Academic and Clinical Perspectives Ontario Centre Of Excellence In Environmental Health

Chronic Complex Conditions

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome,
Fibromyalgia Environmental Sensitivities/Multiple Chemical Sensitivity

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Compendium 3/4 of the Business Case for an OCEEH

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Executive Summary

Introduction

Whereas previously there was little evidence of specific association between many environmental exposures and health problems, now there is mounting evidence of links influenced by genetics and epigenetics in all the chronic complex conditions that have been studied. Understanding is accumulating of potentially related mechanisms and relationships.

While the science is plentiful and dense to read, the implications are very important.

This report includes the following sections.

1. Sections I-II:
   A broad-based scoping, but non-systematic, review of the scientific literature related to environmental associations with chronic complex health conditions (Section I) and focused on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Fibromyalgia (FM), and Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS) (Section II).

   The literature reviewed was, in most part, published by the United States National Library of Medicine in Medline, supplemented on occasion by credible reports by government agencies, professional associations and environmental/patient support organizations.

2. Section III-VI:
   An overview of what might be developed to build the Centre of Excellence on the foundation of the Environmental Health Clinic to prevent chronic environmentally linked conditions, and to care for people with ME/CFS, FM and ES/MCS as close to home as possible, as well as broad expansion of education/health promotion and research (Sections III-VI).

I Accumulating Evidence of Chronic Complex Conditions Relatedness to the Environment

Chronic complex conditions are the leading cause of death and disability worldwide. Almost 80% of Ontarians over the age of 45 have a chronic condition, and 70% of them have more than one. Although poorly managed single conditions can be complex, multimorbidity usually contributes to continuing functional decline, poor quality of life, disability and high personal and system health care costs.

Environmental health, according to Public Health Ontario, encompasses the assessment and control of the physical, chemical, biological, social and behavioural factors in the environment that influence health and disease occurrence. According to the World Health Organization, factors in the environment have both direct pathological and often indirect effects on health and wellbeing from housing, urban development, land use and transport.

While there are genetic susceptibility factors, environmental factors influence 70 to 90% of chronic disease risk. Pollution exposure influences epigenetic change, which increases genes' susceptibility to turn on and off in response to environmental factors. That then increases the

risk, particularly in those individuals with genetic susceptibility factors, to develop environmentally-linked diseases, such as allergies, autoimmune disorders, asthma, diabetes, cardiovascular disease, neuropsychological development disorders and autism in children, as well as progressive neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases.

Chronic conditions such as ME/CFS, FM, and ES/MCS appear to also be linked to the environment in these ways and are increasing in prevalence. These conditions commonly overlap with each other and other chronic conditions and are challenging to manage. However, in spite of high rates of unmet health needs and high rates of disability, with considerable health care dollars being spent, there is almost no focus on research to be able to diagnose, treat and prevent these conditions more efficiently.

Toxic chemicals/agents enter the body not only from exogenous sources (air, water, diet, drugs, consumer products and radiation) but also from endogenous processes, including byproducts of our natural metabolism, inflammation, existing diseases, infections, and gut flora. Thus, the relevant 'environment' is the body's internal chemical environment, i.e. what's inside it.

The common pathological mechanisms of all these diseases and conditions include a burden to detoxification systems, damage to cellular organelles (metabolic subunits), including the energy-generating mitochondria, as well as oxidative stress, reduced cell function, with increased cell death or proliferation, and systemic inflammation, which makes other chronic conditions (multimorbidity) more likely.

The traditional reductionist approach to understanding and treating chronic complex conditions is inadequate because of dysfunction of multiple organ systems and comorbidity.

A systems medicine approach, that includes environment as a determinant of health, recognizes the interactions of organs, cells, genetics and epigenetics, oxidative stress and systemic inflammation in response to exposure to environmental agents.

II Increasing Prevalence and Awareness of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Fibromyalgia (FM) and Environmental Sensitivities/Multiple Chemical Sensitivity

The 2010 Canadian Community Health Survey (CCHS) reported that the number of Canadians who had a diagnosis by a health professional of ME/CFS, FM and ES/MCS has increased markedly since 2005. The prevalence of CFS increased by 23%, FM by 13% , and ES/MCS by 34%.

ME/CFS affects from 0.5 to 3 percent of the population and recovery rates are quite low - around 6%. The dominating complaint is severe, chronic fatigue present for at least 6 months,
3 months in children, which is made worse by exertion, is not substantially relieved by rest, and the post-exertion recovery time is prolonged. It affects women six times the rate of men and it is unknown how often it occurs in children. There are various definitions, which influence estimates of prevalence, diagnosis and guidelines for treatment. Two day cardiopulmonary exercise testing repeated 24 hours after the first test demonstrates reduction in maximal aerobic

capacity, aerobic threshold and increased oxidative stress, and so exercise should be at an individual's own pace. There are extensive alterations in gene expression with at least 7 different genetic subtypes and there is significant comorbidity, including with FM and ES/MCS. Treatment is currently symptom-based and individualized. There is a lack of evidence on the comparative effectiveness of individual therapies.

FM is a chronic, widespread pain disorder, present for at least 3 months. Prevalence ranges from 2-6 percent, with females 6-9 times more commonly affected than men. In children, it is more common in prepubertal or adolescent girls.

FM is thought to be a nervous system disorder, with activation of NMDA and TRPV1 receptors. There is evidence for oxidative stress, reduced mitochondrial function and systemic inflammation. It is frequently comorbid with ME/CFS, ES/MCS and other chronic conditions and there is significant disability. The majority of those who work do so part-time. Multiple treatments including pregabalin and duloxetine medications, physical therapies and exercise are suggested. Many patients find pharmacotherapy is not helpful or discontinue it due to side effects.

ES/MCS has been described as multisystem symptoms triggered by exposure to diverse chemicals at levels not formerly bothering the patients and not affecting most people. Published consensus criteria for the diagnosis have been validated by the Ministry of Health-funded Environmental Hypersensitivity Research Unit (EHRU) at the University of Toronto in collaboration with the Environmental Health Clinic at Women's College Hospital.

ES/MCS affects 2.4-3.4 percent of the Canadian population, women being more affected than men. This may be due to being more responsive to their environment via both the limbic and immune systems, having a greater body burden of chemical exposures, and having less efficient detoxification systems compared to men.

Sensitization of the nervous system to chemicals and subsequent increased sensitivity has been demonstrated in animal models and there is evidence that ES/MCS patients are genetically predisposed to have inferior enzyme systems for detoxification. Because they are less capable of efficiently detoxifying, oxidative stress occurs, which can sensitize TRPV1 receptors. These receptors are widespread and are found in the brain, eye, bladder lining, mast cells, stomach lining, intestines, larynx and bronchial tubes. They are capsaicin (hot pepper) sensitive. Capsaicin sensitivity has been documented in ES/MCS.

ES/MCS is frequently comorbid with ME/CFS and FM and they all are also frequently comorbid with other common conditions, such as chronic headache, chronic migraine headache, irritable bowel syndrome (IBS), allergies, asthma and autoimmune disorders. (APPENDIX A-Overlapping Diagnoses for 23 Chronic Conditions Cohorts)

ES/MCS patients have problems accessing common community resources that most persons take for granted, including communities of worship, grocery stores, shopping centres, community meetings, public libraries, restaurants, movies, use of public transportation, the homes of extended family members and friends, offices of dentists and medical doctors, public parks,

classes at their local universities, and most significantly, access to work. Others' lack of understanding and refusal to make accommodations in the workplace have denied spatial access. (APPENDIX B- ES/MCS Status Report) People with ME/CFS and FM may also have access issues because of lack of energy and reduced activity levels.

Patients with ME/CFS, FM and ES/MCS are stigmatized by their condition and have difficulty accessing appropriate, effective health care.

Earlier diagnosis of these three conditions can reduce referral costs and investigations, and interventions may prevent the onset of comorbidity, leading to a better quality of life for the individual and net savings for the healthcare sector.

III Need for Environmental Health Education and Government-funded Canadian Environmental Health Clinics

Systems-based health training recognizing environment as a determinant of health is lacking in medical schools and there is a lack of connection to public health. There is an absence of education about ME/CFS, FM and ES/MCS, except for annual Environmental Health Clinic or Ontario College of Family Physicians Environmental Health Days, and presentations and Mainpro-C workshops at professional conferences for practising physicians who choose to attend. The Jurisdictional Review of Community Health Centres revealed that most physicians and nurse practitioners are not comfortable diagnosing or treating these disorders.

A feasibility study by the OCFP in 2008 concluded that an adequately funded Environmental Health Centre is long overdue. Presently, the Environmental Health Clinic at Women's College Hospital provides much less clinical service than the Nova Scotia Environmental Health Centre and the planned provision of assessment, treatment and research by the newly established Complex Chronic Diseases Program at British Columbia Women's Hospital and Health Centre.

Nevertheless, the EHC has made an important start with clinical programs, resources, education of health professionals, crucial foundational research, and partnerships for health promotion with the Ontario College of Family Physicians, the Canadian Partnership for Children's Health and Environment and the Canadian Coalition for Green Health Care (APPENDIX B- ES/MCS Status Report). The EHC has developed tools to educate patients in easy-to-understand language how overload of the body's systems can occur, and employ an innovative "Weed, SEEDS and Feed" framework for organizing complex treatments (APPENDIX C- SEEDS of Health).

IV OCEEH-Principles

A medical centre of excellence delivers comprehensive, evidence-based or –informed care, which is multidisciplinary, and yields best quality outcomes and high patient satisfaction. In particular, the OCEEH will utilize and integrate individual and population based approaches: primary care, preventive medicine and public health. It will provide service for environmentally linked illnesses, focused on ME/CFS, FM and ES/MCS, including health services, social services and policy enhancement, research, education and health promotion.

Guidance for assessment and treatment of ME/CFS, FM and ES/MCS will be developed by experienced physicians and researchers in a 3- day clinical forum/workgroup. Based on available evidence, best and promising practices will be classified using the GRADE system. The strength of the recommendations will be determined by four key factors: (1) balance between desirable and undesirable effects; (2) quality of evidence; (3) patients' values and preferences and (4) costs. These collaborators will be encouraged to keep connected to evaluate promising practices with respect to efficacy and adverse effects.

The present level of available treatment is clearly insufficient to induce significant recovery and reduction of disability, especially as measured by ability to return to work. As it is beyond the scope of this review to rate the quality of evidence available for the assessment, diagnosis and treatment of these chronic, complex, environmentally linked conditions, the recommendations relied upon for diagnosis and therapy at present are limited to the information contained in the Mainpro-C modules, accredited by the College of Family Physicians of Canada.

A three-day research forum /workgroup will be held with experienced clinicians and researchers to establish a research agenda, evaluative mechanisms and encourage collaboration in carrying it out through applying for study grants.

