove deleterious. We hypothesized that conformational changes of proteins in disease must be accompanied by molecular surface exposure of previously sequestered amino acid side chains. We observe that low-pH induction of beta sheet structure in recombinant PrP is associated with increased solvent accessibility of tyrosine. Antibodies directed against the prion protein repeat motif Tyr-Tyr-Arg recognize PrP^{Sc}, but not PrP^{C} by immunoprecipitation, plate capture immunoassay, and flow cytometry. Antibody binding to the pathological epitope is saturable, specific, and can be recapitulated *in vitro* by low pH treatment of PrP from normal brain. Conformation-selective exposure of the Tyr-Tyr-Arg epitope provides a probe for the distribution and structure of pathologically misfolded prion protein, and may aid the search for novel diagnostics and therapeutics for prion diseases.

Biography

Dr. Neil Cashman is a neurologist-neuroscientist working in neurodegeneration and neuroimmunology. He was raised in the Boston area, and trained in Worcester (University of Massachusetts Medical School), San Francisco (Children's Hospital of San Francisco), Paris (Hôpital Necker), and Chicago (University of Chicago). He joined the McGill Neurology and Immunology faculties in 1986, and accepted the Diener Professorship of Neurodegenerative Diseases at the University of Toronto Department of Medicine (Neurology) in 1998. His basic laboratory facilities are at the Centre for Research in Neurodegenerative Diseases at the University of Toronto. He also directs the Neuromuscular Clinic at Sunnybrook and Women's College Health Sciences Center in Toronto, and is Founder and Scientific Advisor to Caprion Pharmaceuticals, a Montreal biotechnology company. His special areas of work are the amyloid encephalopathies, such as the prion illnesses and Alzheimer's disease, and motor neuron diseases, particularly amyotrophic lateral sclerosis. He is the author of over 250 publications, and was awarded the Jonas Salk Prize in 2000.

Dr. Byron Caughey, *Senior Investigator, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana*

Treatment of Prion Diseases

Abstract

TSE diseases remain untreatable and fatal. Numerous approaches are being taken to develop TSE therapies and prophylaxes. One approach is to identify inhibitors of the conversion of normal prion protein (PrP^{C} or PrP^{sen}) to TSE-associated forms such as the scrapie form, PrP^{Sc}. Many different chemical classes of inhibitors have been identified via testing in scrapie-infected mouse neuroblastoma cell cultures and

rodents. Several types of compounds such as various polyanions, cyclic tetrapyrroles and polyene antibiotics have been shown to have prophylactic activity *in vivo*. In some cases, such compounds can prolong the lives of animals if treatment is begun after peripheral infection and before the appearance of clinical signs. These lines of evidence show that PrP^{Sc} inhibitors can impede the progression of TSE disease. However, no practical treatments are effective after the onset of clinical signs. The lack of therapeutic efficacy of many of the known inhibitors is likely to be due, at least in part, to a lack of access to the central nervous system. One recently identified inhibitor, the anti-malarial drug quinacrine, is thought to cross the blood-brain barrier and has been tested in human patients with clinical CJD. Unfortunately, only transient benefits of quinacrine treatment have been reported.

To expedite the identification of more effective TSE drugs, we have recently developed a high throughput screen for PrP^{Sc} inhibitors using scrapie-infected mouse neuroblastoma cells. This assay allows a single person to test up to 800 compounds per week. We have applied this screen to a library of 2000 FDA-approved drugs and natural products to identify compounds that could be used readily in humans and animals. The vast majority of these compounds were ineffective. However 258 compounds inhibited PrP^{Sc} accumulation at non-cytotoxic concentrations in cells infected with the RML (Chandler) strain, and 52 were active in cells infected with either the RML or 22L scrapie strains. Comparison of the relative potencies of these compounds revealed a group of 17 inhibitors with 50% inhibitory doses of <1 mM against both strains. Two, quinacrine and lovastatin, were previously known as inhibitors. The remaining 15 are newly recognized as PrP^{Sc} inhibitors and represent several different classes of compounds, most of which are known or likely to cross the blood-brain barrier and have been administered to humans for other purposes. Thus, these new inhibitors have promise as either prophylactic or therapeutic anti-TSE agents. Further testing against scrapie in rodents is underway.

Biography

Byron Caughey received his PhD degree in biochemistry in 1985 at the University of Wisconsin-Madison. After postdoctoral studies in neurochemistry at Duke University Medical Center, he moved to Rocky Mountain Laboratories in 1986 to begin his current research on the transmissible spongiform encephalopathies (prion diseases). He has been a tenured Senior Investigator in the Laboratory of Persistent Viral Diseases since 1994.

Dr. Michael Coulthart, *Chief, National Laboratory for Prion Diseases, Health Canada*

Genetics of Prion Diseases: Overview and Comparative Perspectives

Abstract

The prion protein, encoded by the mammalian host gene PRNP, was first suggested in the mid-1980s to play a key role in the pathogenesis and transmission of transmissible spongiform encephalopathies, or TSEs, now widely known as prion diseases. Since then, a range of biological phenomena, including both frank "inherited" prion diseases and genetic influences on susceptibility and expression of sporadic and transmitted prion diseases, have been linked to variation within and between species in the genetic information contained in PRNP. The objectives of this presentation are 1) to provide a brief overview of current knowledge of the PRNP gene family in mammals and other vertebrates; and 2) to present new data both on a rare pathogenic variant allele (V203I) of human PRNP and on the PRNP coding sequence from the recently reported Canadian BSE case.

Biography

Dr. Coulthart earned his PhD in Genetics and Evolution from McMaster University. After that he did postdoctoral work in molecular evolution at Dalhousie University (with Dr. Michael Gray) and population genetics of human retroviruses at the University of Western Ontario (with Dr. Greg Dekaban). He began work in 1995 with Health Canada as a research scientist in microbial population genetics. In 1998 with the opening of the National Microbiology Laboratory in Winnipeg, Dr. Coulthart was selected to establish Health Canada's first National Laboratory for Host Genetics and Prion Diseases. He is currently Director of that laboratory program, which focuses on research and surveillance on human prion diseases to support public health.

Dr. Jean-Philippe Deslys, *MD, PhD, Head of the Prion Group, Atomic Energy Commission, France CEA (Commissariat à l'Energie Atomique)*

Rapid Diagnosis of BSE

Abstract

Not available at time of printing.

Biography

As well as Head of the Prion Group at the Atomic Energy Commission (CEA), Dr. Deslys is also senior expert at the French Interministerial Committee on TSEs and prions, an expert at the AFSSA. The CEA prion group acts as reference laboratory for

biochemical PrP^{res} detection and characterization of CJD cases collected by the national INSERM network on CJD as well as for the WHO in France. It is involved in different national and European collaborations (Biomed, Biotech and Fair programs). Activities include development of diagnostic tests for TSEs (prion diseases), study of human susceptibility to prion contamination, mechanisms underlying TSEs development in different experimental models (mouse, hamster, monkey) and species barrier in TSEs, notably during primary transmission of BSE to mouse and monkey. The group is also involved in risk assessment of BSE by oral route and by transfusion, development of pharmacological models for fine kinetic studies of different markers and screening of new molecules and validation studies of industrial processes. Among his many publications in the area of prions, Dr. Deslys co-authored the book *Mad Cow Disease: The Risk to Humans* in 2001.

Dr. Antonio Giulivi, *Director, Blood Safety and Health Care Acquired Infections Division, Health Canada*
Dr. Paul Gully gave the presentation as Dr. Giulivi was unable to attend.

The Policy Framework and Transparency in Relation to Human TSEs

Abstract

The entire health continuum includes health care and public health systems. Preventing illness by protecting and promoting health is more cost-effective, efficient and sustainable than treating diseases and injuries afterwards. Public health interventions can take place in many different health settings (including clinics, schools, doctors' offices and hospitals, etc.) and enable different functions such as health surveillance; research, evaluation and knowledge translation; policy, legislation, regulation and planning; and HR planning, development and training.

The Health Canada Decision-Making Framework includes identifying, processing and managing health risks. The decision-making process evolves as follows: 1) identify the issue and its context by conducting literature search and expert conscience; 2) assess risks and benefits by running model calculations; 3) identify and analyse options (consideration of other parameters outside of model by decision-makers); 4) select a strategy; 5) implement the strategy and 6) monitor and evaluate results. This decision-making process requires multi-organization collaborations.

The BSE/vCJD issue and the safety of blood and food can be used as an example to illustrate the process. BSE/vCJD is an emerging issue which theoretically threatens the safety of the blood supply and human health in Canada. The decision making on this

issue, therefore, requires the participation of inter-departmental (Health Canada, CFIA), intra-departmental (PPHB, HPFB and NML) and federal, provincial and territorial governments.

The Framework for Risk Assessment includes risk identification, risk analysis, risk characterization and risk management and communications. The BSE/vCJD decision-making model presented is considered one of the finest.

Biography

The main focus of Dr. Giulivi's work is leading and managing development and promotion of a national management structure for infectious diseases transmitted through blood and transplanted organs and tissues; managing the planning, conceptualization, implementation and enhancement of national strategies and programs for infectious diseases transmitted through blood, etc; identifying needs and priorities to manage emerging issues, trends, developments and opportunities for new interventions related to prevention and control of infectious diseases through blood, etc; coordinating and managing the development of policy options for infectious diseases transmitted through blood and transplanted organs and tissues; and establishment of centres of excellence for surveillance.

His current activities include implementing a National Transfusion Transmitted Injuries Surveillance System and organizing specimen banks for the testing of new pathogens. In his role at Health Canada, Dr. Giulivi also works with Canadian blood regulators at both the national and provincial/territorial levels to help merge the concerns of science and policy and contribute to a climate of hemo-vigilance in Canada. His previous work experience includes clinical/laboratory haematology, bone-marrow transplantation and stem-cells transplantation. Dr. Giulivi is a former Associate National Director of the Canadian Red Cross.

***Dr. Paul R. Gully**, MB, ChB, FRCPC, Senior Director General, Population and Public Health Branch, Health Canada*

Biography

Dr. Gully is the Senior Director General, Population and Public Health Branch. In this position, he works with the Assistant Deputy Minister, PPHB in the management of the branch to enable it to fulfill its mission and mandate.

Dr. Gully joined Health Canada in 1990 and subsequently held a number of positions within the former Laboratory Centre for Disease Control, Health Protection Branch. In

July 2000, he was appointed the first Director General of the new Centre for Infectious Disease Prevention and Control, PPHB.

Dr. Gully is a physician with specialty training in public health in the United Kingdom and Canada. Prior to training in public health, he worked in the United Kingdom (UK), Zambia, Vancouver and the Northwest Territories. Before joining Health Canada, Dr. Gully was attached to the UK Communicable Disease Surveillance Centre. He was also Medical Officer of Health in Saskatoon from 1986-1990.

Dr. Gully has written several publications on infectious disease epidemiology and has held honorary and adjunct academic positions in the UK and Canada. He still works as a physician at the Sexual Health Centre in the city of Ottawa's health department on an occasional basis. He is immediate past-president of the National Specialty Society for Community Medicine.

Dr. Richard S. G. Knight, *BA, BM, BCh, FRCP(E), National CJD Surveillance Unit, Western General Hospital, Edinburgh, United Kingdom*

Prion Diseases: Phenotypes and Phenomenology

Abstract

The different human prion diseases have common neuropathological features (including the deposition of disease-related PrP) and common clinical characteristics (disease affecting the CNS, inevitable progression and fatal nature). However, there is a significant diversity in clinical phenotype that may be explained by differences in prion agent "strains", route of disease acquisition and variations in "host" genotype. The clinical phenotypes of the human prion diseases will be described and related, where possible, to variations in these three factors.

Sporadic CJD (sCJD) has a relatively uniform clinical profile in many cases. However, there are significant variations particularly in the presenting features. Purely visual ("Heidenhain's variant"), purely cerebellar ("Brownell-Oppenheimer's variant") and acute, focal (stroke-like) presentations are well described but there are other, rarer, reported presentations. sCJD is typically a rapidly progressive illness but some cases have unusually long durations. PRNP genotype influences susceptibility to sCJD and aspects of the clinical phenotype. Currently, sCJD is not considered an acquired infection; therefore, it is difficult to use the concepts of "agent strain" and "infection route". Molecular biological studies have demonstrated two distinct forms of PrP in sCJD brains and this has led to a proposed correlation of genotype/protein type with clinical phenotype. However, there are underlying uncertainties about the validity and significance of such correlations.

Iatrogenic CJD (iCJD) has a clinical phenotype largely determined by the particular means of infection. For example, the "peripheral" route of infection relevant to pituitary-derived hGH is associated with a progressive predominantly cerebellar presentation, whereas iCJD due to surgical dura mater use tends to be associated with a picture similar to typical sCJD. PRNP genotype appears predominantly to influence susceptibility.

Variant CJD (vCJD) has a rather different presentation and course to that seen in sCJD and the clinical picture is relatively more uniform. This is in keeping with a common cause for vCJD associated with a different and specific agent strain (BSE). To date, all cases of vCJD have been of one PRNP genotype (129 MM).

Genetic Prion Diseases (gCJD and FFI) occur in a wide variety of clinical phenotypes that depend, at least in part, on the underlying mutation and the PRNP 129 genotype.

Kuru has a relatively uniform clinical phenotype according to published data, but variations exist. PRNP genotype affects susceptibility but it is not clear whether it affects the clinical presentation.