In order to fill the gap in care for people with ME/CFS, FM or ES/MCS, the proposed model for the OCEEH includes a central provincial Hub and ever-widening Spokes providing services as close to home as possible. The Hub will develop education about these disorders and train health care providers in the Spokes. Ongoing research in Hub and Spokes will play a key role.

Treatment will be made available according to GRADE recommendations. Emphasis will be on the provision of education and supportive interventions by health care staff to increase patients' skills and confidence in managing their health problems, including regular assessment of progress and problems, goal setting, and problem-solving support, in a patient- and person-centered manner.

Individual care will be delivered by an interprofessional team collaborating with the patient in shared decision-making. Treatment programs will be individualized because of the uniqueness of each individual's determinants of health and the likelihood of multimorbidity.

The OCEEH will also contribute to the integration of primary care, preventive medicine and public health in communities across Ontario.

V Function and Services in the Hub and Spokes

The model of the OCEEH contains a central Hub and multiple Spokes, expanding across the province. The Hub will be an academic, tertiary healthcare centre, providing specialized investigation and treatment to people referred primarily from primary and secondary healthcare providers, including the physicians in the Spokes. Physical requirements include being reasonably accessible to those patients with ES/MCS, although home visits or teleconferencing may be held initially. The Hub must have close and direct affiliation with a teaching hospital and will be associated with academia. It will be responsible for the provision of health and social

services, education, knowledge transfer, guiding and conducting research, and policy development. Multiple trained medical and other clinical staff will be required. Specialized equipment and space that cannot be shared may also be required.

Health professionals in the Spokes will utilize a comprehensive clinical history, including the environmental exposure history and chronological functional inquiry and will be capable of making the diagnoses and initiating recommended treatments for ME/CFS, FM and ES/MCS. The Spokes will provide generally safe facilities (having a fragrance-free policy and using non-toxic cleaning and laundry products) and a "safe room" with air filtration for severely environmentally sensitive patients or contingencies. They will make use of the environmental exposure history in everyday practice to identify patients at risk for developing chronic conditions linked to the environment. They will work with the Hub to engage in innovative research, including evaluating assessment and treatment tools, and will provide education programs in collaboration with Department of Clinical Public Health at the Dalla Lana School of Public Health, University of Toronto. Eventually, all physicians and nurse practitioners in Ontario will be aware of the environment as a determinant of health and will be able to practise systems-based medicine.

The Hub and Spokes will integrate the responsibilities of individual and public health services, social services and policy enhancement, research, education and health promotion.

VI Building the OCEEH

In order to provide the highest quality of health care for people with ME/CFS, FM and ES/MCS, the Hub must be built before the Spokes, although collaboration with interested spokes may be started as early as possible. The Spokes may be in Community Health Centres and Family Health Teams and will eventually spread to other primary health care practitioners around the province.

The Hub must update the tools presently being used, develop guidance for assessment and treatment, develop and start to participate in research and refine and provide the teaching program for the Spokes, and eventually for all primary health care and public health practitioners in Ontario.

Building the OCEEH requires the steps in Table 5- Creating and Expanding the Foundation and Table 6- Initiating, Maintaining and Expanding the Program. Creating and expanding the foundation, as first steps, should take about 1-2 years.

Table 5 First Steps to Building the OCEEH

Create the Foundation	Expand the Foundation
Immediate increase of EHC medical staff to 4 FTEs, including a Medical Director	Begin education of Spoke health care providers, starting with an introductory course
Begin training of Fellows to expand medical staff	Develop education modules and case-based training for medical students, residents, Spoke providers and primary care providers
Organize research projects for Fellows and clinical staff	Develop education modules for nursing and other health professionals
Organize workshop (preferably 3 days) of clinical and research experts to develop GRADE recommendations, and advise re "promising" practices	Organize workshop (preferably 3 days) of clinical and research experts to set research agenda, including evaluation strategies, and initiate research collaborations
Upgrade and refine methods for data gathering	Develop programs for University Sciences (humanities, natural and social science, environmental policy and urban planning)
Develop specific Hub agreements with the university(ies) and teaching hospital(s)	Develop education modules for patients
Prepare education program for Spokes	Develop modules for self-management
Develop university certificate in Environmental Health, and apply for CFPC special practice designation	Develop safe rooms in Spokes
Develop updated hospital guidelines	Create temporary lodging for patients attending the Hub

Table 6 Next Steps in Building the OCEEH

Initiate Programming	Maintenance and Expansion
Begin provision of care in Spokes, and provide support consultations	Gather research data
Develop teleconference and e-consultation service for provision of consultations in remote areas by Hub and Spokes	Refine assessments and treatment protocols
Further develop Research Agenda and Research Associates	Disseminate knowledge
Initiate research programs; case studies and research protocols	Network
Apply for Research Funding	Continue research in Hub and Spokes
Create a website	Expand Spoke availability in Ontario

I Accumulating Evidence of Chronic Complex Conditions Relatedness to the Environment

▪ Introduction

There is an increasing prevalence of multiple chronic illnesses, which cannot be adequately accounted for by genetics. The rise is due in part to the aging population and changing behaviours associated with the Western lifestyle, notably poor diet and lack of exercise. The Western lifestyle has also contributed to a significant increase in chemical pollution exposures from outdoor and indoor air, food, water, and consumer products.

The burden of chemical pollution impacts on the ability of cells to metabolize internal waste and external toxins and leads to oxidative stress, reduced cell function, cell death (apoptosis) or proliferation, and chronic systemic inflammation. Having a genotype for poor detoxification is a risk factor and genetic predisposition to develop chronic illness can in turn be enhanced by epigenetic changes elicited by environmental pollutant exposures. All these entities have been demonstrated in environmentally linked illnesses, which include neurological,[1 2] cardiovascular,[3 4] respiratory,[5 6] immunologic[7 8] and endocrine disorders.[9 10]

As will be outlined, these same abnormalities are also more likely to be found in patients with three chronic complex conditions: myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia (FM) and environmental sensitivities/multiple chemical sensitivity (ES/MCS). These conditons are commonly occurring and overlapping, but the underlying mechanisms are not yet clear.

Unfortunately, the resources to assess, diagnose, treat and provide support for the more than 550,000 patients with these entities in Ontario are lacking. According to the Canadian Community Health Survey (2010), the prevalence of one or more of ME/CFS, FM and ES/MCS (1,415,000) is slightly less than heart disease or diabetes (Table 1). In addition to commonly overlapping with each other, these conditions also have high rates of co-morbidity with other conditions, such as migraine, headaches, arthritis, stroke and cancer (Appendix A- Overlapping Diagnoses for 23 Chronic Conditions Cohorts- used with permission of author).

In spite of frequent patients' reports (CCHS) of high rates of consulting health care practitioners in search of relief, high rates of unmet needs, and high rates of disability, high amounts of health care dollars are being spent while research dollars are few (Table 1). Because underlying mechanisms for ME/CFS, FM and ES/MCS are not yet well understood, treatment based on etiology has yet to develop. Better management of poorly managed individual conditions and better management of these conditons overlapping with other chronic health problems could make the co-morbid conditions easier to manage as well.

The Environmental Health Clinic at Women's College Hospital is a unique provincial multidisciplinary clinic, established in 1996 by the Ministry of Health to provide comprehensive assessments for physician-referred people with chronic, complex conditions that were commonly overlooked in the Ontario health care system. Initially services were focused on environmental sensitivities/multiple chemical sensitivity (ES/MCS)[11], but myalgic encephalomyelitis/chronic

fatigue syndrome (ME/CFS) and fibromyalgia (FM) were added in 1998, as these conditions were commonly observed clinically to overlap.[12]

Table 1 Canadian Institutes of Health Research Funding for Chronic Health Conditions
(Data extracted from CIHR funding databases using keyword searches, Margaret Parlor, Statistical Analyst, President, National ME/FM Action Network- used with permission of author)

Medical Condition Keyword	Per patient funding Apr 2010 to Mar 2013	Canadians affected CCHS 2010
Parkinson	$399.49	39,000
Alzheimer	$237.71	111,500
Muscular Dystrophy	$157.87	26,000
Epilepsy	$78.89	134,500
Multiple Sclerosis	$73.09	108,500
Tourette	$53.54	18,000
Crohn	$47.47	102,500
Cerebral Palsy	$44.07	36,000
Diabetes	$38.93	1,841,500
Spina Bifida	$26.61	35,000
Heart Disease	$25.25	1,431,500
Dystonia	$20.26	15,500
Bronchitis, Emphysema, COPD	$9.12	805,000
Asthma	$6.90	2,246,500
Arthritis	$5.85	4,454,000
Fibromyalgia	$1.38	439,000
Chronic Fatigue Syndrome	$0.35	411,500
Multiple Chemical Sensitivities	$0.01	800,500

There is mounting evidence of environment and health links influenced by genetics and epigenetics in all chronic complex conditions, and accumulating understanding of potentially related mechanisms and relationships.

This report includes the following sections.

1. Sections I-II:
   A broad-based scoping, but non-systematic, review of the scientific literature related to environmental associations with chronic complex health conditions (Section I) and focused on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Fibromyalgia (FM), and Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS) (Section II).

   The literature reviewed was, in most part, published by the United States National Library of Medicine in Medline, supplemented on occasion by credible reports by government agencies, professional associations and environmental/patient support organizations.

2. Section III-VI:
   An overview of what might be developed to build the Centre of Excellence on the foundation of the Environmental Health Clinic to prevent chronic environmentally linked conditions, and to care for people with ME/CFS, FM and ES/MCS as close to home as possible, as well as broad expansion of education/health promotion and research (Sections III-VI).

- **Environmental Health**

The World Health Organization (WHO) defines health as;

> *"a state of complete physical, mental and social well-being and not merely the absence of disease".*[13]

As stated in 1989, by the European Charter and Commentary emerging from the first WHO Pan-European Meeting of Environment and Health Ministers, environmental health is:

> *"those aspects of human health and disease that are determined by factors in the environment …both the direct pathological effects of chemicals, radiation and some biological agents, and the effects (often indirect) on health and wellbeing of the broad physical, psychological, social and aesthetic environment which includes housing, urban development, land use and transport. It also refers to the theory and practice of assessing and controlling factors in the environment that can potentially affect health."*[14]

According to Public Health Ontario, environmental health encompasses the assessment and control of the physical, chemical, biological, social and behavioural factors in the environment that influence health and disease occurrence.[15]

To summarize, environmental exposures are one of several determinants of health, linked to the community, the home location, occupation, food/beverage choices and various actions, such as wearing scented products, smoking or taking medications.

To promote environmental health and improve the health care for people with poorly recognized chronic, complex conditions ME/CFS, FM, and ES/MCS, the Ontario Ministry of Health and Long-Term Care established the Environmental Health Clinic (EHC) at Women's College Hospital in 1996.[16] Unfortunately funding for this incubator program has not expanded to meet the needs. Presently, the wait list is over one year and patients are limited to two follow-up appointments. Building on the EHC and expanding services to meet the provincial need is the context of this report.