Biography

Dr. Knight is currently consultant neurologist at the National CJD Surveillance Unit, Western General Hospital, Edinburgh. He is also Deputy Director, Joint Supervisor of UK CJD Surveillance with specific responsibility for Genetic and CSF aspects of Surveillance and Research; Chair of the European NEUROCJD Collaborative Group and a Member of UK DH CJD Therapy Group; a Member of the DH/MRC Research Advisory Group on TSEs; and Specialist Adviser to the vCJD Trust Committee. Dr. Knight's particular interests include epidemiology, clinical features and diagnosis of CJD. Recent publications on CJD have appeared in the *British Medical Journal* and *Journal of Neurology*, among others.

Dr. Andrea C. LeBlanc, *Associate Professor, Department Neurology and Neurosurgery, McGill University*

Prions and Apoptosis: Normal Prion Protein Is Neuroprotective

Abstract

While the role of prion protein in transmission of disease is under a great deal of scientific investigation little is known about the normal function of prion protein in the central nervous system (CNS). However, prion protein is highly expressed in the CNS and several motifs are highly conserved in evolution indicating that prion protein may have an important role in the brain. This hypothesis is disputed by the fact that

prion protein null mice appear normal. However, the absence of prion protein increases the susceptibility of neurons to oxidative stress and apoptotic-inducing insults. In our laboratory, we find that prion protein completely protects human neurons against the strong pro-apoptotic protein, Bax. Therefore, an alternative explanation to the lack of phenotype in null mice is that the prion protein function is so important that it is redundant and the normal prion protein function is replicated through other gene products. Alternatively, the mice have to be challenged with an insult to demonstrate a pathological phenotype. In this presentation, I will review the evidence for the neuroprotective functions of prion protein against Bax and oxidative stress, and present potential mechanisms through which prion protein is neuroprotective.

Biography

Dr. LeBlanc is currently Associate Professor, Department of Neurology and Neurosurgery, McGill University. She is also Project Director, Bloomfield Center for Research in Aging, Lady Davis Institute for Medical Research, Jewish General Hospital and a member of other departments at McGill. Dr. LeBlanc obtained her doctorate in biochemistry and molecular biology from Dalhousie University, Halifax, Nova Scotia, and was a post-doctorate fellow at the Mayo Clinic, Minnesota, USA. Dr. LeBlanc has served on many committees at both the national and international levels and has recently been appointed a William Dawson Scholar at McGill University 2003-2008. Her research interests include molecular mechanisms of Alzheimer's disease, molecular mechanisms of prion diseases, and neuronal apoptosis. She has published over 25 articles related to prion diseases over the past five years.

Dr. Neil Mabbott, *Senior Research Scientist, Institute for Animal Health, Edinburgh, United Kingdom*

The Immunobiology of TSE Diseases

Abstract

Creutzfeldt-Jakob disease (CJD) of humans, sheep scrapie and bovine spongiform encephalopathy are neurological diseases termed transmissible spongiform encephalopathies (TSEs) or prion diseases. These diseases are usually acquired by peripheral exposure, e.g., ingestion. Following exposure to TSEs, infectivity usually accumulates in lymphoid tissues before spreading to the central nervous system. Using a mouse scrapie model we have shown that in lymphoid tissues scrapie accumulates in association with FDCs. These cells are critical for neuroinvasion as in their absence disease susceptibility is significantly reduced. In lymphoid follicles FDCs rely on

cytokine stimulation from B-lymphocytes to maintain their differentiated state. Treatments that temporarily inhibit these signalling pathways lead to the temporary inactivation of FDCs. These findings lead to the prediction that treatments that interfere with the integrity of FDCs would also interfere with TSE pathogenesis. Indeed, we have shown that treatments that temporarily inactivate FDCs block scrapie replication in lymphoid tissues and reduce disease susceptibility. The mechanisms by which TSEs initially localize to FDCs are not known. Antigens are retained on FDCs through interactions between complement and cellular complement receptors. We have shown that in the absence of specific complement components (C1q or C3) the spread of disease to the brain is significantly delayed. Thus, in the early stages of infection, complement may contribute to the localization of TSE infectivity to FDCs in lymphoid tissues. Taken together, these data suggest that treatments that interfere with the integrity or function of FDCs offer a potential approach for early intervention in TSE diseases. However, our studies suggest that the duration of the treatment window might vary significantly according to the route of inoculation.

Biography

After completing his PhD thesis in 1995 at the University of Aberdeen, UK, on the role of nitric oxide in the induction of immunosuppression during African trypanosomiasis, Dr. Mabbott moved south to the Institute for Animal Health (Edinburgh, UK). Here his research has focused on the role of the immune system in the pathogenesis of transmissible spongiform encephalopathies (TSEs) such as scrapie, BSE and CJD. Soon after peripheral infection of mice and sheep with scrapie, high levels of infectivity accumulate in lymphoid tissues. Using a variety of immunodeficient mice, his research has shown that following peripheral infection follicular dendritic cells (FDCs) are critical for the replication of scrapie infectivity in lymphoid tissues and in their absence the subsequent spread of disease to the CNS is impaired. These studies led to the prediction that treatments that interfere with the integrity or function of FDCs would likewise interfere with TSE pathogenesis. Indeed, they have shown that reagents that temporarily inactivate FDCs or inhibit their immune complex trapping function block scrapie replication in lymphoid tissues and significantly delay the onset of disease in the brain. Thus these studies suggest treatments which temporarily inactivate FDCs may present an opportunity for early intervention in peripherally transmitted TSE diseases, e.g., vCJD. Dr. Mabbott was awarded the Heine-Medin Medal by the European Society for Clinical Virology at the European Virology Meeting, Glasgow, UK, September 17 to21, 2000, for elucidating the role of follicular dendritic cells in TSE pathogenesis.

Dr. Maura N. Ricketts, *MD MHSc FRCPC, Senior Advisor, Blood Safety Surveillance and Hospital Acquired Infections, Centre for Infectious Disease Prevention and Control Population and Public Health Branch, Health Canada*

Epidemiology and Risk Factors of Prion Diseases

Abstract

At a global level, it is well appreciated that the agent causing BSE had ample opportunity to be distributed internationally through the trade of bovine-based food, feed for animals and live cattle. The principal recipient of food and feed from the UK was continental Europe, and indeed, continental European countries developed their own epidemics of BSE and have had cases of vCJD. However, other regions of the world may be at risk, including the Central and Eastern European countries, some of the Mediterranean and North African countries (with special problems if small ruminants are susceptible to BSE), and parts of South and South-East Asia. In any exposed country, an internally generated epidemic of BSE is possible if there is an opportunity for contaminated feed to be recirculated among ruminant populations, particularly cattle.

As a direct result of recognizing that the risk of exposure to BSE is more widespread than the European continent, there is a global need to establish policies that will protect human and animal populations from exposure to this agent. To determine the appropriate measures to take, a risk analysis must be conducted, and the interventions taken should be commensurate with the level of risk as determined by the risk assessment. The principal area of concern for human populations is food, as this is the only currently recognized route of transmission of the BSE agent to humans. Protection of food requires that the risk of BSE in the native cattle population as well as the risk of the agent being present in each food product (imported or from native herds) must be understood. The reduction of human risk requires an understanding of the distribution of prion infectivity in the tissues of both humans and animals infected with the agents or interest, the fate of high-risk tissues, the factors affecting the infectivity of tissues and a thorough understanding of the potential routes of exposure. The measures taken will be influenced by the exactness (or lack thereof) of scientific knowledge and by risk perception issues. Despite a lack of reliable scientifically based data (or perhaps because of this) all potential exposure routes must be examined and measures taken to avoid human exposure. Inevitably there is a need to develop and implement safety-oriented interventions even where no demonstrated risk exists.

Biography

Dr. Ricketts' professional training is that of most public health physicians – an MD, Master's degree in Health Sciences, and FRCPC in Public Health. Until 1995, she

worked in the surveillance and epidemiology of HIV/AIDS (Health Canada). In 1995, she became medical adviser to the Division of Blood-Borne Pathogens in Health Canada and eventually the Chief of the Division of Prion Diseases. In 1998 Dr. Ricketts was invited to work at the World Health Organization where she has been the subject area specialist for prion diseases for the past five years. In 2001, with Professor Robert Will, she successfully won a grant of E800,000 to conduct surveillance for human TSEs and risk assessments for animal TSEs in countries of Central and Eastern Europe, and China (SEEC-CJD). Her publications include, from the WHO "Understanding the BSE Threat", WHO Consultation on the Revision of the vCJD Case Definition, and the WHO Manual for the Surveillance of Human TSEs, including vCJD, as well as book chapters and reviews on TSEs relating to blood safety, iatrogenic TSEs and the epidemiology and the public health management of TSEs including BSE. Dr. Ricketts began her new position 28 July 2003, where in addition to continuing the SEEC-CJD project, she will work on the development of surveillance for diseases transmitted through cells, tissues and organ transplantation.

Dr. Ron Rogers, *Senior Scientific Advisor, Bureau of Microbial Hazards, Health Canada*

The Canadian BSE Case and Public Health

Abstract

The diagnosis of a single indigenous case of BSE in May 2003 resulted in the re-examination of the existing public health policies to protect human health. The establishment of the Health Canada's policies relating to the possible transmission of disease through animal to human exposure routes did not begin with the diagnosis of this case. Canada's effort to prevent exposure of Canadian consumers to animal TSEs through food, health products and cosmetics began more half a century ago with the implementation of a scrapie control program. Health Canada's policy is that no TSE infected materials enter the food chain. Canada's first case of BSE was diagnosed in an imported animal in 1993. At that time little was known about the transmission of the disease among cattle or other species. As a preventive measure a comprehensive BSE eradication effort was conducted by Agriculture Canada. Although BSE is the only known zoonotic TSE, Health Canada and CFIA jointly continue to develop programs and policies preventing human exposure to all animal TSEs. Specific BSE actions to manage the risks from BSE began with the prohibition of live animal imports from the United Kingdom in 1989 and legally making BSE a reportable disease in 1990. A number of key actions followed. National surveillance programs for CJD and BSE were implemented, a mammalian to ruminant feed ban introduced, policy on bovine derived ingredients in health products initiated, a national blood donor deferral policy

instituted, a joint system for evaluation of a country's BSE status with the USA and Mexico established, import policies for live ruminants and ruminant products put in place, and a national cattle identification program was implemented. Following the confirmation of a native case of BSE an intensive eradication and epidemiological investigation was made by the Canadian Food Inspection Agency. The actions and findings of the CFIA were reviewed by an international panel of BSE experts. Recommendations were made by the panel to the Government of Canada to enhance existing policies. The immediate action taken by Canada was to develop and implement a national specified risk material (SRM) ban. This policy is now in force and is based on the best available science. Questions concerning public health risks profile the uncertainties in BSE/vCJD science and the difficulties faced by risk managers and policy makers.

Biography

Dr. Rogers is the Senior Scientific Advisor in the Bureau of Microbial Hazards at Health Canada. In 1973 he obtained his Doctor of Veterinary Medicine degree and in 1983 a Master's of Science in Epidemiology. Dr. Rogers has worked in positions at the Canadian Food Inspection Agency as TSE Policy Co-ordinator for the Agency; National Manager Disease Control Section, Animal Health; and Chief Epidemiology Disease Control, Animal Health. In those positions Dr. Rogers' responsibilities included the design and implementation of the national surveillance and control programs for bovine spongiform encephalopathy (BSE), chronic wasting disease (CWD) and scrapie, as well as collaboration in scrapie and CWD research projects. Dr. Rogers is currently chairman of Health Canada's Transmissible Spongiform Encephalopathy (TSE) Policy Team, a member of the TSE Science Team at Health Canada, and chairman of the Trilateral TSE Public Health Committee for USA, Mexico and Canada.

Dr. Robert Rohwer, Director, Molecular Neurovirology Unit, Veterans Administration Medical Center, Baltimore, Maryland, USA

Prion Research Infrastructure

Abstract

Not available at time of printing

Biography

Dr. Robert G. Rohwer is director of the Molecular Neurovirology Laboratory at the Veterans Affairs Medical Center in Baltimore, Maryland, and Associate Professor of Neurology at the University of Maryland School of Medicine. He is also President of the Board of Directors of the Baltimore Research and Education Foundation, Inc. Dr.

Rohwer received his PhD in Biophysics from the California Institute of Technology, and trained as a Staff Fellow and Special Expert at the National Institutes of Health under Dr. Carleton Gajdusek, who won the Nobel prize for his pioneering work on the transmissible spongiform encephalopathies (TSEs), a class of fatal neurodegenerative diseases.

For the past 25 years Dr. Rohwer has conducted research on the TSE diseases, including Creutzfeldt-Jakob disease, which infects humans; scrapie, which infects sheep and goats; and Bovine Spongiform Encephalopathy (BSE), a newly emergent disease that infects both cattle and humans. BSE when it infects humans is known as variant-Creutzfeldt-Jakob Disease. His work has focused on the physical and chemical properties of the TSE agent, the etiology and pathogenesis of the disease, detection and elimination of TSE infectivity from human- and animal-derived materials, management of TSE risk in commercial and public health environments, and development of effective and sensitive diagnostics for TSE infection. Dr. Rohwer's studies on the kinetics of inactivation of the TSE agents have provided the scientific foundations for disinfection guidelines in the USA and worldwide. Recently, he and his laboratory team have conducted critical experiments which establish the level, distribution and transmissibility of TSE infectivity in blood. The results of these efforts are being used to shape governmental policies on TSE risk management around the world.

Dr. Rohwer consults on the management of TSE risks for the World Health Organization, the European Commission, Health Canada, the US Food and Drug Administration, the American Red Cross, the US Department of Agriculture, and numerous commercial clients in biotechnology, pharmaceuticals, agribusiness and related industries.

Dr. Surachai Supattapone, *Department of Biochemistry, Dartmouth Medical School, Hanover, New Hampshire, USA*

Host Factors Required for Amplification of Protease-Resistant PrP Molecules in vitro

Abstract

Prions, the infectious agents of transmissible spongiform encephalopathies, are composed primarily of a misfolded protein designated PrP^{Sc}. Prion-infected neurons generate PrP^{Sc} from a host glycoprotein designated PrP^{C} through a process of induced

conformational change, but the molecular mechanism by which PrP^{C} undergoes conformational change into PrP^{Sc} remains unknown. We employed an *in vitro* amplification technique adapted from the Protein Misfolding Cyclic Amplification (PMCA) method of Saborio and Soto to investigate the mechanism of prion-induced protein conformational change biochemically.

Using this modified technique, we amplified protease-resistant PrP^{Sc}-like molecules (PrP^{res}) >10-fold by mixing diluted scrapie-infected brain homogenate and normal brain homogenate without ultrasonication. PrP^{res} amplification *in vitro* exhibits species and strain specificity, depends upon both time and temperature, is optimized at neutral pH, and does not require divalent cations.

Using this system, we have identified novel host factors required for efficient *in vitro* PrP^{res} amplification. The results of our ongoing investigations using this approach will be discussed.

Biography

Dr. Supattapone was born 1965 in Bangkok, Thailand. His education includes Chemistry Honors Johns Hopkins University in Baltimore, Maryland (1984); DPhil Physiology Oxford University, England as Rhodes Scholar (1991); MD and PhD Neuroscience Johns Hopkins University School of Medicine (1992), where his thesis project identified and purified the inositol trisphosphate (IP_3) receptor under the mentorship of Solomon H. Snyder. From 1992-1994, Dr. Supattapone was a resident in Internal Medicine at Massachusetts General Hospital, Boston, Massachusetts. In 1994-1995, he was a Fellow in Infectious Diseases at UCSF in San Francisco, California, after which he became a Post-doctoral Fellow, Adjunct Instructor, and Adjunct Assistant Professor at UCSF working under the mentorship of Stanley B. Prusiner on research projects such as structure-function analysis of the prion protein, discovery of branched polyamine dendrimers as potential prion therapeutics, and invention of a non-corrosive prion disinfectant. In 1998, Dr. Supattapone received both the Burroughs Wellcome Career Development Award and the National Institutes of Health (NIH) physician-scientist (K08) award. He is currently an Assistant Professor of Biochemistry and Medicine at Dartmouth Medical School, Hanover, New Hampshire, where he is working on the biochemical investigation of prion formation, and invertebrate models of prion disease.

Dr. Witold K. Surewicz, *Department of Physiology and Biophysics and Department of Chemistry, Case Western Reserve University, Cleveland, Ohio, USA*

Biophysics of Prion Proteins

Abstract

Given the difficulties encountered in obtaining highly purified material from the brain, the biophysical and structural studies with PrP have been largely performed using the bacterially-expressed recombinant prion protein. An intrinsic limitation of this protein is the lack of post-translational modifications such as glycosylation and the GPI anchor. Nevertheless, the recombinant PrP appears to faithfully recapitulate the structure and folding of brain PrP, providing a model for studying the mechanism of the PrP^{C} to PrP^{Sc} conversion. Our data show that, under certain experimental conditions, the recombinant wild-type PrP can be converted from a normal alpha-helical conformation to an oligomeric beta-sheet-rich form with characteristics similar to those of brain PrP^{Sc}. The propensity for the conversion to a scrapie-like form is greatly increased in the case of some PrP variants containing mutations associated with familial forms of prion disease (e.g. F198S, D178N). In contrast to the wild-type PrP, the mutant proteins undergo a spontaneous conversion even in the absence of any denaturing agents. Analysis of experimental data indicates that the PrP^{C} to PrP^{Sc} conversion likely involves monomeric folding intermediate(s) of the prion protein. The final part of this presentation will describe recent studies with the recombinant polypeptide corresponding to the disease-associated huPrP145Stop variant. This polypeptide undergoes a self-propagating conversion from an unstructured monomer to amyloid fibrils. The conversion appears to have characteristics of a nucleation-dependent polymerization. Experiments with this polypeptide and its truncated variants have allowed us to identify a specific region that appears to constitute a critical determinant of self-propagating conformational conversion, not only for huPrP145Stop, but likely also for the full-length prion protein.

Biography

Dr. Witold K. Surewicz was born in Lodz, Poland. In 1982 he received a PhD degree in Biophysics from the University of Lodz. The following year he moved to Canada for a postdoctoral training in the laboratory of Dr. Richard Epand, Department of Biochemistry at McMaster University. From 1986 to 1994, Dr. Surewicz served as a Research Officer in the laboratories of the National Research Council of Canada in Ottawa, Ontario. In 1994 he has relocated to the USA, first to the University of Missouri in Columbia and then to Case Western Reserve University in Cleveland, Ohio, where he is currently a Professor in the Department of Physiology and Biophysics. Dr. Surewicz's research interests are in the area of prion diseases, amyloids and biophysical chemistry of proteins. He has published over 100 research papers and

serves on editorial boards of a number of journals including *Amyloid*, *Archives of Biochemistry and Biophysics* and *Journal of Biological Chemistry*.

Dr. David Taylor, *MBE, Principal Research Scientist (retired), Institute for Animal Health, Neuropathogenesis Uint, Edinburgh, United Kingdom*

Prion Decontamination

Abstract

The unconventional agents that cause transmissible spongiform encephalopathies (TSEs) such as bovine spongiform encephalopathy (BSE), scrapie in sheep, and Creutzfeldt-Jakob disease (CJD) in humans, have been shown to be relatively resistant to a wide variety of inactivation procedures that are effective with conventional microorganisms. It is anticipated that the agent that causes variant CJD will share this property (because it is the BSE agent) but this has not yet been formally demonstrated. Even some inactivation procedures that were previously considered to be completely effective are now known to provide a substantial degree of, but not complete, inactivation. Such procedures include exposure to 1M sodium hydroxide for an hour at room temperature, gravity-displacement autoclaving at 132°C for an hour, or porous-load autoclaving at 134-138°C for 18-60 minutes. Nevertheless, the recommended use of sodium hypochlorite solutions containing at least 20,000 ppm of available chlorine still appears to be an effective method although it is not a particularly user- or product-friendly procedure. The main practical problem with vCJD is that a greater range of tissues appear to become infected in affected individuals, compared with the situation in the classical sporadic form of CJD. There is thus the enhanced potential for surgical instruments to become contaminated with the vCJD agent, and pass the infection on to others if the processing systems fail to completely remove or inactivate infectivity on the instruments. Although there had only been around 130 cases of vCJD in the UK by July 2003, it is still unknown what the future scale of the disease will be. Despite the doubts about the efficiency of achieving complete inactivation by either sodium hydroxide exposure or autoclaving, a number of studies have indicated that complete inactivation can be achieved by combining these procedures consecutively or simultaneously, even at an autoclaving temperature of 121°C. In addition, an indication that these conditions provide a good degree of overkill has been provided by studies in which the 301V strain of mouse-passaged BSE agent was completely inactivated after boiling in 1M sodium hydroxide for only one minute. The 301V agent is known to replicate to relatively high titres in mouse-brain, and is the most thermostable mouse-passaged agent that has yet been identified.

Biography

David M. Taylor, PhD, MBE, is a recently retired scientist. As a Principal Research Scientist at the Institute for Animal Health's Neuropathogenesis Unit in Edinburgh, UK, he worked extensively on the problem of inactivating TSE agents. Dr. Taylor was awarded Membership of the Order of the British Empire (MBE) by Queen Elizabeth for his contribution to TSE research. He has published numerous research papers and book chapters. Dr. Taylor's current affiliations are as follows:

- Member of the UK Department of Health Creutzfeldt-Jakob Disease Incidents Panel
- Member of the UK Joint Advisory Committee on Dangerous Pathogens/Spongiform Encephalopathy Advisory Committee
- Member of the EC Working Group on Safe Disposal and Recycling Methods for Animal By-Products Not Intended for Human Consumption
- Member of the Institute of Medicine's TSE Committee

Dr. David Westaway, *Associate Professor, Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada*

A Genetic Assay for PrP^C Activity

Abstract

The function of PrP^C has proven a long-standing puzzle in prion biology. Based upon the observation that Dpl, a PrP-like protein, produces apoptosis in cerebellar neurons and that PrP^C antagonizes this effect *in vivo* we have created a cellular assay for Dpl/PrP^C interactions. In this transfection assay N-terminally deleted PrP alleles lacking the copper-binding octarepeats were not protective against the toxic action of Dpl, whereas an allele lacking the signal peptide for GPI anchor addition retained activity. Conversely, two Dpl alleles with overlapping internal deletions in close proximity to the single copper binding site were non-toxic whereas a Dpl allele lacking the signal peptide for GPI anchor addition retained activity. While the exact mechanism and cellular site of action of Dpl and PrP monitored in this assay remain to be established, these data are not obviously compatible with the prevailing hypothesis that PrP and Dpl compete for an extracellular protein ligand.

Biography

Dr. David Westaway is a molecular biologist with a special interest in the use of genetically-engineered transgenic mice to recreate and decipher human neurologic disorders. He obtained a first-class degree in Biochemistry from the University of

Sussex, England and a PhD in Biochemistry at the University of London. He completed postdoctoral training with two Nobel Laureates, Harold Varmus and Stanley Prusiner, both at the University of California San Francisco. With Professor Prusiner, David participated in much of the early work to define the molecular biology of the prion diseases. Dr. Westaway moved to the Centre for Research in Neurodegenerative Disease, University of Toronto, in 1994, where he holds appointments as Associate Professor and Head of Prion Research. Dr. Westaway's recent work on prion diseases involves the discovery of the doppel gene and the role of copper-binding in PrP's neuroprotective activity. With regard to Alzheimer's disease, Dr. Westaway's lab has generated new transgenic models of this disease with amyloid or tau pathologies. Dr. Westaway is a CIHR investigator, a Zenith Scholar of the Alzheimer's Association of the USA, and a Premier's Research Excellence Award (PREA) holder from the Government of Ontario. His work is supported by CIHR, the Alzheimer Society of Ontario, and the Alzheimer's Association (USA).

Dr. Inga Zerr, *Neurologist at the Neurologic University Hospital, Georg-August University, Göttingen*

Diagnosis of Prion Diseases

Abstract

Human transmissible spongiform encephalopathies (TSE) may be acquired as infectious diseases, they may be inherited in an autosomal dominant fashion, or they may occur sporadically. The most widely distributed TSE form in humans, sporadic Creutzfeldt-Jakob disease (CJD), typically affects patients in their sixties. Rapidly progressive dementia is usually followed by focal neurological signs and typically myoclonus. Six phenotypes of sporadic CJD have been described; these phenotypes are characterized by clinical syndrome, neuropathological lesion profile, codon 129 genotype and type of the abnormal prion protein (PrP^{Sc}). The clinical diagnosis in sporadic CJD is supported by the detection of periodic sharp and slow wave complexes in the electroencephalogram (EEG), hyperintense signals in basal ganglia on magnetic resonance imaging, and elevated levels of neuronal proteins in the cerebrospinal fluid (such as 14-3-3). The sensitivity of these diagnostic techniques varies significantly between phenotypes. In variant CJD, the clinical features are different from sporadic CJD, and the disease onset is characterized by psychiatric features, ataxia, and painful dysaesthesia. The disease duration in variant CJD is longer than in sporadic CJD (fourteen months and six months, respectively). In contrast to sporadic form, hyperintense signals in the posterior thalamus ("pulvinar sign") are seen in variant CJD. Following recent developments in diagnostic pre-mortem techniques, clinical

criteria for probable sporadic and probable variant CJD were established. Alzheimer's disease and Lewy body dementia are the most frequent differential diagnoses in sporadic CJD in elder patients, whereas chronic inflammatory disorders of the central nervous system have to be considered in younger patients.

Biography

Dr. Inga Zerr is a neurologist at the Neurologic University Hospital, Georg-August University, Göttingen. Her scientific research activities include: cerebrospinal fluid research, clinical diagnosis of Creutzfeldt-Jakob disease, pre-mortem diagnostic techniques in TSE, epidemiological studies on transmissible spongiform encephalopathies, risk factors of CJD, differential diagnosis of dementia and treatable dementia: Hashimoto´s encephalopathy. Dr. Zerr has participated in and coordinated many national, European Union and WHO research initiatives and risk assessment working groups. She is widely published in the area of CJD. Currently she is heading the research group on diagnosis of human spongiform encephalopathies, CJD Surveillance Unit, Göttingen, Germany.

Appendix V

MEETING THE CHALLENGE OF PRION DISEASES

Prion Diseases in Canada: An Overview

Background

Canada's single case of home-grown bovine spongiform encephalopathy (BSE), popularly known as mad cow disease, has exposed Canada's economic vulnerability to prion diseases. Because of its established association with variant Creutzfeldt-Jakob disease (vCJD), a fatal and presently incurable illness, the case has also retriggered alarm about its potential impact on human and animal health in Canada.