- **Chronic Complex Conditions**

Chronic illnesses are conditions that traditionally last one year or more and require ongoing medical attention and/or limit activities of daily living.[17] Common chronic conditions include cardiovascular and cerebrovascular disease, cancer, diabetes, metabolic syndrome, obesity, neurodegenerative disorders, chronic lung and kidney disease, and immune dysfunction such as autoimmune diseases, allergies and asthma.

According to the World Health Organization (WHO), chronic diseases have overtaken infectious diseases as the leading cause of death and disability worldwide.[18] Non-communicable diseases now account for 59% of the world's 57 million annual deaths, and 46% of the global burden of disease and the prevalence and resulting number of related deaths are expected to increase substantially due to population growth and aging, and environmental risk factors. Escalating rates of neurocognitive, metabolic, autoimmune and cardiovascular diseases cannot be ascribed

only to genetics, lifestyle, and nutrition. Early life and lifelong ongoing pollutant exposures and bioaccumulation also contribute to the cause of chronic disease.[19 20 21 22]

The picture for Ontario is similar. Chronic disease is most frequent among older Ontarians. According to the 2003 Canadian Community Health Survey, almost 80% of Ontarians over the age of 45 or 3.7 million people were living with a chronic condition. Chronically ill Ontarians are also likely to have more than one chronic disease; 70% of them over the age of 45 have multiple conditions.[23]

The co-occurrence of multiple diseases in the same individual is called multimorbidity**.** When there are multiple morbidities, chronic disease is considered complex, although there are other factors at play. For example, social, cultural, environmental situations and finances may account for the different consequences of identical health conditions in different different people (Figure 1).[24] A single condition (e.g. schizophrenia) in a person living on the street is complex, whereas well-controlled diabetes, hypertension and hyperlipidemia in a married employed man is not.[22] Chronic complex disease (CCD) requires the attention of multiple health care providers or facilities[25] and possibly community (home)-based care.[26]

Because of the high and increasing prevalence of these disorders, economists and health planners are already questioning the sustainability of our medical and social systems, due to the massive impact of the aging population.[27] In a study of approximately 3000 patients, it was found that the health care utilization and cost were significantly increased among patients with multimorbidity.[28] In Ontario, chronic diseases account for 55% of direct and indirect health costs, which includes years of healthy life lost from premature death and lost productivity from disability as well as direct health care costs.[29]

What is important to the individual is that comorbid illnesses have an additive or even synergistic and significantly negative impact on quality of life.[30] The major consequences of multimorbidity are continuing functional decline, disability, poor quality of life, and high personal health-care costs.[31 32 33 34] The Health Council of Canada reports that 50% of people with multimorbidity report moderate or severe disability in daily living.[35] There is an increasing trend of multimorbidity in younger patient demographics.[36] The impact of multimorbidity from the patient perspective has been explored, indicating that individuals feel the current system is not addressing the basic needs of their health problems.[37 38 39 40]

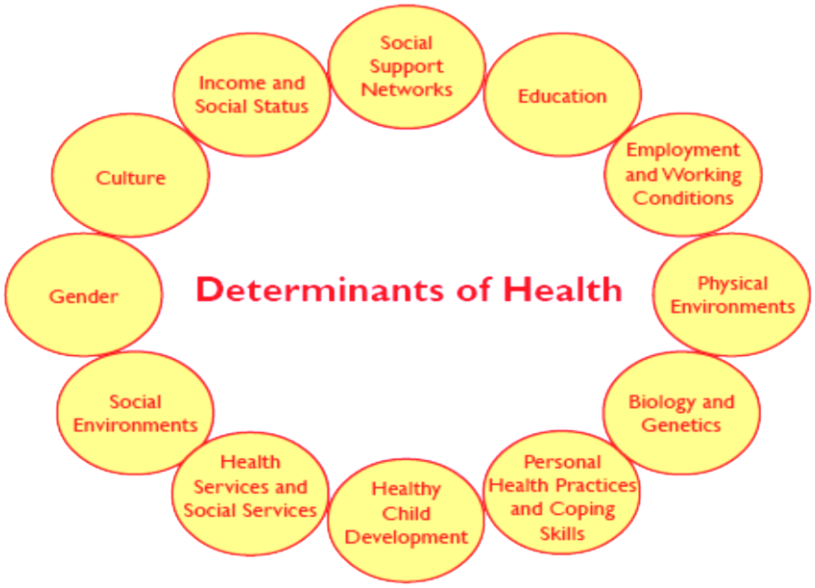
Chronic complex diseases and conditions also have a significant impact on family members and healthcare providers, who are frequently inadequately trained to understand the complex interrelationships of comorbid illnesses.[41 42] Physicians do not yet have guidelines to treat multimorbidity.[43] Specialists are usually responsible for a single disease among many. Applying guidelines for each individual disease simultaneously provides uncertain benefit and potential harm.[44 45 46] What is good for an individual condition may not be good for patients with multiple conditions.[47 48]

Chronic illnesses are frequently comorbid because they share common risk factors and conditions. The concept of multiple determinants of health comes from the realization that there

are multiple complex factors which combine or interact to impact on individuals and population groups.[35]

Whether people are healthy or not is determined by their circumstances and environment. The World Health Organization states that factors such as where we live, the state of our environment, genetics, our income and education level, and our relationships with friends and family all have considerable impacts on health.[49]

Figure 1



Source: Health Canada, "Health and Environment: Critical Pathways," *Health Policy Research Bulletin*, Issue 04, October 2002, p. 3.

- **Genetics and the Environment**

Although many experts argue about how quickly genetic evolution can occur, there is general consensus that very little change in the human genome will occur in just two or three generations (60 years). Clearly, genetic transformation and evolution are not majorly contributing to the rapid and significant changes in health patterns that have recently emerged.[50] Genetics might predict susceptibility, but environmental factors are thought to cause 70 to 90% of chronic disease risk.[51]

The human genome was categorized from 1990-2003[52] and poses protective and susceptibility factors to human health. As the World Health Organization stated, *"Most diseases involve many genes in complex interactions, in addition to environmental influences"*,[53] and they quote evidence re genetic polymorphisms influencing or protecting from cancer, cardiovascular disease and diabetes and many other chronic conditions.

In addition, the science of epigenetics and how environmental stimuli influence genes to turn on and off their expression of metabolic enzymes, is in its infancy and is evolving rapidly.[54] [55] [56]

Disease is often the result of vulnerable genes being triggered by specific determinants. Mounting evidence suggests that without activation, some disease processes will not develop, and removal of the initiating trigger may allow developing illness to abate or subside.[57]

- **Epigenetics**

Expression or silencing of genes occurs by removing or replacing their coverings, i.e. modifying the epigenome. The epigenome is the wrappings (chromatin and histone) around our DNA. It covers and protects the DNA, but most importantly, it activates and deactivates individual genes. The term epigenetics is used to describe any process that refers to changes in the genome, which alters gene activity and expression without actually changing the DNA or genomic sequence itself.[58] [59] [60] [48] [49]

Emerging evidence suggests that air pollutants can influence epigenetic changes[61] [62] [63] and these changes are even more likely to occur with genetic predisposition to poor detoxification.[64] In fact, there are numerous studies demonstrating that epigenetic changes are triggered by oxidative stress.[65] [66] [67] [68] [69] [70] [71] [72] [73]

Mounting evidence suggests that inappropriate epigenetic changes and subsequent misinterpretation of the genetic code is linked to numerous chronic illnesses. A large number of animal studies provide evidence that supports the role of environmental epigenetics in disease susceptibility.[74] These studies show that there are many agents that provoke epigenetic changes, including heavy metals, pesticides, diesel exhaust, tobacco smoke and other environmentally toxic and persistent chemicals.[75] [76]

In particular, epigenetic modulation by ambient air pollution can play a role in regulating the expression of genes important in the pathogenesis of inflammation in asthma.[77] [78] Ambient air pollutants can affect DNA methylation and result in changes in chromatin structure.[79]

For example, living in a more polluted North American city such as Fresno California (high particulate matter and ozone) is associated with epigenetic changes which contribute to impairment in regulatory T cell function seen in asthmatics.[80] In a longitudinal cohort study of non-smoking women in New York City, polyaromatic hydrocarbons (PAH) exposure during pregnancy, derived largely from traffic-related air pollutants, was measured using personal air monitors. This study also demonstrated that the prevalence of asthma (>25%) was among the highest in the US. Prenatal PAH exposure was associated with epigenetic changes, in particular with genes involved in the pathogenesis of asthma.[81] [82]

The resulting acquired susceptibility from epigenetic change is expected to interact with environmental factors and with genetic susceptibility to increase risk for environmental disease.[83]

- **Early and Late Exposures**

In 2011, the Canadian Environmental Law Association, the Ontario College of Family Physicians and the Environmental Health Institute of Canada produced an extensive scoping review of the literature.[84] Their main findings include:

- The in utero and perinatal environment all play major roles in the risk of later life disease
- There is more and more confirmation for the role of early life exposures to environmental contaminants and a lifelong vulnerability to chronic disease.
- The following chronic diseases or conditions were studied, and were found to be associated with early life environmental chemical exposures:
    - cardiovascular disease
    - cardiac birth defects
    - low birth weight
    - obesity
    - type 2 diabetes
    - Alzheimer's disease
    - Parkinson's disease
    - developmental neurotoxicity
    - cancer (breast, prostate, testicle)
    - respiratory disease (asthma).

In addition, this review found the same agents were associated with these conditions (Table 2), and subsequently colleagues in the Canadian Partnership for Children's Health and Environment were able to mount a public information campaign targeted towards parents. They translated the research findings into "Top 5 tips: Creating Healthy Home Environments for Kids" that was widely distributed as a brochure and fact cards, translated into multiple languages, and a video (www.healthyenvironmentforkids.ca).

Table 2

Chemicals/Pollutants Most Frequently Linked to Early Exposures and Later Chronic Diseases

- **Air pollution/Tobacco smoke**
- **Lead**
- **Mercury**
- **Bisphenol A**
- **Phthalates**
- **Organophosphate pesticides**
- **POPs (e.g. organochlorine pesticides, dioxins, PCBs, PBDEs, polyvinyl chloride)**
- **VOCs**

Cooper K, Marshall L - used with permission of the authors

The World Health Organization declared chronic disease to be the number one healthcare challenge of the 21st century.[85]

For instance, the incidence of allergies has been increasing.[86] [87] [88] The prevalence of food allergy in children under the age of 18 increased by 18% percent from 1997 to 2007[89] and the prevalence of peanut allergy has doubled.[90] Anaphylactic reactions, which are severe and potentially life-

threatening allergic reactions, have increased as well.[91] [92] The increase in incidence of allergies impacting the respiratory system has been related to pollution exposure.[93] [94]

The prevalence of autoimmune disorders is increasing, and the increase is associated with environmental exposures, such as solvents[95] [96] and air pollution.[97]

There has been a sharp increase in the global prevalence, morbidity and mortality associated with asthma over the last 40 years, particularly in children.[98] Up to 37% of teenagers are affected by asthma symptoms, making it one of the most common chronic diseases in childhood.[99] Approximately 300 million people worldwide currently have asthma and its prevalence increases by 50% every decade.[100] Pollution influences the development of asthma.[101] [102]

Long term exposure to pollution outdoors is linked with diabetes,[103] [104] and considered a risk factor for its development. [105] [106] [107] [108] Chemical exposure is related to both type 1[109] [110] [111] and type 2 diabetes,[112] [113] and a 2010 animal study even linked it to developing obesity.[114] Persons with diabetes are particularly susceptible to the acute effects of air pollution,[115] [116] increasing the risk for complications requiring hospitalization.[117]

The number of heart attack-related hospitalizations has increased steadily.[118] The American Heart Association has established a link between air pollution exposure, in particular particulate matter, with cardiovascular morbidity and mortality.[119] [120] Chronic exposure to particulate air pollution enhances the risk of developing cardiovascular disease.[121] [122] [123] Living near traffic increases the risk for heart attack,[124] doubles the risk for death[125] and women are at greater risk.[126] Overall mortality is higher in the most polluted cities.[127] Living in areas with higher outdoor pollution reduces the long term chances of surviving a stroke.[128]

Multiple studies have also found detrimental cardiovascular effects from environmental air pollutants due to the exacerbation of known risk factors, including atherosclerosis and increased blood pressure.[129] [130] [131] [132] [133] [134] [135]

People who are genetically poor detoxifiers are also more susceptible to the cardiovascular and respiratory effects of air pollution.[136] [137] In particular, having such an abnormality has been shown to have an adverse impact on the effects of pollution exposure by modifying heart rate variability,[138] [139] lengthening of the QT interval on electrocardiograms,[140] contributing to the risk of endothelial inflammation caused by traffic particles,[141] and increasing homocysteine levels,[142] all of which are risk factors for heart disease. Having an abnormal genotype for detoxification can adversely affect lung function, including increasing the risk of ozone-induced asthma[143] [144] [145] and wheezing.[146]

The brain is especially vulnerable to chemical exposures. Accumulating evidence links air pollution exposure to central nervous system (CNS) oxidative stress, pathology and disease. [147] [148] [149] Epidemiology studies have shown that exposure to high levels of air pollution is associated with a deficit in neuropsychological development in children,[150] [151] [152] [153] [154] behavioural deficits,[155] autism[156] [157] [158] and cognitive decline in the elderly.[159] [160] [161] [162] [163] [164]

Human studies have also revealed that individuals living in highly polluted cities show Alzheimer's disease (AD)-like and Parkinson's disease (PD)-like pathology, when compared to individuals living in cities with less pollution.[165] [166] More specifically, high levels of air pollution are associated with elevated markers of neurodegenerative disease in humans, including tau phosphorylation, diffuse β amyloid plaque deposition, and a synuclein aggregation.[167] [168] [169] Parkinson's and late onset Alzheimer's, are also associated with poor detoxification genotypes.[170] [171] [172] [173] [174] Trichloroethylene, a chlorinated solvent widely used as a degreasing agent in industry, is a common environmental contaminant and an exposure risk factor for the development of Parkinson's disease.[175] [176] [177] The epidemiological and toxicological evidence is also repeatedly identifying both occupational and ambient exposure to pesticides as a significant factor.[178] [179] [180] [181] [182] [183] [184] [185] [186]

Human reports also revealed that air pollution causes oxidative stress, neuroinflammation, and microglial activation in the brain.[187] Consistent with human reports, animal studies have found that exposure to air pollution causes lipid peroxidation,[188] DNA damage,[189] elevated cytokines,[190] [191] [192] protein nitration and chemokine increases,[193] aggregated alpha synuclein[194] and activation of microglia.[195] [196]

Preliminary evidence exists for abnormal detoxification genotypes contributing to susceptibility to developing progressive multiple sclerosis.[197]

- **Body Burden**

There are distinctions between external exposures, how much actually enters the body and accrued internal bioaccumulation. Some agents are rapidly metabolized and excreted and do not remain in the human body. Other compounds may remain in the human body for a period of time depending on the efficiency of inherent detoxification mechanisms, which vary from one individual to another, some people having more effective detoxification mechanisms than others.[198] [199] They can also vary with the chemical properties of the agent. Some compounds are poorly excreted and tend to bioaccumulate in tissues. Repeated or continuous exposure will offset the ability of the body to lower the accrued amount.

North Americans carry as many as 212 contaminants in their bodies and women have higher levels of many of these chemicals than men.[200] The exposures in utero are due to contaminants crossing the placenta. Toxic chemicals/agents enter the body not only from exogenous sources (air, water, diet, drugs, consumer products and radiation) but also from endogenous processes, including byproducts of our natural metabolism, inflammation, existing diseases, infections, and gut flora.[201] Thus, the relevant 'environment' is the body's internal chemical environment, i.e. what's inside it.[202]

All our daily and accumulated exposures to volatile and semivolatile organic compounds (VOCs SVOCs), by-products of indoor chemistry, outdoor pollutants such as ozone and particulate matter, and numerous additives and pesticides found in food add to the burden of our natural detoxification systems.

Chronic illnesses are increasing and 'relatively new' illnesses, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia (FM) and environmental

sensitivities/multiple chemical sensitivity (ES/MCS) are increasingly reaching our awareness. According to the Statistics Canada Canadian Community Health Surveys in 2005 and 2010, these newer conditions are also increasing in prevalence.[203] The simultaneous occurrence of the rise in pollution and resulting increase in body burden is associated with the increasing prevalence of chronic illness, which suggests that these phenomena are potentially linked.

- **Linking Divergent Chronic Conditions and the Environment**

Biologically, these chronic illnesses and conditions are distinct, but there are common, overlapping pathological mechanisms. These include a burden to detoxification systems, damage to cellular organelles, oxidative stress, changes in cell function, and systemic inflammation.

- **Detoxification**

The liver is a major organ for detoxification. It breaks down toxic agents and converts oil soluble products into more water soluble metabolites, which can be efficiently eliminated from the body by the kidneys.[204] This degradation, or biotransformation, is primarily accomplished by two liver enzyme systems called Phase I and II.[205] Waste products can be eliminated from the body through bile and stool, urine, and sweat.[206]

Every cell is naturally equipped with a detoxification system to deal with internal wastes, and that same system is used to detoxify and eliminate foreign chemicals (xenobiotics) which are potentially harmful. Xenobiotics are encountered by humans on a daily basis and undergo metabolism and detoxification to produce numerous metabolites, some of which also have the potential to cause toxic effects.[207] Waste that cannot be completely degraded or easily eliminated by the cell must be altered in order to remove it from the body. When the cell is unable to rapidly detoxify waste or toxic foreign substances, damage can occur.

- **Cellular Organelles**

Cells obtain energy by combining glucose with oxygen. This critical role in energy metabolism is performed by cell organelles (cell subunits that perform specific functions) called mitochondria.[208] Mitochondria are specialized subunits which are fundamental to cell life and cell death. They consume about 98% of the oxygen we inhale.[209] That we must breathe oxygen to stay alive is simply the consequence of the demand of our mitochondria for oxygen.

Mitochondria are the source of the energy, strength and vitality for every cell. As the powerhouse of cells, they provide energy for cell division, production or destruction of proteins and other substances, cell signaling, and transportation of large molecules across the cell membrane. Depending on the cell's energy requirements, there are hundreds or thousands of well-functioning mitochondria traveling around the cell, distributing readily available energy wherever it is needed. Metabolically, this is where the action is inside a cell. The byproducts of this metabolism are toxic waste products, to be destroyed or eliminated, but unfortunately, the mitochondria sit in the middle of it all.

These byproducts are called reactive oxygen species or oxidants or free radicals. They are electronically unstable molecules capable of stripping electrons from any other molecules they

meet in an effort to achieve stability. Doing so creates more unstable molecules which can then attack their neighbours in domino-like chain reactions.

Free radicals are produced in small amounts under normal physiological conditions, derived from essential metabolic processes. They are the waste products of the energy produced by mitochondria. When their production is increased, or their detoxification is inadequate, molecular damage occurs inside cells. This damaging process is called oxidative stress.

- **Oxidative Stress**

Oxidative stress represents an imbalance between the production of reactive oxygen species and the ability to neutralize or detoxify them. It refers to any of the resulting various pathologic changes seen in living cells in response to excessive levels of reactive oxygen species. We can observe the imbalance directly by measuring the levels of oxidants or free radicals, or we can assume it is occurring by finding low levels of antioxidants.[210]

We know oxidative stress is occurring when we find evidence of damage and destruction inside cells.[211] [212] [213] [214] Oxidative stress damages DNA,[215] especially mitochondrial DNA,[216] lipids from cell and organelle membranes[217] and various proteins,[218] and we can measure the resulting by-products of this damage in blood or urine.[219] [220] [221] [222] [223]

- **Changes in Cell Function**

Oxidative stress and DNA damage can cause significant changes in cell function. The mitochondria are most likely to be damaged because they produce free radicals as waste products of their production of energy, and are immersed in them, making them highly vulnerable to attack. In research labs, we can assess mitochondrial function by stimulating cell activity and measuring the levels of substances normally used by working mitochondria. When the mitochondria are activated, and are functioning well, there is a marked reduction in these substances as they get used up.[224] [225]

- **Systemic Inflammation**

The literature robustly demonstrates pollution leads to oxidative stress and systemic inflammation, which in turn contributes to the onset and exacerbation of cardiovascular disease,[226] [227] chronic obstructive lung disease,[228] and neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases.[229] [230] It worsens symptoms, increases medication use, decreases function and increases health care utilization and mortality.[231] Those with an abnormal genotype for detoxification tend to be more susceptible to developing such chronic illnesses.