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are devastating neurodegenerative illnesses that are invariably fatal. In humans, they are comparatively rare but they can, and have, become widespread in certain animal populations such as sheep, cattle and deer.

Because prion diseases have only been identified as such relatively recently, comparatively little research has been done on them. This presents challenges and opportunities for the Canadian human and animal health research community.

Prions are infectious proteins that cause normal prion-precursor proteins in the brain to misfold and clump together, which is a marker for the death of brain cells. Neuronal cells do not readily regenerate and when they degenerate a hole is left in the brain tissue.

In 1997, Stanley Prusiner of the University of California won the Nobel Prize for his discovery of prions. He coined the term by juggling the first letters of his definition of prions—"proteinaceous infectious particles."

Human prion diseases identified in the last century include Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome, a rare familial form of CJD, fatal familial insomnia and variant Creutzfeldt-Jakob disease (vCJD). Another is Kuru, linked to cannibalism, which killed more than 3,000 Fore tribe members in Papua New Guinea by the end of the 20th century. A recent British study on kuru suggests that human prion diseases may date back to prehistoric times.

Animal prion diseases include scrapie in sheep and goats, chronic wasting disease (CWD) in deer and elk, transmissible mink encephalopathy and feline spongiform encephalopathy. Scrapie was first recorded in sheep in Britain in 1732. Scrapie has been endemic in Canadian sheep since the 1930s. It is not believed that scrapie can be transmitted to humans, although scientific research on this question has not ruled it out completely.

CWD, a disease that affects deer and elk, is found exclusively in the western United States and Canada. It was first identified in Colorado in 1967 and is now found in several US states. In 2000, it was identified in farmed animals in Saskatchewan and later in Alberta. No new cases of CWD have been found in farmed elk in Saskatchewan for more than a year after suspect herds were destroyed, although two white-tailed deer tested positive for CWD on a farm in Alberta within the last year. A dozen wild deer in Saskatchewan also tested positive within the last couple of years. The risk posed to humans by CWD is unknown.

BSE, a progressive fatal disease of the nervous system of cattle, was formally diagnosed in 1986 by the Central Veterinary Laboratory in Weybridge, England. British investigators suspected that BSE was linked to the use of ruminant-derived meat and bone meal in ruminant feed, a practice that began around 1900. In Britain, a ruminant feed ban came into force in July, 1988.

It was not until March 20, 1996 that the British government announced that their CJD Surveillance Unit identified a "previously unrecognized and consistent disease pattern" (vCJD) likely connected to exposure to BSE. Until this announcement, the British government repeatedly told the public that British beef was safe. In retrospect, the campaign of reassurance was a mistake because the public felt misled and confidence in the government pronouncements represented a further casualty of BSE.

Within a week, the European Commission banned the export from Britain of live animals, beef and beef-related products, mammalian-derived meat and bone meal, and bovine materials used in medicinal, cosmetic or pharmaceutical products. In an effort to control damage, the British government introduced a widespread slaughter scheme to ensure that all bovine animals over the age of 30 months would not enter the human food chain.

From 1987 to 2003, more than 180,000 cases of BSE were reported in the United Kingdom. Hundreds of thousands of animals were slaughtered, leading to the collapse of the British beef and cattle export market, at one point worth 720 million pounds (approximately Can$1.6 billion) a year and employing 130,000 people. In April 2000, the British government estimated the total net cost of the BSE crisis to the Exchequer of 3.7 billion pounds (approximately Can$ 8 billion) to the end of the 2001/02 financial year. European Union countries contributed a further 487 million pounds (approximately Can$ 1 billion) towards the British government's expenses. Public monies were primarily spent on BSE and prion disease research, compensation payments and departmental running costs.

BSE cases peaked at 37,280 in the U.K. in 1992 and have since declined. However, there were still more than 1,000 cases in the U.K. last year and the disease continues to take its toll in continental Europe and Israel.

Less than a decade ago, some scientists predicted that vCJD would reach epidemic proportions. However, human resistance to the disease may be much stronger than once suspected. In the last seven years, and as of September 2003, a total of 145 persons have died of definite or probable vCJD worldwide, the bulk of those in the U.K.

Economic Impact of BSE in Canada

The closure of export markets in May that swiftly followed the announcement of Alberta's isolated BSE case has had a devastating impact on Canada's beef and beef processing industry. Indeed, the widening costs of the ban by the US and other countries on imports of Canadian cattle and beef products were a contributing factor to the sudden halt in Canadian economic growth in the second quarter of the year. With the adverse fallout from SARS, Canada's gross domestic product actually contracted during the second quarter. In early September, the Bank of Canada predicted the lingering effects of these and other special factors such as Ontario's blackout and western Canadian forest fires would likely keep economic growth in the third quarter of the year below the country's potential.

A study prepared for the Canadian Animal Health Coalition estimated that the cost to Canada of our beef and cattle industry being excluded from export markets for four months would be around $2.5 billion. This assumed the ban would start to be lifted in mid-September. But in early September the reopening of the US border was only extended to a limited amount of boneless cuts under a special export permit plan.

The Animal Health Coalition report noted that the impact of the ban goes well beyond the actual beef chain, affecting sectors such as bovine genetics, dairy, feedlots, rendering and processing plants, trucking and various other support businesses. There was concern, for instance, about the outlook this fall for breeders offering pedigreed cows and bulls for sale. The export ban didn't extend to semen and embryo sales, but this business was brought to a standstill.

As the report pointed out, the ultimate costs of the single BSE case will also depend on how Canada's trading partners react as the ban is lifted. Additional costs of $1.5 billion are estimated for a delayed recovery if the marketplace is reluctant to accept Canadian beef products or to some extent trade remains restricted.

There is no Canadian precedent for knowing with confidence how trade will resume. As one industry official put it, the trouble with BSE is that it is easy to close borders but difficult to reopen them.

Human and Animal Health Research Challenges

- Foremost of the challenges to health researchers is the apparent inviolability of the prion. So far, mutations of the prion protein gene are the only established originating cause for the conversion of the normal molecule into disease-producing molecules. While the normal proteins that are precursors to prions can be found naturally in the body, their function is unknown. The mechanism by which they change from normally functioning precursors to abnormally folding proteins is poorly understood. Scientists have not found a way to slow or stop the protein accumulations associated with the diseases.
- Comparatively little research has been done on prion diseases. Prions were only identified relatively recently and most of the research on prion diseases was done within the last few decades.
- The comparative rarity of human prion diseases makes them difficult to study, although there are intriguing parallels with major neurological diseases which merit further study. Prion diseases—which could be considered "orphan" diseases—lack a public forum. The Canadian Institutes of Health Research now spend $1.2 million on prion research annually. In the US, the National Institutes of Health spend US$28 million annually. Also, in fiscal year 2002, the US Department of Defense set aside US$42.5 million for 30 to 35 awards for research into the prevention, treatment, inactivation and diagnosis of TSE diseases. Awards are for one– to five–year periods and will be announced this year.
- Before the identification of BSE, it appeared that prion diseases rarely, if ever, crossed species barriers. However, BSE is known to have infected close to 20 species by natural exposure and a greater number within an experimental setting.
- TSEs have long incubation periods. These range from months for mice, up to 15 years for vCJD, 30 years for CJD, and more than 40 years for kuru. These time frames make research studies challenging, especially in large animal studies. Another challenge of the long incubation period is that an epidemic may become well established before it is even recognized to exist.
- Prion diseases are very difficult to diagnose. Unlike viral or bacteriological infections, prions trigger no known response by the immune system. When disease symptoms finally appear, the progression of the disease is rapid. In sporadic CJD, the most common human TSE, death usually occurs within weeks or months of onset. Definitive diagnosis of prion diseases requires brain biopsies—which are prohibitively expensive and even unreliable in the case of animals—or necropsy, neither of which is useful as a diagnostic tool.

- Much more needs to be known about the transmission of the disease. For example, classical CJD, which affects about 30 Canadians a year, can be sporadic, hereditary or caused by direct infection. The bulk of CJD cases are sporadic with no known risk factor such as eating infected meat. Sporadic disease might be caused if a prion-precursor protein folds abnormally and accidentally triggers the disease. About 10 to 15% of CJD cases are hereditary or familial. It has been estimated that one percent of CJD cases were caused by various medical procedures such as cornea grafts and the use of contaminated instruments in neurosurgery. The disease was also transmitted by the injection of human growth hormones in the treatment of dwarfism, a treatment no longer used because the human-derived hormones have been replaced by synthetic ones. Kuru in humans, CWD in deer and elk, and BSE are known to be transmitted orally. However, it appears that genetic susceptibility or genetic resistance to TSEs may also be key factors.
- A challenge presented by both prion diseases and other brain diseases is the difficulty of getting drugs across the blood-brain barrier. This is also an obstacle to finding blood-based screening assays for ante-mortem diagnostics.
- Prion diseases are invariably fatal and no known treatments exist. Future treatments may include chemicals to block protein aggregation or misfoldings. Immuno-therapy is another treatment possibility.
- Access to facilities with adequate security measures and biocontainment infrastructures is another challenge for Canadian researchers. Researchers must also be prepared to take on the risks and inconveniences of working in level 2 and 3 containment facilities. Although TSEs are less infectious than viruses or bacteria, they are not treatable. While it is comparatively safe to work with certain animal prions such as scrapie-infected mice and hamsters, the risk increases when working with human prions.

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Dr. Michael B. Coulthart, Director, Health Canada's Host Genetics and Prion Disease program at the National Microbiology Laboratory, Winnipeg.

Dr. Peter Flood, Professor Emeritus, Veterinary Biomedical Sciences, University of Saskatchewan, Saskatoon.

Dr. Bhagirath Singh, Scientific Director, Institute of Infection and Immunology, Canadian Institutes of Health Research, Professor, Department of Microbiology and Immunology, The University of Western Ontario.

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Canadian Food Inspection Agency (www.inspection.gc.ca).

Canadian Institutes of Health Research (www.cihr-irsc.gc.ca).

Centre for Research in Neurodegenerative Diseases (www.utoronto.ca/crnd/research.htm).

Health Canada (www.hc-sc.gc.ca).

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Margret Brady Nankivell
September 18, 2003

Appendix VI

MEETING THE CHALLENGE OF PRION DISEASES

Public Opinion in Canada on Bovine Spongiform Encephalopathy (BSE)

The CIHR Institute of Infection and Immunity is hosting an international conference focused on education and research related to prions and prion diseases on September 25, 26 in Edmonton, Alberta. The purpose of this document is to provide background information for this workshop on public concerns related to BSE as represented in several recent public opinion surveys.

Ipsos-Reid Survey (May, 2003)

Question: ***As you may know, there has been a lot of attention in the news recently about Mad Cow disease. The disease affects cows and is transferable to humans who eat contaminated beef. Based on what you have seen, read or heard, how concerned are you about Canada being affected by Mad Cow disease?***

- Overall, 51% of respondents were concerned about Canada being affected; 49% were unconcerned. Concern was stronger:
  - in rural areas (56%) than in urban areas (50%)
  - among respondents with less than a high school education (64%) than those with a university education (41%)
  - among those earning less than $30K (60%) than among those earning more than $60K (42%).
- 58% of respondents agreed with the statement: *I don't think anyone in Canada will become infected with the human form of Mad Cow disease*.
- 65% of respondents agreed with the statement: *I am concerned about the safety of the food that I eat*.
- 82% of respondents agreed with the statement: *I trust Canada's Food Inspection Agency to protect me from food-borne illnesses such as Mad Cow disease*. [1]

Ipsos-Reid Survey (June, 2003)

- 62% of Canadians say that they think the health care system is unprepared to deal with future threats to human health, based on the recent outbreaks of Severe

[1] Canadian Ipsos-Reid Express. May 27-29, 2003.

Acute Respiratory Syndrome (SARS), West Nile virus and Mad Cow disease. This view is slightly stronger among:

- residents of Atlantic Canada (72%) than those in Quebec (59%) or Alberta (58%)
- older (68%) and middle-aged (64%) Canadians than young adults (55%)
- women (68%) than men (56%)
- Canadians without a high school diploma (72%) than those with some university or other post-secondary education (61%) or with a university degree (59%).[2]

Pollara Survey (June, 2003)

- One mad cow has one-third of Canadians surveyed thinking about eating less beef, according to a new Pollara survey commissioned by the Consumers' Association of Canada. The other two-thirds of respondents in the nationwide survey say the Mad Cow crisis won't affect their eating habits.[3] Among the third who are reluctant to eat beef, 11% say they are going to cut back substantially or completely.[4]

Decima Survey (July, 2003)

Question: ***Are you very concerned, somewhat concerned, a little concerned or not at all concerned that you, or someone in your family, might become personally affected sometime this year by each of the following types of public health risk: a) SARS, b) the West Nile Virus, c) BSE, also known as Mad Cow disease?***[5]

	Very concerned (%)	Somewhat concerned (%)	A little concerned (%)	Not at all concerned (%)
a) SARS	16	18	27	39
b) The West Nile Virus	18	27	29	25
c) BSE	**10**	**11**	**21**	**58**

2 Poll conducted by Ipsos-Reid on behalf of the Canadian Federation of Nurses' Unions. Wednesday, June 4, 2003.

3 *London Free Press*. June 17, 2003.

4 *Toronto Star*. *2 in 3 still have appetite for beef: Poll*. June 16, 2003.

5 Decima Research Inc. *Canadians show little concern about the triple threat of West Nile Virus, SARS and BSE*. July 2, 2003.

Question: ***Do you feel that public health authorities are currently doing everything they can to protect Canadians from these types of public health risks?***

- 74% Yes
- 20% No
- 3% Depends (different response by type of risk)
- 3% Don't know/No answer

Opinion on Public Reactions

- In the UK, the mad cow disease tragedy for farmers and human victims of CJD served to reinforce the public mistrust of government. However, skeptical public reactions are not reactions to (supposedly misconceived) risks as such, or to media representations of these, but rather are public judgements of dominant scientific and policy institutions and their behaviours.[6]

Paul Tomlinson, EdD
September 2, 2003

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6 Renato A. Schibeci. *National Research Priorities Submission 32*. National Research Priorities Task Force. Biotechnology Australia. April, 2002. (adapted)

Appendix VII

MEETING THE CHALLENGE OF PRION DISEASES

Canadian Facilities for TSE Research

The National Microbiology Laboratory, Winnipeg

Health Canada's National Microbiology Laboratory (NML) in Winnipeg is the leading microbiology laboratory in Canada. Founded in 2000, it was originally a federal reference laboratory for clinical microbiology. Now the 200 employee facility has evolved into a combination research and service organization.

Within NML, Health Canada invested several million dollars to establish a prion disease lab, which measures about 3,000 square feet. The laboratory is home to the Host Genetics and Prion Disease program (HGPD) that focuses on the infectious agents and host responses of TSEs. The program plays a pivotal role in improving the national capability for timely detection, risk management and research in the various forms of prion diseases.

HGPD provides support to Health Canada's CJD Surveillance System, researches biological mechanisms of TSEs and works toward developing new ways to detect and monitor the diseases. It also collaborates with the Canadian Food Inspection Agency on animal TSE initiatives and plays an essential role in training, education and outreach programs to raise general awareness of the nature and importance of TSEs.

NML has level 2 and 3 biosafety laboratories. Biocontainment laboratories must meet rigorous standards specifying the handling of equipment and infectious material within the laboratory, the decontamination of laboratory waste, documentation of materials and ventilation. Standards are set for chemical sterilization, autoclaving (steam sterilization) and incineration.

Where possible, work with TSE agents is done in a dedicated laboratory. Most animal TSE agents can be handled in a level 2 laboratory, but BSE, which is considered a foreign animal disease, requires a level 3 laboratory.

HGPD's national biorepository can hold about 250,000 samples. Only a small portion of that capacity is used including pre-mortem specimens for the CJD Surveillance System. Therefore, the biorepository has significant unused capacity that could be used to support additional research.

HGPD is developing microarray technology and other methods of molecular screening to measure host responses to infection at the cellular level. It has also introduced bioinformatics infrastructure and expertise to the NML. In the current "post-genomics" era, when comprehensive approaches to biology are growing rapidly and revolutionizing how laboratories define their work, HGPD's strategy is to apply new tools and knowledge, when possible, to the problems posed by TSEs.

The NML is part of the federal, provincial and territorial health network so it has a direct influence on public health issues. Its mandate is to bring science and technology to bear on practical problems. Responsible and responsive management is a key feature of the lab, says HGPD's director Dr. Michael Coulthart.

Canadian Food Inspection Agency

The Canadian Food Inspection Agency (CFIA) has two national TSE reference laboratories, the National CWD/Scrapie Reference Laboratory in Nepean, Ontario, and the National BSE Reference Laboratory in Winnipeg. These laboratories concentrate on disease control diagnostics, research on diagnostic test development, surveillance and confirmatory testing. In addition, they provide quality control and quality assurance services for laboratories testing for TSE diseases.

Other laboratories participating in TSE surveillance in Canada include the CFIA labs in Lethbridge, Alberta, and St.-Hyacinthe, Quebec, as well as Alberta's Agri-Food Surveillance Systems Branch of the Food Safety Division in Edmonton. TSE surveillance is also done by Prairie Diagnostic Services, in Saskatoon, the University of Guelph's Laboratory Services and le ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec (MAPAQ), and the Laboratoire de Pathologie Animale de Ste.-Foy.

CFIA's Nepean Research Institute has animal colonies for small rodent studies as well as a large facility for sheep with scrapie. The biosafety level 2 laboratory is purchasing a TSE-dedicated housing unit meeting the safety standards for mouse inoculation studies.

The CFIA laboratories became involved in BSE studies in the late 1980s and have been testing cattle brains submitted for rabies diagnoses. The research focus for the laboratories is to develop tests to identify TSE diseases in living animals. For example, evidence suggests that sheep develop scrapie in peripheral tissues before the disease moves to the brain. Early in the incubation period of the disease, a sheep can be tested by taking a biopsy of its third eyelid that might show prion protein accumulation. CWD is similar to scrapie and can be found in the lymphatic system. There is no evidence to suggest that either scrapie or CWD can be passed naturally to other species.

Centre for Research in Neurodegenerative Diseases, University of Toronto

The Centre for Research in Neurodegenerative Diseases (CRND) at the University of Toronto has three 1,500 square foot laboratories dedicated to prion research. It will

soon open a level 3 biocontainment mouse facility at Toronto's Sunnybrook and Women's College Health Sciences Centre.

Dr. Neil Cashman's laboratory focuses on developing prion diagnostics and vaccines. In June, 2003, the journal *Nature Medicine* published a paper by Dr. Cashman's team on its discovery of a potential target on infectious prions. If a test could detect prions in blood or other easily accessible tissues, it would eliminate the need to slaughter entire herds of cattle to check for the disease.

Dr. Cashman has a standard level 1 wet laboratory and a small level 2 laboratory for biochemistry and immunological studies of experimental prions in mice and hamsters.

The laboratory is also investigating potential links between prion diseases and other major neurological diseases that involve accumulations of abnormally folded proteins. Dr. Cashman is a physician-scientist. Researchers and technicians who work in his laboratory are trained to orient basic scientific techniques towards practical outcomes such as human and animal diagnostics, treatments and vaccines.

Dr. Catherine Bergeron is a neuropathologist who heads CRND's human prion neuropathology lab. Her laboratory is an important part of Health Canada's CJD Surveillance System to investigate the risk of Creutzfeldt-Jakob disease transmission through the Canadian blood system and serves as a reference laboratory for this disease. Dr. Bergeron's work is carried out in a level 2 biosafety laboratory with enhanced ventilation standards.

Dr. David Westaway's laboratory also studies prion proteins. Besides working on model systems to recreate sporadic prion diseases, his laboratory is interested in the prion-like doppel which has many similarities to the prion protein. The doppel protein is a normal protein expressed by all studied vertebrates, and it may play a role in sperm maturation. Dr. Westaway's laboratory also performs biochemical studies of the normal prion protein and is researching how copper binds to the prion protein. An area of focus in the current work is how copper-binding activity relates to the neuroprotective action of PrP, a prion protein.

The level 3 mouse facility at Sunnybrook and Women's College Health Science Centre is a 700 square foot laboratory for mice models of scrapie and the only area on the Sunnybrook and Women's campus where mouse experimental prions can be tested. When the facility opens, it will hold up to 800 mice.

The University of Toronto is also building a large mouse facility at the Centre for Cellular and Biomolecular Research that should be operational by 2005. It is not yet known whether this facility will provide dedicated areas for prion experiments.

Canadian Research Institute for Food Safety

The Canadian Research Institute for Food Safety (CRIFS) is a research network of scientists from the University of Guelph, federal government and the Ontario government. Opened in 2002, the laboratory facility in Guelph, Ontario, consists of four level 2 biocontainment laboratories and a level 3 laboratory that will begin the commissioning process in October.

The Canada Foundation for Innovation (CFI) and the Ontario Innovation Trust (OIT) provided core funding for the $8 million CRIFS facility. The level 3 laboratory alone cost close to $3 million.

The new level 3 laboratory is designed to be flexible so it can work with a number of different highly hazardous food and animal-to-human pathogens, including TSE agents. Level 3 pathogens include anthrax, West Nile virus and *Mycobacterium tuberculosis*. Level 2 pathogens such as *E. coli* O157:H7 (responsible for the Walkerton, Ont. outbreak), *Salmonella* and *Listeria* will also be studied in the lab. CRIFS's director, Dr. Mansel Griffiths expects that the level 3 laboratory will be used for research into bioterrorism agents. BSE surveillance work now done by the University of Guelph's Laboratory Services may move into the level 3 facility.

The laboratory is equipped for molecular biology research and processing equipment to examine the effects of non-traditional technologies—such as High Pressure, Pulsed Electric Fields and Radiofrequency—on pathogens in foods. It also has a variety of imaging instruments including a confocal laser scanning microscope, photon counting cameras and access to a high-performance computer network that links several universities.

The level 3 laboratory is about 800 square feet. It does not have the facility to handle large numbers of animals. However, the university has applied for more funding to build a level 3 large animal containment facility at Guelph's Veterinary College.

CRIFS represents a multi-disciplinary collaborative approach to research, equipment and facilities.

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Dr. Michael B. Coulthart, Director, Health Canada's Host Genetics and Prion Disease program at the National Microbiology Laboratory, Winnipeg.

Dr. Mansel Griffiths, Director, Canadian Research Institute for Food Safety, Professor and Industrial Dairy Chair in Microbiology, University of Guelph, Guelph, Ontario.

Dr. David W. Strangway, President and CEO, Canada Foundation for Innovation, Ottawa.

Dr. Robert Rohwer, Director, Molecular Neurovirology Laboratory at Veterans Affairs Medical Center, Baltimore, Maryland.

Dr. Bhagirath Singh, Scientific Director, Institute of Infection and Immunology, Canadian Institutes of Health Research, Professor, Department of Microbiology and Immunology, the University of Western Ontario.

Web Sites

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Health Canada (www.hc-sc.gc.ca).

Margret Brady Nankivell
September 18, 2003

Appendix VIII

Meeting the Challenge of Prion Diseases

Glossary of Terms and Acronyms

Alleles	Any of the alternative forms of a gene that may occur at a given gene locus.
Advanced Meat Recovery System	Meat recovered by machinery without breaking bone and exposing marrow. (Definition varies in different parts of the world.)
Amyloid	A substance consisting of protein, in combination with polysaccharides, which is deposited in some organs and tissues under abnormal conditions.
Beef and Beef Products	Products containing bovine tissue.
Bioassay	A test for a disease in which a live animal is used.
Bovine spongiform encephalopathy (BSE)	A slowly progressive and ultimately fatal neurodegenerative disease of cattle. One of the family of transmissible spongiform encephalopathies.
Central Nervous System (CNS)	That part of the nervous system encompassing the brain, spinal cord and cranial nerves.
Chromosome	A DNA or RNA molecule, comprising all or a portion of the total genetic instructions of a virus, cell or organism, and functioning as the physical basis for organized replication, repair, transmission and expression of genetic information.
Chronic wasting disease of deer and elk (CWD)	A slowly progressive and ultimately fatal neurodegenerative disease of deer and elk. One of the family of transmissible spongiform encephalopathies.
Codon	A sequence of three bases in a gene or its messenger RNA that specifies a particular amino acid in the encoded protein.
Creutzfeldt-Jakob disease (CJD)	A slowly progressive and ultimately fatal neurodegenerative disease of humans. One of the family of transmissible spongiform encephalopathies.

Epidemiology	The study of disease in populations.
Familial	Tending to occur in more members of a family than expected by chance alone.
Fatal familial insomnia (FFI)	A rare human familial neurodegenerative disease caused by a prion mutation.
Feline spongiform encephalopathy (FSE)	A slowly progressive and ultimately fatal neurodegenerative disease of felidae. One of the family of transmissible spongiform encephalopathies.
Gene	A segment of a chromosome that specifies the amino acid sequence of a protein and/or RNA molecule, along with signals for regulation of expression of those encoded molecules.
Genotype	The genetic makeup of an individual organism.
Gerstmann-Sträussler-Scheinker syndrome (GSS)	A rare familial spongiform encephalopathy of humans, known to be associated with mutations in the PrP gene.
Heterozygous	A genetic term to describe having two different alleles of the same gene.
Histology	The study of cells and tissues at the microscopic level.
Homozygous	A genetic term to describe having two identical alleles of the same gene.
Intracerebral (i/c)	A route of inoculation directly into the brain.
Ileum	The last portion of the small intestine.
Incubation	The period of time between infection with a disease and the onset of clinical signs.
Infectious	Capable of being transmitted.
Infective Dose ID50	The amount of infectious material required to cause disease in approximately 50% of inoculated animals.
Intraperitoneal (i/p)	A route of inoculation into the abdominal cavity.
Intravenous (i/v)	Inoculation into a vein.