- **Reductionism, Systems Biology and Systems Medicine**

The principle of reductionism is the belief that complex systems can be understood by studying their most fundamental parts.[232] It is the way we attempt to explain complex phenomena; we try to define the functional properties of the individual components of complex systems. Reductionism dominates traditional medical science and affects the way we diagnose, treat, and prevent diseases.[233] The natural inclination of medical practitioners is to isolate the single factor that is most responsible for the observed abnormality and to treat that factor. Implicit within this practice is the approach that every disease has a potential single target for medical treatment. For

example, the target in infection is the bacteria; for cancer, it is the tumour. The disease becomes the central focus, not the whole person biologically participating in and affected by the disease. With the reductionist approach alone, we cannot completely understand the mechanisms of abnormal chronic, complex medical conditions by looking at how the individual parts work in isolation.[234 235 236]

Chronic diseases and conditions are commonly comorbid, and involve multiple organ systems. On a cellular level, they include genetics, epigenetics, oxidative stress, systemic inflammation and influences from the environment. They develop over time because of the complex interactions and imbalances among all the different systems involved.[237] Furthermore, a person's sleeping habits, diet, living conditions, age, sex, other co-morbid illnesses, and emotional stress may all have contributed to the onset, continuation, and exacerbation of his or her disease process. It is now widely recognized that chronic diseases arise as a result of a complex interaction of environmental and genetic risk factors.[238]

Systems biology is the study of the behavior of complex biological organization and processes.[239] Defining it is difficult. It involves the application of experimental, theoretical, and computational techniques to the study of biological organisms at all levels, from the molecular, through the cellular, to the organ, organism, and populations. Its aim is to understand biological processes as integrated systems instead of as isolated parts.[240] Most major universities in Canada, the United States, Europe and Asia now have education and research departments in systems biology.[241]

Chronic illness is about the failure of multiple systems. Systems medicine is the application of systems biology approaches to medical research and medical practice.[242] A systems medicine approach that recognizes the interactions between all the components responsible for human clinical dysfunction is required to better understand and manage chronic disease, rather than perceiving the disease as a single abnormal mechanism occurring in isolation, and then trying to treat it accordingly.[243]

The increasing awareness of chronic complex conditions ME/CFS, FM, and ES/MCS has revealed they have not had a single body system on which medical specialists for that system could focus. Hence, endocrinologists, infectious disease specialists, rheumatologists, allergists, repiratory physicians et cetera seldom have sufficient management strategies for these conditions. Collaboration among various health care professionals to manage the failure of multiple systems in these conditions may also point the way to more effectively manage other chronic complex conditions.

- **Summary**

Chronic complex conditions are the leading cause of death and disability worldwide. Almost 80% of Ontarians over the age of 45 have a chronic condition, and 70% of them have more than one. As does poor management of a single condition, multimorbidity contributes to continuing functional decline, disability, poor quality of life and high personal health care costs.

The physical environment is one of the multiple determinants of health, but environmental health encompasses the assessment and control of the physical, chemical, biological, radiological, social and behavioural factors in the environment that influence health and disease occurrence.

Environmental factors are thought to cause 70 to 90% of chronic disease risk. Pollution exposure influences epigenetic change, which increases genes' susceptibility to turn on and off in response to environmental factors, and then increases the risk to develop environmentally linked conditions, particularly in those individuals with genetic susceptibility factors.
Exposure to pollution, particularly in eatly life, increases the risk for developing environmentally-linked diseases, such as allergies, autoimmune disorders, asthma, diabetes, cardiovascular disease, neuropsychological developmental disorders and autism in children, and progressive neurodegenerative disorders, such as Parkinson's and Alzheimer's.

Chronic conditions such as ME/CFS, FM, and ES/MCS appear to also be linked to the environment in these ways and are increasing in prevalence. These conditions commonly overlap with each other and other chronic conditions and are challenging to manage. However, in spite of high rates of unmet health needs and high rates of disability, with considerable health care dollars being spent, there is almost no focus on research to be able to diagnose, treat and prevent these conditions more efficiently.

Toxic chemicals/agents enter the body not only from exogenous sources (air, water, diet, drugs, consumer products and radiation) but also from endogenous processes, including byproducts of our natural metabolism, inflammation, existing diseases, infections, and gut flora. Thus, the relevant 'environment' is the body's internal chemical environment, i.e. what's inside it.

The common pathological mechanisms of all these diseases and conditions include a burden to detoxification systems, damage to cellular organelles (metabolic subunits) including the energy-generating mitochondria, as well as oxidative stress, reduced cell function, with increased cell death or proliferation, and systemic inflammation, which makes other chronic conditions (multimorbidity) more likely.

The traditional reductionist approach to understanding and treating chronic complex conditions is inadequate because of dysfunction of multiple organ systems and comorbidity.

A systems medicine approach, that includes environment as a determinant of health, recognizes the interactions of organs, cells, genetics and epigenetics, oxidative stress and systemic inflammation in response to exposure to environmental agents.

II Increasing Prevalence and Awareness of Three Chronic Complex Conditions: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Fibromyalgia, and Environmental Sensitivities/Multiple Chemical Sensitivity

- **Introduction**

The 2010 Canadian Community Health Survey (CCHS) reported that the number of Canadians reporting a diagnosis of ME/CFS, fibromyalgia and ES/MCS has increased markedly since 2005. The prevalence of CFS increased by 23%, FM by 13%, and MCS by 34%. The numbers are increasing perhaps because the incidence is increasing- these illnesses usually do not resolve and more people get added to the total; and more doctors are now making the correct diagnosis. On the other hand, one can also argue that the numbers are likely underestimated because some doctors don't know how to make the diagnoses and others refuse to accept the legitimacy of these illnesses. Nevertheless, the numbers are significant in that these people frequently have a significant reduction in quality of life. In fact, 69% of the patients assessed at the Environmental Health Clinic at Women's College Hospital are no longer able to work.[244]

Thus far, these conditions do not have readily available clinical biological markers for diagnosis.

Although individually unique, ME/CFS, FM and ES/MCS display the same overall pattern as the above reviewed chronic complex diseases. They are increasing in prevalence. They overlap with each other and other chronic conditions. Please see APPENDIX A- Overlapping Diagnoses for 23 Chronic Conditions Cohorts. They demonstrate abnormal genotypes, oxidative stress, reduction in number and function of mitochondria, systemic inflammation and multimorbidity.

▪ Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

o ME/CFS Description and Prevalence, including Women and Children

The description of ME/CFS has continued to evolve over the past 20 years because of the multiple complicating symptoms, which add to the difficulty of nailing it down precisely.[245] [246] [247] [248] [249] [250] Severe chronic fatigue is the dominating complaint. It is made worse by exertion, is not substantially relieved by rest, and the post-exertion recovery time is prolonged. The fatigue is commonly both physical and cognitive.[251] [252] ME/CFS affects up to three percent of the population, may follow an infection, and usually does not go away.[253]

ME/CFS affects women at six times the rate of men.[254] Moreover, women exhibit more severe fatigue, worse physical functioning, more bodily pain, poorer emotional functioning and significantly greater impairment of work activities.[255] [256]

ME/CFS also occurs in children, especially adolescents. The prevalence is considerably lower than among adults[257] and the prognosis is better.[258] However, they report significantly more illness impairment, especially in school attendance, than those with other chronic conditions such as juvenile idiopathic arthritis and emotional disorders.[259]

In children and adolescents, ME/CFS occurs at a developmentally vulnerable time, which adds to the disability. It affects self-concept, autonomy, body image, socialization, sexuality and academic problems, which have a significant psychosocial impact. [260] Those affected report difficulty explaining their illness to peers and being believed, and they experience bullying.[261]

ME/CFS is relatively common in young people (prevalence 0.4% to 2.0%)[262] [263] [264] and is very disabling, as 45% report more than 50% school absences with a mean time out of school estimated at more than one academic year.[265]

One recent study assessed the impact of adolescent ME/CFS on the parents.[266] They described anger and frustration as consequences of struggling to access health care for their children. The anger and frustration was attributed to their interactions with the medical profession, feeling helpless and not knowing where to turn to for support and practical advice. Furthermore, the parents described problems with judgmental blaming attitudes by physicians, which made them feel abandoned and disrespected. They specifically described doctors as blaming their parenting.

- **ME/CFS Diagnostic Criteria**

The diagnosis of ME/CFS is made by comparing the patient's symptom pattern with the diagnostic criteria, and then eliminating other conditions which would display these symptoms.

There are no definitive laboratory tests or physical findings[267] but what distinguishes it from other causes of chronic fatigue is that minimal exertion will exacerbate the fatigue, and the recovery time is pathologically prolonged. Sometimes it can take days or weeks to recover, instead of minutes or hours.

Various diagnostic criteria and management guidelines for ME/CFS have been published:

- Oxford criteria[270]
- National Institute of Health and Clinical Excellence (NICE) guidelines[268]
- Carruthers BM. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners. An Overview of the Canadian Consensus Document[269]
- Centers for Disease Control and Prevention (USA).[270]
- Myalgic encephalopathy (ME) and chronic fatigue syndrome (CFS): management guidelines for general practitioners. (Australia) ISBN 0 7308 9334 0[271]
- International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS.). ME/CFS: A Primer for Clinical Practitioners [272]

These management guidelines differ somewhat in their approach. One reason for this is that they use different definitions to define the illness. The Canadian criteria emphasize the importance of managing/pacing activity including exercise. Management guidelines in England (NICE), Canada (Carruthers) and Australia use the Canadian criteria. The difference in definitions is of great importance in order to establish the most effective therapeutic recommendations.

The various definitions of ME/CFS require other symptoms and patterns, including chronic pain such as recurrent headaches and fibromyalgia, disturbed or less than refreshing sleep, cognitive complaints, gastrointestinal complaints and sensitivities to foods, medications, odours and/or

chemicals. There are multiple system complaints and the immune system appears to be playing a role.[273] [274] [275]

The Oxford Criteria[276] were developed in 1991. Two broad syndromes can be defined:
1. Chronic fatigue syndrome (CFS):

- A syndrome characterized by fatigue as the principal symptom.
- A syndrome of definite onset that is not life long.

i. The fatigue is severe, disabling, and affects physical and mental functioning.
ii. The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time.
iii. Other symptoms may be present, particularly myalgia, mood and sleep disturbance.
iv. Certain patients should be excluded from the definition. They include:
    a. Patients with established medical conditions known to produce chronic fatigue (eg severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician.
    b. Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.

2. Post-infectious fatigue syndrome (PIFS)
This is a subtype of CFS which either follows an infection or is associated with a current infection (although whether such associated infection is of aetiological significance is a topic for research). To meet research criteria for PIFS patients must:

i. fulfil criteria for CFS as defined above, and
ii. should also fulfil the following additional criteria:
iii. There is definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable).
iv. The syndrome is present for a minimum of 6 months after onset of infection.
v. The infection has been corroborated by laboratory evidence.

In reporting studies it should be clearly stated which of these two syndromes is being studied.

The fatigue described in this paper describing the Oxford criteria does not consider the exacerbation of symptoms and the prolonged recovery time. This difference in the description of the fatigue is critical, and has contributed to the conflict in the medical literature regarding the effect of graded exercise therapy (GET). Studies which use the Oxford criteria tend to show clinical improvement. But the Oxford Criteria also encompass those who have depression or unexplained chronic fatigue. In other words, the subjects in many of the studies supporting the effectiveness of graded exercise do not necessarily meet the criteria used by the later consensus definitions for ME/CFS.