Kuru	A human transmissible spongiform encephalopathy found in the Fore people of Papua, New Guinea.
Lymphoid Tissue	Tissue involved in the production of lymph, lymphocytes and antibodies, consisting of lymph nodes, thymus, tonsils, spleen and Peyer's Patches.
Maternal Transmission	Transmission from dam to offspring either *in utero* or in the immediate postpartum period.
Meat and bone meal (MBM)	Animal-derived protein produced by rendering, and used as a protein source in animal feed.
Mechanically recovered meat (MRM)	Meat obtained using high pressure to recover the residual raw meat adhering to the bones after other boning processes have been completed. (Definition varies in different parts of the world.)
Messenger RNA	A nucleic acid molecule composed of a sequence of nucleotide bases, corresponding to the portion of a gene sequence that specifies a protein.
Neurodegenerative	Disorder of the nervous system characterized by the progressive loss of nervous tissue.
Neuron	A nerve cell.
Offal	The internal organs and entrails of animals.
Peripheral nerves	Those nerves outside the central nervous system.
Peyer's Patches	An aggregation of lymph nodules on the small intestine.
Prion	See PrP. The word *prion* was coined from the elements of the phrase *proteinaceous infectious particle*.
Protease	An enzyme that catalyzes the splitting of bonds between amino acids in proteins.
PrP	Prion protein, the protein product of the human PRNP locus and its homologous genes in other vertebrates. Originally referred to Protease-resistant Protein, the disease-associated form of this protein product.
PrP^{c}	The native, normally expressed form of PrP, named as per its "cellular" location.

PrP^{Sc}	The native disease-associated isoform of PrP, originally named for its association with scrapie. Now often used generically to refer to the disease-associated form of PrP in prion diseases other than scrapie.
PRNP	The human gene that encodes PrP. Also used in other species to mean the same thing, although the mouse nomenclature is *Prnp*.
PrP^{vCJD}	The native disease-associated isoform of PrP found in variant Creutzfeldt-Jakob disease.
PrP gene	Synonymous with PRNP, and useful only as an ad hoc shorthand for "the gene that encodes PrP".
PrP^{sen}	Approximately synonymous with PrP^{C}, but with reference to the protease sensitivity of the normal cellular form of PrP. Sometimes used to refer to the native form of PrP expressed artificially from recombinant DNA constructs, which are also typically protease sensitive.
PrP^{res}	A generic term referring to the disease-associated form of PrP that is recognizable by its partial resistance to proteolytic digestion, and thus partially synonymous with PrPSc when the latter is applied generically. Also commonly used to denote the highly protease-resistant 27-30 kilodalton product of partial proteolysis of native disease-associated PrP.
Rendering	This process has different connotations in different countries, and includes edible and inedible rendering. The processing of offal and other discarded parts of animal carcasses to make products such as meat and bone meal and tallow.
SBO	Specified bovine offals.
Subcutaneous (s/c)	Inoculation under the skin.
Scrapie	A slowly progressive and ultimately fatal neurodegenerative disease of sheep and goats. One of the family of transmissible spongiform encephalopathies.
Sporadic Disease	A disease that occurs in single cases here and there.
Specified risk material (SRM)	Comprises a range of ruminant animal parts, including the skull (with brain and eyes), tonsils, spinal cord, vertebral column and dorsal root ganglia, thymus, spleen, and intestines.

SSC	Scientific Steering Committee of the European Commission
Strain Typing	The identification of different TSE strains by determining the length of incubation period and pattern of brain damage in experimentally infected animals.
Thermostable	Retaining its character or active quality at moderately high temperatures.
Titre	A measure of the concentration of a substance.
Transmissible mink encephalopathy (TME)	A slowly progressive and ultimately fatal neurodegenerative disease of mink. One of the family of transmissible spongiform encephalopathies.
Transmissible spongiform encephalopathy (TSE)	A disease of the neurological system involving spongy degeneration of the brain with progressive dementia.
Vacuole	Any space or cavity found within or between cells in any type of tissue.
Variant CJD (vCJD; also called new variantCJD).	A transmissible disease of humans, believed to be caused by exposure to the agent causing BSE in cattle.

Appendix IX

MEETING THE CHALLENGE OF PRION DISEASES

Contact Information for Participants

Dr. Babita Agrawal
Assistant Professor
University of Alberta
611-HMRC
Edmonton, AB T6G 2S2
Tel.: 780-492-0929
Fax: 780-492-9828
E-mail: bagrawal@ualberta.ca

Ms. Nitasha Anand
Medical Student
Queen's Univerity
Kingston, ON
E-mail: 1na1@qlink.queensu.ca

Dr. Negar Asdaghi
PhD Student
University of Alberta
RM 161, HMRC Building
116 Street and 85 Avenue
Edmonton, AB T6G 2R3
Tel.: 780-492-8603
Fax: 780-492-6361
E-mail: nasdaghi@ualberta.ca

Dr. David R.C. Bailey
A/Director General, Food Safety Branch
Agriculture and Agri-Food Canada
930 Carling Ave., Rm 776
Ottawa, ON K1A 0C5
Tel.: 613-759-7851
Fax: 613-759-7772
E-mail: baileyd@agr.gc.ca

Dr. Arumaga Balachandran
Veterinary Pathologist
Canadian Food Inspection Agency
National Reference Laboratory for Scrapie and CWD
Animal Diseases Research Institute
3851 Fallowfield Road
Ottawa, ON
K2H 8P9
Canada
Tel.: 613-228-6698 ext 4854
Fax: 613-228-6103
E-mail: balachandrana@inspection.gc.ca

Mr. Gerald Baron
Postdoctoral Fellow
National Institutes of Health
Rocky Mountain Laboratories
NIAID
903 South 4th Street
Hamilton, MT 59840
Tel.: 406-363-9251
Fax: 406-363-9286
E-mail: gbaron@niaid.nih.gov

Dr. Lynn Bates
Veterinary Program Officer
Canadian Food Inspection Agency
613-269 Main Street
Winnipeg, MB R3C 1B2
Tel.: 204-983-2203
Fax: 204-983-8022
E-mail: lbates@inspection.gc.ca

Dr. Ermias Belay
Medical Epidemiologist
Centers for Disease Control and Prevention
1600 Clifton Road, MS A-39
Atlanta, GA 30333
Tel.: 404-639-4655
Fax: 404-639-3838
E-mail: ebelay@cdc.gov

Ms. Vanessa Bennett
Marketing Manager
Roche Diagnostics
201 Armand-Frappier
Laval, QC
Tel.: 450-686-3039
E-mail: vanessa.bennett@roche.com

Dr. John Berezowski
Veterinary Epidemiologist
Alberta Agriculture, Food and Rural Development
Agri-Food Systems Branch
O.S. Longman Building
6909-116 St.
Edmonton, AB T6H 4P2
Tel.: 780-427-6847
Fax: 780-422-3438
E-mail: john.berezowski@gov.ab.ca

Dr. Catherine Bergeron
University of Toronto
Centre for Research in Neurodegenerative Diseases
Tanz Neuroscience Building
6 Queen's Park Crescent West
Toronto, ON M5S 3H2
Tel.: 416-978-1877
Fax: 416-978-1878
E-mail: c.bergeron@utoronto.ca

Dr. Judith Bossé
Vice President, Science
Canadian Food Inspection Agency
59 Camelot Dr.
Ottawa, ON K1A 0Y9
Tel.: 613-225-2342
Fax: 613-228-6680
E-mail: dundasj@inspection.gc.ca

Mr. Ray Bradley
BSE Consultant
41 Marlyns Drive
Burpham
Guildford, England GU4 7LT
Tel.: 00 44-1483-575575
Fax: 00 44-1483-575575
E-mail: raybradley@btinternet.com

Dr. Paul Brown
Senior Investigator
National Institutes of Health
Laboratory of Central Nervous System Studies
Building 36, Room 4A-19
MSC 4123
Bethesda, MD 20892
Tel.: 301-496-5292
Fax: 301-496-8295
E-mail: brownp@ninds.nih.gov

Mr. Jock Buchanan-Smith
Administrator
Beef Cattle Ranch Council
Beefinfo Technologies
RR 22
Cambridge, ON N3C 2V4
Tel.: 519-822-1859
Fax: 519-822-0770
E-mail: beeftech@attcanada.ca

Dr. William R. Buchta
General Manager
Diversified Livestock Fund of Alberta Ltd.
Box 202
Alberta Beach, AB T0E 0A0
Tel.: 780-924-3174
Fax: 780-924-3153
E-mail: bbuchta@oanet.com

Dr. Herbert Budka
Professor
Institute of Neurology
University of Vienna
AKH 4J
Waehringer Guretel 18-20
A-1097 Vienna, Austria
Tel.: 43 1 40 400 5500
Fax: 43 1 40 400 5511
E-mail: h.budka@akh-wien.ac.at; oerpe@akh-wien.ac.at

Ms. Elizabeth Burgess-Pinto
Project Coordinator
University of Alberta
Faculty of Nursing
CSB 3rd Floor
Edmonton, AB T6G 2E1
Tel.: 780-492-6427
Fax: 780-492-6508
E-mail: eburgess@ualberta.ca

Mr. Guillaume Camard
Communication Manager
Bio-Rad Laboratories
3, boulevard Raymond Poincaré
92430 Marnes-la-Coquette,
Tel.: 33 1 47 95 62 61
Fax: 33 1 47 95 62 60
E-mail: guillaume_camard@bio-rad.com

Dr. Neil Cashman
Professor
Centre for Research in Neurodegenerative Diseases
University of Toronto
Tanz Building
6 Queen's Park Crescent
Toronto, ON M5S 3H2
Tel.: 416-978-1875
Fax: 416-978-1878
E-mail: neil.cashman@utoronto.ca

Dr. Bill Casley
Research Scientist
Health Canada
Biologics and Genetic Therapies Directorate
Banting Building
Tunney's Pasture 2201C
Ottawa, ON K1A 0L2
Tel.: 613-957-3096
Fax: 613-941-8933
E-mail: bill_casley@hc-sc.gc.ca

Dr. Byron Caughey
Senior Investigator
National Insitutes of Health
DHHS/DIR/NIAID/RML/LPVD
903 South 4th Street
Hamilton, MT 59840
Tel.: 406-363-9264
Fax: 406-363-9286
E-mail: bcaughey@nih.gov

Dr. Avi Chakrabartty
Associate Professor
University of Toronto
Ontario Cancer Institute
610 University Avenue
Toronto, ON M5G 2M9
Tel.: 416-946-4501 x4910
Fax: 416-946-6529
E-mail: chakrab@uhnres.utoronto.ca

Dr. Eva Y. W. Chow
Scientist
Alberta Agriculture, Food and Rural Development
6th Floor, O.S. Longman Building
6909-116 St.
Edmonton, AB T6H 4P2
Tel.: 780-427-8339
Fax: 780-415-4527
E-mail: eva.chow@gov.ab.ca

Dr. Robert Clarke
Executive Director
McLaughlin Centre for Population Health Risk Assessment
Institute of Population Health
University of Ottawa
1 Stewart Street
Ottawa, ON K1N 6N5
Tel.: 613-562-5280
Fax: 613-562-5380
E-mail: rclarke@uottawa.ca

Mr. Anthony Coles
Policy Analyst
Health Canada
Centre for Infectious Disease Prevention
Director General's Office
100 Colonnade Road, Rm..013A
Ottawa, ON K1A 0K9
Tel.: 613-948-6841
Fax: 613-946-5070
E-mail: anthony_coles@hc-sc.gc.ca

Dr. Michael Coulthart
Chief, National Laboratory for Prion Diseases
Health Canada
National Microbiology Laboratory
1015 Arlington Street
Winnipeg, MB R3E 3R2
Tel.: 204-789-6026
Fax: 204-789-5021
E-mail: mike_coulthart@hc-sc.gc.ca

Dr. Catherine Curtis
Veterinary Pathologist
Canadian Food Inspection Agency
Animal Diseases Research Institute
CFIA Lethbridge Laboratory
Box 640, Twp Rd. 9-1
Lethbridge, AB T1J 3Z4
Tel.: 403-382-5527
Fax: 403-381-1202
E-mail: curtisc@inspection.gc.ca

Dr. Stephanie Czub
Canadian Food Inspection Agency
59 Camelot Drive, Rm. 206W
Ottawa, ON K1A 0X9
Tel.: 613-225-2342
Fax: 613-228-6631
E-mail: czubs@inspection.gc.ca

Ms. Rolande D'Amour
Nurse Consultant
Nocosomial and Occupational Infections Section
Health Care Acquired Infections Division
Centre for Infectious Disease Prevention and Control
PL 0603E1
Tunney's Pasture
Ottawa, ON K1A 0L2
Tel.: 613-948-5836
Fax: 613-998-6413
E-mail: rolande_damour@hc-sc.gc.ca

Dr. Jean-Philippe Deslys
Atomic Energy Commission, France
CEA, DSV/DRM, Groupe d'Innovation Diagnostique et Thérapeutique sur les Infections à prions, CEA de Fontenay-aux-Roses, BP6,
92265 Fontenay-aux-Roses,
Tel.: 33 (0)1 46 54 82 79
Fax: 33 (0)1 46 54 77 26
E-mail: jdeslys@villon.saclay.cea.fr

Dr. Sylvie Dufresne
Microbiologist
TSO3
2505, Dalton
Sainte-Foy, QC G1P 3S5
Tel.: 418-651-0003 ext 224
Fax: 418-653-3576
E-mail: sdufresne@tso3.com

Ms. Leigh Edgar
Conservation Researcher
Canadian Wildlife Federation
350 Michael Cowpland Drive
Kanata, ON K2M 2W1
Tel.: 613-599-9594 ext. 247
Fax: 613-599-4428
E-mail: leighe@cwf-fcf.org

Dr. Cyprian Enweani
Network Chief
Canadian Food Inspection Agency
101-620 Royal Avenue
New Westminster, BC V3M 1S2
Tel.: 604-666-8854
Fax: 604-666-1963
E-mail: enweanic@inspection.gc.ca

Dr. David Evans
Professor and Chair
University of Alberta
Medical Microbiology and Immunology
Edmonton, AB T6G 2H7
Tel.: 780-492-2308
Fax: 780-492-7521
E-mail: devans@ualberta.ca

Dr. Ross Findlater
Chief Medical Health Officer
Saskatchewan Health
3475 Albert Street
Regina , SK S4S 6X6
Tel.: 306-787-3235
Fax: 306-787-3237
E-mail: rfindlater@health.gov.sk.ca

Mr. Nelson Fok
Associate Director, Environmental Health
Capital Health Authority
300, 10216-124 Street
Edmonton, AB T5N 4A3
Tel.: 780-413-7936
Fax: 780-482-5383
E-mail: nf

Dr. Ann Fortin
Coordinator
Secrétariat du système du sang
Ministère de la Santé et des Services sociaux
1075. chemin Sainte-Foy
Quebec, QC G1S 2M1
Tel.: 418-266-6710
Fax: 418-266-6779
E-mail: ann.fortin@msss.gouv.qc.ca

Dr. Brian Foster
Senior Science Advisor
Health Canada
Therapeutic Products Directorate
Holland Cross 3102C3
1600 Scott Street
Ottawa, ON K1A 1B6
Tel.: 613-957-3506
Fax: 613-941-5035
E-mail: brian_foster@hc-sc.gc.ca

Mr. Malcolm Gains
PhD Student
Lady Davis Institute for Medical Research
Bloomfield Centre for Research in Aging
3999 cote Ste-Catherine
Montreal, QC H3T 1E2
Tel.: 514-340-8222 ext 3529
Fax: 514-340-8295
E-mail: mgains@po-box.mcgill.ca

Dr. Aziz Ghahary
Professor
University of Alberta
Department of Surgery
161 HMRC
Edmonton, AB T6G 2B7
Tel.: 780-492-0061
Fax: 780-492-6361
E-mail: aghahary@ualberta.ca

Mr. Nick Giannakoulis
Manager, Program Policy and Analysis
Health Canada
Centre for Infectious Disease Prevention and Control
100 Colonnade Rd, Rm. 237D
Ottawa, ON K1A 0L2
Tel.: 613-946-7623
Fax: 613-952-5070
E-mail: nick_giannakoulis@hc-sc.gc.ca

Dr. Antonio Giulivi
Director, Blood Safety and Health Care Acquired Infections Division
Health Canada
Centre for Infectious Disease Prevention and Control
Building #6, Rm 1442, AL 0601E2
Tunney's Pasture
Ottawa, ON K1A 0L2
Tel.: 613-957-1789
Fax: 613-952-6668
E-mail: antonio_giulivi@hc-sc.gc.ca

Dr. Zhilong Gong
Research Associate
University of Alberta
Department of Public Health Services
10-110 CSB
Edmonton, AB T6G 2G3
Tel.: 780-492-7776
Fax: 780-492-7800
E-mail: zgong@ualberta.ca

Dr. Jennifer Griffin
Research Associate
University of Toronto
Centre for Research in Neurodegenerative Diseases
Tanz Neurosciences Centre
6 Queen's Park Crescent West
Toronto, ON M5S 3H2
Tel.: 416-978-0772
Fax: 416-978-1878
E-mail: jennifer.griffin@utoronto.ca

Dr. Karen Grimsrud
Deputy Provincial Health Officer
Alberta Health and Wellness
Provincial Health Office
24th floor, Telus Plaza North Tower
10025 Jasper Avenue
Edmonton, AB T5J 2N3
Tel.: 780-415-2797
Fax: 780-427-7683
E-mail: karen.grimsrud@gov.ab.ca

Dr. Paul Gully
Senior Director General, Population and Public Health Branch
Health Canada
130 Colonnade Road, AL 6501C
Ottawa, ON K1A 0K9
Tel.: 613-954-9663
Fax: 613-954-8529
E-mail: paul_gully@hc-sc.gc.ca

Dr. John Hamerton
Distinguised Professor Emeritus
University of Manitoba
Dept. of Biochemistry and Medical Genetics
Faculty of Medicine
301 Basic Medical Sciences Building
Winnipeg, MB R3E 0W3
Tel.: 204-789-3531
E-mail: hamertn@ms.umanitoba.ca

Dr. Greg Hammond
Director, Public Health Branch
Manitoba Health
Tel.: 204-788-6701
Fax: 204-948-2204
E-mail: ghammond@gov.mb.ca

Ms. Anita Hanrahan
Director of Communicable Disease Control
Capital Health Authority
Plaza 124, Suite 300
10216-124 Street
Edmonton, AB T5N 4A3
Tel.: 780-413-7944
Fax: 780-413-7950
E-mail: ahanraha@cha.ab.ca

Mr. Bob Hills
Manager, TSE Secretariat
Health Canada
Health Products and Food Branch
HPB Building 7, Rm 0189, AL 0700B5
Tunney's Pasture
Ottawa, ON K1A 0L2
Tel.: 613-957-9005
Fax: 613-946-4589
E-mail: bob_hills@hc-sc.gc.ca

Dr. G. Douglas Inglis
Research Scientist
Agriculture and Agri-Food Canada
Lethbridge Research Centre
5403-1st Avenue South
Lethbridge, AB T1J 4B1
Tel.: 403-317-3356
Fax: 403-382-3156
E-mail: inglisd@agr.gc.ca

Dr. Gerard Jansen
Neuropathologist, BSSHCAID
Health Canada
Building #6
AL 0301E2
Tunney's Pasture
Ottawa, ON
K1A 0L2
Tel.: 888-489-2999
FAX: 613-952-6668
E-mail: gerard_jansen@hc-sc.gc.ca

Ms. Marilyn Johnson
Immunochemistry Technologists
Alberta Agriculture, Food and Rural Development
Agri-Food Systems Branch
Food Safety Division
1st Floor, O.S. Longman Building
6909-116 St.
Edmonton, AB T6H 4P2
Tel.: 780-427-8304
Fax: 780-422-3438
E-mail: marilyn.johnson@gov.ab.ca

Dr. Michael Joyce
Postdoctoral Fellow
Department of Medical Microbiology and Immunology
622 HMRC
University of Alberta
Edmonton, AB T6G 2S2
Tel.: 780-492-9819
Fax: 780-492-9828
E-mail: maj2@ualberta.ca

Dr. Doug Kennedy
President
Icosahedron Consulting, Inc.
159 Lowe Rd.
1RR #4
Ashton, ON K0A 1B
Tel.: 613-257-5837
Fax: 613-257-5837
E-mail: icosa@allstream.net

Dr. Kevin Keough
Chief Scientist
Health Canada
Office of the Chief Scientist
Tunney's Pasture
Ottawa, ON K1A 0K9
Tel.: 613-941-3003
Fax: 613-941-3007
E-mail: kevin_keough@hc-sc.gc.ca

Dr. Michael King
Canadian Hemophilia Society
9035 Saskatchewan Drive
Edmonton, AB T6G 2B2
Tel.: 780-908-0771
E-mail: mackerel@telusplanet.net

Dr. Richard Knight
Professor
National CJD Surveillance Unit
Western General Hospital
Edinburgh, Scotland
E-mail: r.knight@ed.ac.uk

Dr. Rakesh Kumar
Associate Professor
University of Alberta
Faculty of Medicine
1-71 MSB
Edmonton, AB T6G 2H7
Tel.: 780-492-7545
Fax: 780-492-7521
E-mail: rkumar@ualberta.ca

Dr. Andrea LeBlanc
Associate Professor
McGill University
3755 cote Ste-Catherine
Montreal, QC H3T 1E2
Tel.: 514-340-8222 ext 4976
Fax: 514-340-8295
E-mail: andrea.leblanc@mcgill.ca

Ms. Annie Leduc
Assistante de Recherche
Université de Montréal
Pavillon Principal
Faculté de médecine dentaire
Local B-507
2900 Boulevard Édouard-Montpetit
Montreal, QC H3C 3J7
Tel.: 514-343-2774
Fax: 514-343-2233
E-mail: annie.leduc@umontreal.ca

Dr. Keith Lehman
District Veterinarian
Canadian Food Inspection Agency
205, 7000 - 113 Street
Edmonton, AB T6H 5T6
Tel.: 780-495-3065
Fax: 780-495-3359
E-mail: lehmank@inspection.gc.ca

Dr. Marty Lehto
Post-Doctoral Fellow
University of Toronto
Centre for Research in Neurodegenerative Diseases
Tanz Neurosciences Centre
6 Queen's Park Crescent West
Toronto, ON M5S 3H2
Tel.: 416-978-0772
Fax: 416-978-1878
E-mail: marty.lehto@utoronto.ca

Dr. Gary Little
Senior Staff Veterinarian
Canadian Food Inspection Agency
Animal Health and Production Division
59 Camelot Drive, Rm. 2049
Ottawa, ON K1A 0Y9
Tel.: 613-225-2342 ex 3862
Fax: 613-228-6630
E-mail: glittle@inspection.gc.ca

Dr. Neil Mabbott
Senior Research Scientist
Institute for Animal Health
Ogston Building
West Mains Road
Edinburgh, Scotland EH9 3JF
Tel.: 44 131 319 8220
Fax: 44 131 668 3872
E-mail: neil.mabbott@bbsrc.ac.uk

Dr. Norm Machell
Technical Service Veterinarian
Schering-Plough Animal Health
RR 3, Site 8
Box 9
Olds, AB T4H 1P4
Tel.: 403-556-8586
Fax: 403-556-8501
E-mail: norm.machell@spcorp.com

Dr. Rupasri Mandal
Post-Doctoral Research Fellow
University of Alberta
Environmental Health Sciences
Department of Public Health Services
10-110 CSB
Edmonton, AB T6G 2G3
Tel.: 780-492-6850
Fax: 780-492-7800
E-mail: rmandal@ualberta.ca

Dr. Richard Marchand
Medical Advisor
InoMed
5375 Lafond
Montreal, QC H1X 3G6
Tel.: 514-240-3387
E-mail: marchanr@globale.net

Dr. Andrew L. Mason
Associate Professor, Medicine
University of Alberta
Division of Gastroenterology
Rm 208 College Plaza
8215-112 Street
Edmonton, AB T6G 2C8
Tel.: 780-492-8712
Fax: 780-492-7964
E-mail: andrew.mason@ualberta.ca

Dr. Ram Mehta
President
PBR Laboratories, Inc.
4290-91A St Blk C
Edmonton, AB T6E 5V2
Tel.: 780-450-3957
Fax: 780-450-3960
E-mail: pbr@pbr.ca

Ms. Teresa Mersereau
Communicable Disease Control Senior
Team Lead
Alberta Health and Wellness
23rd fl Telus Plaza North Tower
10025 Jasper Avenue
Edmonton, AB T5J 2N3
Tel.: 780 415-2798
Fax: 780 422-6663
E-mail: teresa.mersereau@gov.ab.ca

Dr. Brian Miller
Veterinarian
Alberta Agriculture, Food and Rural
Development
Agri-Food Systems Branch
Food Safety Division
1st Floor, O.S. Longman Building
6909-116 St.
Edmonton, AB T6H 4P2
Tel.: 780-427-8201
Fax: 780-422-3438
E-mail: brian.miller@gov.ab.ca

Dr. Masako Miyazaki
Special Advisor
University of Alberta
Faculty of Rehabilitation Medicine
208 Corbett Hall
Edmonton, AB T6G 2G4
Tel.: 780-492-9127
Fax: 780-988-5660
E-mail: masako6@shaw.ca

Dr. Stephen S. Moore
Professor and Research Chair, Bovine Genomics
University of Alberta
Agricultural, Food and Natural Sciences
Edmonton, AB
Tel.: 780-492-0169
Fax: 780-492-4265
E-mail: stephen.moore@ualberta.ca

Mr. Sorin Musat-Marcu
President
HistoBest Inc.
8308-114 Street
Edmonton, AB T6G 2E1
Tel.: 780-439-3122
Fax: 780-439-5777
E-mail: info@histobest.com

Dr. Stephen Norman
A/Director
Canadian Food Inspection Agency
Biocontaiment, Safety and Facility Services Division
159 Cleopatra Drive
Ottawa, ON K1A 0Y9
Tel.: 613-221-7021
Fax: 613-228-6129
E-mail: normans@inspection.gc.ca

Dr. Gerald Ollis
Chief Provincial Veterinarian
Alberta Agriculture, Food and Rural Development
Agri-Food Systems Branch
Food Safety Division
1st Floor, O.S. Longman Building
6909-116 St.
Edmonton, AB T6H 4P2
Tel.: 780-427-6406
Fax: 780-427-1437
E-mail: gerald.ollis@gov.ab.ca

Mr. David Omahen
Graduate Student/Neurosurgery Resident
University of Alberta
707-11007-83rd Avenue
Edmonton, AB T6G 0T9
Tel.: 780-433-0381
E-mail: domahen@ualberta.ca

Dr. Adbel Omri
Professeur agrégé
Laurentian University
Department of Chemistry and Biochemistry
Office S-416
935 Ramsey Lake Road
Sudbury, ON P3E 2C6
Tel.: 705-675-1151 ext 2190
Fax: 705-675-4844
E-mail: aomri@nickel.laurentian.ca

Mr. Harry Peery
Graduate Student
University of Saskatchewan
Department of Pharmacology
107 Wiggins Road
Saskatoon, SK S7N 5E5
Tel.: 306-966-6295
Fax: 306-966-6295
E-mail: hep435@mail.usask.ca