In the medical literature, the most common definition used is the CDC (1994) definition by Fukuda:[277]

1. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.
2. The concurrent occurrence of **four or more** of the following symptoms:
    - substantial impairment in short-term memory or concentration;
    - sore throat;
    - tender lymph nodes;
    - muscle pain;
    - multi-joint pain without swelling or redness;
    - headaches of a new type, pattern, or severity;
    - unrefreshing sleep; and
    - post-exertional malaise lasting more than 24 hours.

These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

The Canadian Expert Consensus Panel, constituted by Health Canada, published the first diagnostic ME/CFS criteria for clinical use in 2003.[278] Dr. Alison Bested, formerly an EHC Staff Physician and now Medical Director of the Complex Chronic Diseases Program in Vancouver was a member of this Panel. In contrast to the Fukuda Criteria, this newer clinical case definition made it compulsory that, to be diagnosed with ME/CFS, a patient must become symptomatically ill after minimal exertion. It also clarified other neurological, neurocognitive, neuroendocrine, autonomic, and immune manifestations of the condition. This new definition narrowed and specified the characteristic of the fatigue in this syndrome. It also expanded the number and variety of symptoms required for the diagnosis of ME/CFS.

The following outlines the Canadian case criteria for the clinical diagnosis of ME/CFS:[279]

1. New onset, unexplained, persistent physical and mental fatigue that substantially reduces activity
2. Post-exertional malaise or fatigue with pathologically slow recovery
3. Sleep dysfunction
4. Pain in muscles and joints
5. Neurologic/cognitive manifestations
6. At least 1 symptom in 2 or more categories:
    a. autonomic e.g. orthostatic hypotension, palpitations, irritable bowel syndrome
    b. neuroendocrine e.g. low temp, premenstrual syndrome
    c. immune manifestations e.g. lymphadenopathy, allergy
7. Illness persisting at least 6 months (3 months in children); onset usually distinct, but can be gradual

Table 3 Comparison of ME/CFS Diagnostic Criteria

Case Definition of Fukuda		Oxford Criteria	Case Definition of Canadian Consensus Document	
Requires the Presence of Profound Fatigue, Defined as Follows:	**Also Requires four or More of the Following Features:**	**Requires the Presence of Severe Disabling Fatigue as the Main Symptom and Further Defined as Follows:**	**Requires the Presence of the Following Features:**	**Also Requires one Symptom From two of the Following Categories:**
Symptom duration of ≥6 mo Causes a substantial reduction in occupational, personal, social, or educational activities Unrelieved with rest Other medical or psychiatric conditions excluded	Post-exertional malaise lasting >24 hr Impaired memory or concentration Non-refreshing sleep Muscle pain Pain in multiple joints without signs of inflammation Headaches of new type or severity Sore throat Tender cervical or axillary lymph notes	Symptom duration of ≥6 mo Affects both physical and mental functions Symptoms are present ≥50% of the time Definite onset and not lifelong Other medical or psychiatric conditions excluded	Symptom duration of ≥6 mo for adults and ≥3 mo for children New onset of unexplained, persistent, or recurrent physical or mental fatigue that substantially reduces activity levels **Post-exertional malaise** Sleep dysfunction Pain in muscles and joints Neurologic/cognitive manifestations Other medical or psychiatric conditions excluded	**Autonomic manifestations** (e.g. orthostatic intolerance, lightheadedness, extreme pallor, nausea, irritable bowel syndrome, urinary freq., bladder dysfunction, palpitations with or without cardiac arrhythmias, exertional dyspnea) **Neuroendocrine manifestations** (e.g. loss of thermostatic stability, intolerance of extremes of heat and cold, marked weight change, loss of adaptability, worsening of symptoms with stress) **Immune manifestations** (e.g. tender lymph nodes, recurrent sore throat, recurrent flulike sxs, general malaise, new sensitivities to food, medications, or chemicals)

In August, 2013, the United States Health and Human Services proposed to contract (sole source) with the Institute of Medicine (IOM) to develop "clinical diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome". However, patient groups objected, and so the process was on hold temporarily, but now will proceed in spite of a letter from 35 of the leading researchers and clinicians to Health and Human Services Secretary Kathleen Sebelius to say they had reached a consensus on using the Canadian Consensus Criteria.[280]

- **ME/CFS Pathological Mechanisms**

ME/CFS has often been documented following exposure to an acute pathogen.[281] For instance, long-term fatigue, CFS/ME, or both have been reported after infectious mononucleosis,[282] viral meningitis[283] and giardia.[284] In addition, higher titres of several well-known pathogens have been detected in patients with CFS/ME. One of the most well-studied microbes in this syndrome is Epstein–Barr virus since patients often have higher titers of IgM to the EBV viral capsid antigen.[285] Also, antibodies against cytomegalovirus and human herpes virus-6, and Parvovirus B19 have been detected more often in some ME/CFS patients.[286] [287]

On the other hand, the species and prevalence of any one microbe identified in a particular cohort varies from one study to the other, limiting their utility for inferring causation. However, this observed association with infection may be significant because there is evidence that intracellular microbes such as EBV, HHV-6 and CMV can directly interfere with the expression of human genes, contributing to dysregulation of vitamin D receptors, potentially leading to the changes in the endocrine and immune function seen in ME/CFS.[288] [289] [290] Some evidence also exists for the possibility that chronic intracellular infection, such as mycoplasma, contributes to ME/CFS.[291] [292]

But there is no trial evidence that antibiotic treatment is effective. Similar observations have been made for Gulf War syndrome that antibiotic treatment is ineffective.[293] Others have argued that pulsed, low dose antibiotics are required (Marshall protocol)[294] for ME/CFS, but there is no evidence in the medical literature that antibiotic therapy was found to be generally effective, although patients have reported it may help in some cases.[295]

A systematic review of the medical literature reveals that the weight of available evidence points towards a reduced physiological exercise capacity in ME/CFS, when compared to sedentary controls.[296] Pacing self-management provides a modest improvement in symptom severity in daily functioning.[297]

There are several studies of ME/CFS which have used cardiopulmonary exercise testing.
The first results from these studies were mixed. Some found that the exercise capacity of ME/CFS patients was normal,[298] [299] [300] while others found a reduced[301] [302] [303] [304] capacity. However, repeating the exercise test on the following day demonstrates significant exertional malaise and prolonged recovery in patients with ME/CFS.[305] Healthy subjects score the same the next day but ME/CFS patients do worse, with evidence for reductions in maximal aerobic capacity (VO2 max) and anaerobic threshold.[306] [307] ME/CFS patients have impaired mitochondrial energy metabolism.[308] [309] [310] [311] With exertion, they reach the anaerobic threshold within two minutes. Because they can't replace the mitochondrial energy fast enough, their exercise capacity test scores are even worse 24 hours later.[312] [313] [314] [315] Their oxidative stress levels rise faster and stay high longer. This explains why minimal exertion aggravates the fatigue with subsequent prolonged recovery time. It explains why there are many practitioners, experienced in treating these patients, who have witnessed that graded exercise therapy (GET) according to a fixed schedule may be harmful, rather that helpful for ME/CFS.[316]

There is increasing evidence in ME/CFS, similar to fibromyalgia, for the role of central sensitization[317] and even more robust evidence for oxidative stress. [318] [319] [320] [321] [322] [323] [324] There is also evidence for change in muscle cell function due to oxidative stress in ME/CFS.[325]

Exercise studies on ME/CFS patients show that there is reduced muscle excitability[326] and impaired recovery[327] with simultaneous increases in oxidative stress.[328] [329] ME/CFS patients produce more metabolic byproducts from exercise compared to normal individuals[330] and they have subsequent reduced mitochondrial function.[331] [332] [333]

This distinct pattern of fatigue in ME/CFS is important from a therapeutic standpoint. Patients with ME/CFS have great difficulty responding to pre-formatted graded exercise programs, as recommended by some practitioners.[334]

Thus far, TRPV1 receptor abnormalities have not been directly measured in any ME/CFS studies, although these patients demonstrate increased gene expression of these receptors after moderate exercise.[335] Like other environmentally linked illnesses, there is evidence for systemic inflammation.[336] [337] [338]

In a quantitative PCR genetic analysis of ME/CFS patients' blood compared to controls, differential expression of 88 genes was noted in the ME/CFS patients, 85 of which were upregulated and 3 downregulated. Authors were then able to identify 7 different subtypes of ME/CFS with differences in symptom profiles, severity and Short Form-36 scores.[339]

The present available guidelines for the assessment and treatment of ME/CFS are conflicting. What is necessary is to test consensus definitions for validation of their criteria. Using the two day consecutive cardiopulmonary exercise test may help settle the argument as ME/CFS patients show substantially decreased function on the second day compared to normals. This test is potentially an objective, sensitive and specific biomarker for ME/CFS.

- **ME/CFS Comorbidity**

ME/CFS is comorbid with other entities, including irritable bowel syndrome, chronic tension-type headache, and interstitial cystitis,[340] migraine,[341] metabolic syndrome,[342] major depressive disorder,[343] and post traumatic stress disorder.[344] ME/CFS is also frequently comorbid with FM and ES/MCS.[345] Please see APPENDIX A-Overlapping Diagnoses for 23 Chronic Conditions Cohorts.

- **ME/CFS Management Strategies**

Dealing with symptoms and life interruptions of chronic complex conditions can be very taxing and frightening indeed. Each person is an individual who has used various mechanisms to cope with the changes related to illness, and other challenging incidents in life. Diverse supportive strategies have been tried to strengthen people's ability to move forward in managing their illnesses and return to better function and quality of life.

One commonly chosen goal of treatment for chronic complex conditions is to improve the daily routines of life which influence health, such as diet, exercise, reduction of chemical exposures and sleep hygiene. The intervention described as cognitive behavioural therapy (CBT) supports the skills for improvement. It is important to distinguish the CBT used in traditional psychotherapy from that which is used as a treatment for chronic complex conditions such as ME/CFS.[346] The latter uses some of the same tools and techniques as traditional CBT, but includes condition-specific strategies and should be considered as lifestyle enhancement therapy.

Problem-solving and goal setting are just some of the tools used to assist the patient in working towards an improved structured pattern of life. When necessary, the patient is taught to identify and challenge maladaptive thoughts and triggers which interfere with change.[347]

A Cochrane Database systematic review of 15 studies using the homework component of cognitive behavioral therapy (CBT) concluded that CBT homework is effective in reducing the symptoms of fatigue at post-treatment compared with usual care.[348] However, the evidence at follow-up is limited to a small group of studies with inconsistent findings. At treatment end, 40% of the CBT group showed clinical improvement in contrast to only 26% in usual care, but changes were not maintained at a 1 to 7 month follow-up because people dropped out.

Exercise in the form of graded exercise or paced activity, was assumed to be an integral component of CBT. Ten studies attempted to increase activity and reduce rest time as part of the CBT intervention, which may explain the high dropout rate.

There is evidence from a four-arm trial that CBT with graded exercise (GET) can be more effective for ME/CFS than specialist medical care or adaptive pacing.[349] There has also been a strong rebuttal.[350] For example, the subjects included in the cited study met the criteria for the broad Oxford definition of ME/CFS, which can also capture those with chronic fatigue of another origin, and depression.

Although it is difficult to research the precise techniques, several modalities have been shown to help. For example, focused attention or self hypnosis might be helpful for chronic pain.[351] [352] [353] Other mind-body approaches, including progressive muscle relaxation, meditation, laughter, mindfulness based approaches, guided imagery, yoga, and biofeedback, can be effective in chronic pain.[354] Group delivered courses with healthcare professional input may have more beneficial effects than individual therapy for some patients.[355]

Motivational interviewing (MI) has also been tried. Specific MI techniques include:[356]

1. using reflective listening to express empathy and clarify the patient's perspectives, without evaluating or lecturing the patient about what *should* be done;
2. questioning discrepancies between current behavior and important goals and reflecting them to the patient, encouraging him or her to consider how changing current behavior might reduce this discrepancy (e.g., how reducing bed rest might further the patient's goal of increasing physical activity);
3. avoiding arguing with or confronting the patient about behavior change by "rolling with resistance"; and
4. supporting self-efficacy, the patient's belief that he or she is capable of successfully performing a specific behavior.

Incorporating specific motivational enhancement strategies into CBT adds to engagement and helps to facilitate change.[357] [358] In order to be successful in reaching health goals, patients must advance through the five stages of change:[359]

1. precontemplation
2. contemplation
3. preparation

4. action
5. maintenance

When used alone or in combination, according to the needs of the individual, all the above modalities may promote more successful outcomes in self-management for chronic complex conditions such as ME/CFS, including making positive changes in diet, exercise and pain management.[360 361 362 363 364 365 366]

There is a lack of evidence on the comparative effectiveness of therapies alone or in combination with other treatments, and further studies are required to inform the development of effective treatment programs. One of the goals and measurement of success of self-management programs should be the maintenance of effective treatments.

- **ME/CFS Disability and Prognosis**

A literature search of clinical follow-up of patients following a diagnosis of ME/CFS[367] found that full recovery from untreated ME/CFS is rare, but the prognosis for an improvement in symptoms is less gloomy. The percentage of patients not working varies considerably, from 27 to 65%, and return to work at follow-up ranges from 8 to 30%. The observed wide range is because many studies included both chronic fatigue and chronic fatigue syndrome. The characteristic of the fatigue of ME/CFS is that minimal exertion exacerbates the fatigue, and recovery is prolonged. This defining characteristic is illustrated by the above mentioned reduced exercise capacity scores 24 hours post exertion, which is due to impaired mitochondrial function and increased oxidative stress.

Post exertional fatigue is a strong predictor of an inactive work status and full work incapacity in the long term.[368] Thus, the prognosis for ME/CFS with respect to return to work is generally poor.[369] The more severe the fatigue is, the worse the prognosis for recovery.[370]

There are some studies that suggest that cognitive behavioral therapy and graded exercise can improve the functional ability and return to work status for those with ME/CFS.[371] Most notable is the PACE trial, which has been criticized for flawed methodology.[372 373 374 375 376 377 378] One reason these studies demonstrated improvement is because they used case criteria which did not restrict the subjects to those with post exertional fatigue. This criterion is required to meet the Canadian case criteria for the clinical diagnosis of ME/CFS. Pushing these patients to increase exercise is potentially harmful.[379 380]

The majority of women with ME/CFS report some improvement in physical functioning over time, but the improvement is still far short of recovery. Furthermore, those who have a more negative outcome are more likely to have comorbid fibromyalgia.[381]

Fibromyalgia

- **Description and Prevalence, including Women and Children**

Fibromyalgia is a chronic, widespread pain disorder, present for at least 3 months. It frequently follows tissue injury. Although pain is felt in muscle or joint areas, there has been no physical abnormality found in these tissues. Pain onset is usually insidious, sometimes beginning in a

localized area. It may initially be intermittent and progressively becomes more persistent. Pain may vary in location and intensity from day to day, and can be modulated by factors such as weather or stress. Cold and humid weather tends to be associated with increased symptoms. The most frequently reported sensory symptom in fibromyalgia is pressure induced pain.[382] Fibromyalgia also includes fatigue, non-restorative sleep, cognitive dysfunction and mood variability, as well as other bodily (somatic) symptoms.[383]

Prevalence rates for fibromyalgia in the United States vary from 2-6 percent of the population[384] with a female-to-male ratio of 6:1.[385] In Canada, the prevalence rate for fibromyalgia is 2-3 percent, with females affected six to nine times more commonly than males.[386] [387] In children, it is more common in prepubertal or adolescent girls,[388] and estimates for the prevalence of juvenile fibromyalgia range from 1.3-6.2 percent.[389] [390] [391] Juvenile fibromyalgia is similar to the adult presentation and is characterized by persistent and widespread musculoskeletal pain, sleep difficulty, fatigue, and mood disturbance. Patients with juvenile fibromyalgia experience substantial impairment in physical, school, social, and emotional functioning,[392] [393] [394] and the majority of them continue to have ongoing symptoms and functional disability into late adolescence and early adulthood.[395] There are few studies of treatment of juvenile fibromyalgia. Meta-analytic reviews of cognitive behavioral therapy (CBT) clinical trials arrive at different conclusions regarding the effectiveness of CBT on pain and function.[396] [397] Pain is reduced by only 14%, which is lower than the 30% reduction in pain thought to be clinically meaningful.[398] However, these and other reviews indicate significant improvement in coping. Enhancing the ability to engage more in activities such as going to school, doing chores, going out with friends can be achieved without increasing the pain.[399]

- **FM Diagnostic Criteria**

In 1990, the American College of Rheumatology (ACR) published the diagnostic criteria for fibromyalgia:[400]

- a history of widespread pain, which has been present for at least three months. The pain is considered widespread when all of the following are present:
  - pain in both sides of the body
  - pain above and below the waist.
  - axial skeletal pain (cervical spine, anterior chest, thoracic spine or low back pain) must be present.
  - palpation induces pain in at least 11 of 18 designated tender point sites.

A proliferation of studies followed publication of the 1990 criteria. According to Medline (US National Library of Medicine), 361 English-language original articles with "fibromyalgia" as a keyword were published in the 20 years before the criteria existed, compared with 3844 in the 20-year period after the publication.[401] The 1990 ACR criteria generated numerous benefits. Studies have begun to unravel the etiology and impact of the disorder, treatment strategies have improved, and patients have also benefited from increased recognition and diagnosis of the disorder. However, the ACR criteria have also been criticized. The most notable criticism has been regarding the use and interpretation of the tender-point count.[402] [403] [404] [405] [406] [407]

A strong argument for continuing to count tender points as part of the clinical evaluation is that it is a measure of severity.[408] [409] However, the number of tender points does not fully capture the

essence of the illness. For example, there is almost always accompanying fatigue, which is often severe.[410] [411] The 1990 ACR criteria also lack consideration of associated symptoms, which impact on function and level of disability.[412] [413]

In the early 2000's, Health Canada constituted an Expert Medical Consensus Panel representing clinicians, academic teachers and researchers to study fibromyalgia at the same time as their appointed panel studied ME/CFS. Their findings were published in 2003 and 2004 as a Clinical Working Case Definition of Fibromyalgia. They built upon a history of widespread pain and tender point examination by including additional clinical symptoms and signs. It was required that patients, in addition to the ACR criteria, report two or more symptoms from the following: neurological manifestations, neurocognitive manifestations, fatigue, sleep disturbance, autonomic and neuroendocrine manifestations and stiffness.[414] These criteria have been widely followed internationally and are posted on the Ontario College of Family Physicians' website.[415]

In 2010, the ACR proposed new diagnostic criteria, which removed the requirement for tender points.[416] The criteria included measuring the severity of the widespread pain, fatigue, poor sleep restoration and cognitive complaints.[417] This encouraged doctors to quantify and follow symptom severity, although there was disagreement that this captured the essence of the condition.[418] The new criteria proposed two validated measurements to discriminate between patients with fibromyalgia and those with other non-inflammatory pain disorders: the widespread pain index (WPI), i.e., a count of number of painful body regions, and the Symptom Severity (SS) scale, a measure of cognitive symptoms, sleep, fatigue, and additional somatic symptoms.

In 2012, a multidisciplinary team, the Canadian Fibromyalgia Guidelines Committee (CFGC), representing healthcare professionals from relevant fields managing fibromyalgia patients, published evidence-based guidelines for the diagnosis, management and illness trajectory of persons with this disorder. Although there has been some debate over the contents, the diagnostic guidelines have been endorsed by the Canadian Rheumatology Association (CRA) and the Canadian Pain Society:[419]

- the diagnosis is based clinically on the chief complaint of pain and associated symptoms of fatigue, sleep disturbance, cognitive changes, mood disorder and other somatic symptoms.
- there are no confirmatory tests for fibromyalgia.
- the examination of tender points to confirm a diagnosis is not required. The physical examination is within normal limits apart from tenderness of soft tissues. There is still some debate about the removal of the mandatory requirement of 11/18 tender points.[420] [421]
- investigations should be limited to simple laboratory testing, unless the clinical picture suggests some other diagnosis.

The 2012 CFGC criteria include mood disorder in the syndrome of fibromyalgia. The guidelines state that mood disorder, including depression and/or anxiety, is present in up to three quarters of persons with fibromyalgia. The basis for this number comes from one study of 73 individuals seen in tertiary care centres.[422] However, community samples are less likely to be as impaired as tertiary-care samples.[423] According to the 2010 Canadian Community Health Survey, only 25% of Canadians reporting a diagnosis of FM also reported a diagnosis of mood

disorder. The data derived exclusively from tertiary centres should not be used to estimate and emphasize the prevalence of psychiatric comorbidity among the general population of individuals with fibromyalgia.

A syndrome is a group of symptoms occurring together that are sufficiently common and distinctive to be characteristic and indicative of some underlying cause. Thus it can be argued that the increased comorbidity of mood disorders requires that they must be included in the syndrome. Non-pain related symptoms in the 2012 Canadian guidelines include sexual dysfunction and posttraumatic stress disorder. Yet, there is no mention of chronic rhinitis or chronic urticaria, which may also be associated with fibromyalgia.[424] [425] [426]

Mood disorders are also more likely to be comorbid with other physical diseases such as allergy[427] and asthma[428] and impact on the severity of poor lung function[429] They are considered risk factors for the incidence of diabetes and cardiovascular disease, affecting severity and outcomes.[430] [431] However, the increased comorbidity of mood disorders does not make them part of these diagnoses.