Dr. Linda Pilarski
University of Alberta/Cross Cancer Institute
Cross Cancer Institute
11560 University Avenue
Edmonton, AB T6G 1Z2
Tel.: 780-432-8925
Fax: 780-432-8928
E-mail: lpilarsk@ualberta.ca

Ms. Maya Ponte
Graduate Student
University of California at San Francisco
2614 41st Street #4
Washington, DC 20007
Tel.: 202-965-7770
E-mail: mponte@itsa.ucsf.edu

Dr. Chris Power
Professor
University of Calgary
Clinical Neurosciences
Faculty of Medicine (Medical School)
3330 Hospital Drive NW
Calgary, AB T2N 4N1
Tel.: 403-220-5572
Fax: 403-283-8731
E-mail: power@ucalgary.ca

Dr. Shane Renwick
Director, Animal Health Laboratory Services
Canadian Food Inspection Agency
Biocontaiment, Safety and Facility Services Division
159 Cleopatra Drive
Ottawa, ON K1A 0Y9
Tel.: 613-221-7019
Fax: 613-221-6656
E-mail: renwicks@inspection.gc.ca

Dr. Maura Ricketts
Senior Medical Advisor
Health Canada
Blood Safety Surveillance and Health Care Acquired Infections Division
Health Canada Building 6, Tunney's Pasture
Address Locator 0601E2
Ottawa, ON K1A 0K9
Tel.: 613-948-7518
Fax: 613-952-6668
E-mail: maura_ricketts@hc-sc.gc.ca

Dr. Ron Rogers
Senior Scientific Advisor
Health Canada
Bureau of Microbial Hazards
Health Products and Food Branch
1 Ross Avenue, AL 2203G3
Tunney's Pasture
Ottawa, ON K1A 0L2
Tel.: 613-952-9706
Fax: 613-954-1198
E-mail: ron_rogers@hc-sc.gc.ca

Dr. Robert Rohwer
Director, Laboratory of Molecular Neurovirology and Associate Professor of Neurology at the University of Maryland, Baltimore
Baltimore Research and Education Foundation, Inc.
10 N. Greene Street
Mailstop 151
Baltimore, MD 21201
Tel.: 410-605-7000 ext 6462
Fax: 410-605-7959
E-mail: rrohwer@umaryland.edu

Mr. Xavier Roucou
Postdoctoral Fellow
Lady Davis Institute for Medical Research
Bloomfield Centre for Research in Aging
3999 cote Ste-Catherine
Montreal, QC H3T 1E2
Tel.: 514-340-8222 ext 3529
Fax: 514-340-8295
E-mail: xavier.roucou@staff.mcgill.ca

Dr. Erling Rud
Research Scientist
Health Canada
Sir Frederick Banting Research Centre
Building 22, PL 2203E, Room C308
Tunney's Pasture
Ottawa, ON K1A 0L2
Tel.: 613-957-8049
Fax: 613-941-6625
E-mail: erling_rud@hc-sc.gc.ca

Dr. Fabio Rupp
Regional Director, North America
Prionics AG
919 Mackenzie Drive
Sunnyvale, CA 94087
Tel.: 408-242-6170
E-mail: frupp@comcast.net

Dr. Luis Schang
Assistant Professor
University of Alberta
315 HMRC
Depts. of Biochemistry and Medical
Microbiology and Immunology
Edmonton, AB T6G 2S2
Tel.: 780-492-6265
Fax: 780-492-3383
E-mail: luis.schang@ualberta.ca

Dr. Erick Schmidt
President
Biospheres Technologies Inc.
4130-69 Ave
Edmonton, AB T6B 2V2
Tel.: 403-704-3493
Fax: 403-783-2744
E-mail: kelm@telusplanet.net

Dr. Jacynthe Séguin
Agente de recherche
Université de Montréal
Pavillon Principal
Faculté de médecine dentaire
Département de stomatologie
Laboratoire de microbiologie
pièce D524, 2900 Boulevard Édouard-
Montpetit
Montreal, QC H3C 3J7
Tel.: 514-343-6111 ext 3381
Fax: 514-343-2233
E-mail: j.seguin@umontreal.ca

Dr. Alec Sehon
University Distinguished Professor (Retired)
and Senior Scholar
University of Manitoba
Immunology Department
Faculty of Medicine
Winnipeg, MB
Tel.: 204-489-4837
Fax: 204-488-7207
E-mail: sehona@ms.umanitoba.ca

Dr. James J. Sejvar
Neuroepidemiologist
Centers for Disease Control and Prevention
1600 Clifton Road, MS A-39
Atlanta, GA 30333
Tel.: 404-634-4657
Fax: 404-639-3838
E-mail: zea3@cdc.gov

Dr. Leslie Shinobu
Sunnybrook and Women's College Health Sciences Centre
Research S119
2075 Bayview Avenue
North York, ON M4N 3M5
Tel.: 617-480-6100 ext 3254
E-mail: leslie.shinobu@sw.ca

Dr. Ameeta Singh
Infectious Diseases Medical Consultant
Alberta Health and Wellness
Provincial Health Office
23rd floor, Telus Plaza North Tower
10025 Jasper Avenue
Edmonton, AB T5J 2N3
Tel.: 780-415-2825
Fax: 780-422-5149
E-mail: ameeta.singh@gov.ab.ca

Dr. Bhagirath Singh
Scientific Director
CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute
The University of Western Ontario
1400 Western Road, Suite 214
London, ON N6G 2V4
Tel.: 519-661-3228
Fax: 519-661-4226
E-mail: bsingh@uwo.ca

Mr. Bill Slater
Regional Food Liaison Officer
Health Canada
Health Products and Food Branch
1440, 10123-99 Street
Edmonton, AB T5J 3H1
Tel.: 780-495-3682
Fax: 780-495-2624
E-mail: bill_slater@hc-sc.gc.ca

Dr. Ole Sorensen
Research Scientist and Biosafety Officer
Alberta Agriculture, Food and Rural Development
Agri-Food Laboratories Branch
6909-116 Street
Edmonton, AB T6H 4P2
Tel.: 780-427-8277
Fax: 780-415-4527
E-mail: ole.sorensen@gov.ab.ca

Dr. Ken Stepushyn
Veterinary Program Specialist
Canadian Food Inspection Agency
8801 East Saanich Road
Sidney, BC V8L 1H3
Tel.: 204-983-2203
Fax: 204-983-8022
E-mail: stepushynk@inspection.gc.ca

Mr. Bill Stockl
Special Projects
Cristallo Holdings Inc.
206, 10458 Mayfield Road
Edmonton, AB T5P 4P4
Tel.: 780-444-7133
Fax: 780-444-2486
E-mail: bill.stockl@canglobe.ab.ca

Ms. Faith Stratton
Provincial Medical Officer of Health
Newfoundland and Labrador Department of Health
Division of Disease Control
Department of Health and Community Services
PO Box 8700
St. John's, NF A1B 4J6
Tel.: 709-729-3430
Fax: 709-729-0730
E-mail: fstratton@gov.nf.ca

Dr. Surachai Supattapone
Assistant Professor, Biochemistry and Medicine
Dartmouth Medical School
7200 Vail Building, Room 302
Hanover, NH 03755
Tel.: 603-650-1192
Fax: 603-650-1193
E-mail: supattapone@dartmouth.edu

Dr. Witold Surewicz
Professor, Department of Physiology and Biophysics
Case Western Reserve University
2109 Adelbert Road
Cleveland, OH 44106
Tel.: 216-368-0139
Fax: 216-368-1693
E-mail: wks3@po.cwru.edu

Dr. David Taylor
Consultant
SEDECON 2000
147 Oxgangs Road North
Edinburgh, Scotland EH13 9DX
Tel.: 0044 131 441 3897
Fax: 0044 131 441 3897
E-mail:
david.taylor@sedecon2000.freeserve.co.uk

Dr. Jean A. C. Triscott
Program Director, Care of the Elderly Program and Associate Professor, Department of Family Medicine
10230-11 Avenue
Edmonton, AB T5G 0B7
Tel.: 780-474-8826
Fax: 780-474-8846
E-mail: jtriscot@cha.ab.ca

Dr. Lorne Tyrrell
Dean
University of Alberta
Faculty of Medicine (Dentistry)
2J2 Walter Mackenzie Centre
8440 112nd Street
Edmonton, AB T6G 2R7
Tel.: 780-492-9728
Fax: 780-492-7303
E-mail: lorne.tyrrell@ualberta.ca

Ms. Francine Villeneuve
Senior Program Officer
Health Canada
Health Research
Office of the Chief Scientist
Sir Frederick Banting Building, PL 2202C
2nd Floor, Room 290-14
Tunney's Pasture
Ottawa, ON K1A 0K9
Tel.: 613-946-5607
Fax: 613-957-1589
E-mail: francine_villeneuve@hc-sc.gc.ca

Dr. Murray Waldman
St. Johns Rehabilitation Hospital
91 Leuty Avenue
Toronto, ON M4E 2R2
Tel.: 416-686-3383
Fax: 416-226-6285
E-mail: murraywaldman@hotmail.com

Dr. HaiLin Wang
Postdoctoral Fellow, Department of Public Health Sciences
University of Alberta
Environmental Health Sciences Program
Faculty of Medicine and Dentistry
10-102 Clinical Sciences Building
Edmonton, AB T6H 2G3
Tel.: 780-492-7796
Fax: 780-492-7800
E-mail: hlwang@ualberta.ca

Ms. Leslie Warick
Nursing Consultant
23rd Floor TPNT
10025 Jasper Avenue
Edmonton, AB T5J 2N3
Tel.: 780-422-1930
Fax: 780-422-6663
E-mail: leslie.warick@gov.ab.ca

Dr. Joel H. Weiner
Associate Dean (Research)
University of Alberta
2J2.11 WMC
Edmonton, AB T6G 2R7
Tel.: 780-492-9723
Fax: 780-492-7303
E-mail: joel.weiner@ualberta.ca

Dr. Ileana Wenger
Veterinarian
OC Flock Management
Box 610
Bowden, AB T0M 0K0
Tel.: 403-224-2463
Fax: 403-224-2431
E-mail: hdf@rttinc.com

Dr. David Westaway
Centre for Research in Neurodegenerative Diseases
University of Toronto
Tanz Building
6 Queen's Park Crescent
Toronto, ON M5S 3H2
Tel.: 416-978-1875
Fax: 416-978-1878
E-mail: david.westaway@utoronto.ca

Dr. Kumanan Wilson
University Health Network
Toronto General Hospital
ENG-254
200 Elizabeth Street
Toronto, ON M5G 2C4
Tel.: 416-340-3662
Fax: 416-595-5826
E-mail: kumanan.wilson@uhn.on.ca

Dr. Murray Woodbury
Chair, Specialized Livestock Research Program
Western College of Veterinary Medicine
Department of Large Animal Clinical Sciences
University of Saskatchewan
52 Campus Drive
Saskatoon, SK S7N 5B4
Tel.: 306-966-7170
Fax: 306-966-7159
E-mail: woodbury@usask.ca

Dr. John T. Wu
Laboratory Scientist
Alberta Agriculture, Food and Rural Development
O.S. Longman Building
6909-116 St.
Edmonton, AB T6H 4P2
Tel.: 780-427-8324
Fax: 780-415-4527
E-mail: john.wu@gov.ab.ca

Dr. Lisa Young
Biosafety Specialist, A/Head
Canadian Food Inspection Agency
Biocontaiment, Safety and Facility Services Division
159 Cleopatra Drive
Ottawa, ON K1A 0Y9
Tel.: 613-221-7073
Fax: 613-228-6129
E-mail: youngl@inspection.gc.ca

Dr. Inga Zerr
CJD-Surveillance
Neurologische Klinik
Universitatsklinikum Gottingen
Robert-Koch-Str. 40
D-37075 Gottingen, Germany
Tel.: 49 551 39-6636
Fax: 49 551 39-7020
E-mail: epicjd@med.uni-goettingen.de

Support

Dr. Judy Bray
Assistant Director, Special Projects
CIHR Institute of Infection and Immunity
160 Elgin Street
Postal Locator 4809A
Ottawa, ON K1A 0W9
Tel.: 613-954-7223
Fax: 613-941-1040
E-mail: jbray@cihr-irsc.gc.ca

Mr. Bruce Moor
Administrative Officer
CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute
The University of Western Ontario
1400 Western Road, Suite 214
London, ON N6G 2V4
Tel.: 519-661-3228
Fax: 519-661-4226
E-mail: bmoor@uwo.ca

Ms. Carol Richardson
Manager, Programs and Evaluation
CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute
The University of Western Ontario
1400 Western Road, Suite 214
London, ON N6G 2V4
Tel.: 519-661-3228
Fax: 519-661-4226
E-mail: carol.richardson@fmd.uwo.ca

Consultants

Strachan•Tomlinson and Associates
31 Euclid Avenue
Ottawa, ON K1S 2W2
Tel.: 613-730-1000
Fax: 613-730-0014
E-mail: stractom@cyberus.ca
Process Design and Facilitation: Dorothy Strachan
Project Management: Peter Ashley

Professional Writer

Ms. Nikki Kelvin
305 Huron Street
London, ON N6A 2K1
Tel.: 519-433-2035
E-mail: nikkikelvin@sympatico.ca;
nkelvin@uwo.ca