The guidelines state that mood disorders and fibromyalgia are likely distinct. But stating that mood disorders are also part of the syndrome of fibromyalgia may be misleading to clinicians and potentially harmful to patients. Furthermore, there is no mention of ES/MCS in these guidelines, despite the fact that the Canadian Community Health Survey found that 15% the patients with fibromyalgia report chemical sensitivities, and other authors have found more.[432] [433] [434] [435] [436] [437] [438] Patient organizations have raised considerable concern that the 2012 Canadian diagnostic criteria will lead to confusion, further deterioration in service for fibromyalgia patients, and an increase in stigma.[439]

- **FM Pathological Mechanisms**

Fibromyalgia is considered to be a CNS disorder[440] [441] [442] in which the processing of pain is abnormal[443], involving central sensitization.[444] This is the term used to describe an increased central nervous system response to a normal sensory input.[445] It is thought due to activation of NMDA[446] [447] [448] and TRPV1 receptors.[449] [450] These receptors are activated by oxidative stress,[451] [452] which has been demonstrated in fibromyalgia.[453] In particular, TRPV1 receptors are activated by chemical exposures.[454] [455] The oxidative stress also contributes to the neuron malfunction in fibromyalgia by reducing mitochondrial function.[456] There is evidence for systemic inflammation.[457] [458]

Genetic polymorphisms affecting the catechol-o-methyltransferease (COMT) enzyme may predispose to fibromyalgia through abnormal function of the hypothalamic-pituitary-adrenal (HPA) axis, including hyperactive adrenocortical trophic hormone (ACTH) release and adrenal hyperresponsiveness. These polymorphisms may affect ability to inactivate catecholamines and catecholamine-containing drugs.[459]

- **FM Comorbidity**

Fibromyalgia is frequently comorbid with chronic fatigue and cognition complaints.[460] [461] Patients with fibromyalgia frequently complain of poor memory, severe enough to affect job performance and to lead to disability.[462] Sleep is also disturbed.[463] Overnight polysomnograms

show abnormal alpha wave intrusion.[464] They have less sleep efficiency, a higher proportion of stage 1 non-REM sleep, and twice as many arousals per hour of sleep.[465]

In particular, fibromyalgia is frequently comorbid with, and is impacted by, ME/CFS,[466] ES/MCS,[467] [468] IBS,[469] vulvodynia,[470] cervical myofascial pain syndrome,[471] migraine headache,[472] elevated body-mass index (BMI),[473] [474] sleep apnea,[475] [476] chronic rhinitis,[477] chronic urticaria,[478] psoriasis,[479] endometriosis, [480] lupus and rheumatoid arthritis.[481] Please see APPENDIX A-Overlapping Diagnoses for 23 Chronic Conditions Cohorts.

- **FM Management Strategies**

According to the 2012 Canadian Fibromyalgia Guidelines Committee (CFGC), similar to a treatment framework published in the United States by the Mayo Clinic,[482] the ideal management of FM will address pain as well as the composite of symptoms that comprise this syndrome.[483] Specific points made by the CFGC include:

- Primary care physicians are encouraged to establish a diagnosis of fibromyalgia as early as possible without need for specialist confirmation.
- Ideal care is centered in primary care.
- Treatment plans should incorporate self-management techniques, goal setting and healthy lifestyles, with acknowledgement of psychological distress when present.
- Patient goals and their levels of achievement should be recorded as a useful strategy to follow outcome.
    - Tender point examination should not be used as an outcome measure.
- Treatment requires a multimodal approach.
- Self-management is facilitated by multi-component therapy.
- Attention should be paid to individual symptoms in a patient-tailored approach.
- Patients should be encouraged to identify specific goals regarding health status and quality of life at the initiation of treatment, with reevaluation of goals during follow-up
- Non-pharmacologic treatments have a positive effect with improvements in self-reported outcome measures including physical status.

  - Non-pharmacologic treatments appear more effective than most pharmacological interventions.

  - These include cognitive behavioural therapy, motivational interviewing, meditation, EMG-biofeedback therapy, imagery, hypnosis, mind-body therapies, transcranial magnetic stimulation, transcranial direct current stimulation, acupuncture, Tai Chi, Qigong, and hydrotherapy.
- Persons with fibromyalgia should participate in a graduated exercise program of their choosing.
- Pharmacologic treatments should be initiated in low doses with gradual and cautious upward titration to minimize side effects.

  - Only pregabalin and duloxetine have been approved by Health Canada for management of fibromyalgia. All other pharmacological treatments constitute "off label use".

  - Continued medication use requires diligent evaluation, with attention to the need for continued use and emergence of adverse effects.
- Clinical outcome can be measured by a simple narrative report of symptom status, without the use of specific questionnaires.

- Psychological counseling and cognitive behavioral therapy may be helpful for associated psychological distress, including fear of pain and activity.
- Any new symptom requires appropriate clinical evaluation and should not immediately be attributed to fibromyalgia.
- Other comorbid illnesses need to be addressed.

Other guidelines have been developed and can be compared to the ACR and CFGC guidelines.[484] The European League Against Rheumatism (EULAR) gave cognitive behavioral therapy a much lower strength of recommendation.[485] There were no recommendations provided for patient education or multi-component treatment, both of which are essential for management of chronic, complex conditions.

- **FM Disability and Prognosis**

Patients with fibromyalgia report persistent widespread pain, fatigue, and substantial functional limitations, which may lead to high health resource use and lost productivity.[486]

Patients with fibromyalgia frequently complain of poor memory, severe enough to affect job performance and lead to disability. There are subsequent economic consequences for both patient and employer, as well as the healthcare system.[487] Factors such as diminished productivity, temporary work disability, permanent work disability, or early retirement are responsible for up to 70-80% of the total cost of this disease,[488] [489] [490] with a loss of 17 to 30 work days per year by patients with fibromyalgia.[491] [492] More than one third of women with fibromyalgia are disabled.[493] The majority (70%) of those who work do it part-time.[494] The economic burden increases with severity.

The Fibromyalgia Impact Questionnaire (FIQ) was developed to meet the need for comprehensive fibromyalgia patient evaluation. It is a validated questionnaire,[495] which has been used to assess people in the community who have chronic pain[496] to determine the impact of fibromyalgia on everyday life[497] and to measure disability[498] as well as outcomes in drug studies, exercise treatment, multidisciplinary approaches and treatment program evaluation. It is designed to quantify the overall impact of fibromyalgia over many dimensions using visual analog scales (e.g. function, pain level, fatigue, sleep disturbance, psychological distress etc.). The average score for fibromyalgia is 50. Almost all patients with a score above 79 are disabled from work.[499]

Results from epidemiological research in several countries clearly demonstrate the socioeconomic burden of fibromyalgia and its comorbidities. These results highlight the urgent need for more research on pathophysiology and treatment challenges.[500]

Unfortunately, finding appropriate care for patients with fibromyalgia may be difficult. The majority of Ontario rheumatologists do not wish to be responsible for their care, and the new guidelines say patients with FM should be seen by family physicians, not rheumatologists, despite the fact that the American College of Rheumatology developed the criteria for the diagnosis of fibromyalgia. More than half of rheumatologists still believe that fibromyalgia is primarily a psychosomatic illness.[501]

▪ Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS)

o ES/MCS Description and Prevalence, including Women and Children

The staff physicians at the Environmental Health Clinic at Women's College Hospital produced a 42-page Environmental Sensitivities/Multiple Chemical Sensitivities Status Report, Advances in Knowledge and Current Service Gaps dated October 31, 2010 and updated on February 17 and June 2, 2011. To meet the needs of non-English-speaking populations, the report has now been translated into French and German. A copy is provided (ATTACHMENT B- ES/MCS Status Report), and so not as much detail has been provided in this compendium as for ME/CFS and FM.

In 1994, the Ontario Ministry of Health funded an Environmental Hypersensitivity Research Unit (EHRU) at the University of Toronto, on the recommendation of the Ministry-appointed Ad Hoc Committee on Environmental Hypersensitivity Disorders, chaired by then Family Court Judge George M. Thomson (later Deputy Attorney General for Ontario and Canada).[502] The EHRU first clarified the distinguishing definitional characteristics, and then took blood samples from cases and controls that revealed genetic detoxification abnormalities in cases. These were considered likely ES/MCS susceptibility factors.[503]

ES/MCS is a chronic, polysymptomatic condition. Multiple systems are involved, but the system most likely to be provoked is the CNS. The term sensitization has been used in the research of brain function in animals for over 40 years. It is the progressive increase in the size of a response because of repeated stimulations.[504] In immunology, it is called allergy. In psychology, it is the process of becoming highly sensitive to specific emotional events or situations (e.g. in social anxiety disorder). In ES/MCS, it is the sensitization of the brain to many substances at levels that previously had no relevance. The EHRU noted that 4 neurological symptoms were more common in cases than controls, discussed on p. 43.

One study reported the five most common symptoms with ES/MCS are tiredness/lethargy, difficulty concentrating, muscle aches, memory difficulties and long-term fatigue.[505]

Affected persons report recurrent flares of illness, with symptoms individual to them, when exposed to low levels of environmental chemicals (e.g., pesticides, solvents), common foods (e.g., milk, chocolate, wheat, sugar), multiple drugs, other ingestants (e.g., alcohol, chlorinated water)[506] and electromagnetic devices.[507] These flares can vary with the substance, dose, combination and frequency of exposures.

People are continuously exposed to electromagnetic fields (EMFs) in everyday life. Whether they can be harmful to human health continues to be a matter of great debate.
Some individuals experience symptoms in proximity to wireless systems, when using cordless or cell phones, when exposed to baby monitors or some types of artificial light, or in response to various other common electromagnetic exposures, such as cell phone towers. These individuals are being referred to the Environmental Health Clinic at Women's College Hospital with increasing frequency.

Self-reported electric and magnetic field hypersensitivity has been described for more than 25 years.[508] Population surveys suggest that about 3 to 5% of the population report being symptomatic when near electrical devices.[509] [510] The most common symptoms are fatigue, dizziness, headache, and difficulties concentrating. Other symptoms frequently involve the skin (itching, burning, stinging), respiratory and gastrointestinal systems. The major features of this self-reported disorder are the onset or exacerbation of symptoms with proximity to electrical devices or power lines and telephone towers, and the reduction or disappearance of symptoms when the source is off, or not nearby. In the populations surveyed, claiming to be doctor-diagnosed with ES/MCS was the strongest predictor of also reporting being hypersensitive to EMFs.[511]

Some authors argue that robust evidence is lacking to support the theory that people can be sensitive to EMFs, basing their opinion on a review of more than 40 blind or double-blind provocation studies.[512] [513] They therefore attribute the EMF hypersensitivity to somatoform disorders.

However, the human brain can detect weak EMFs, as evidenced by changes in brain electrical activity.[514] [515] The medical literature describes other effects of EMFs,[516] such as risk of brain tumors, damage to sperm, behavioural problems in young children,[517] and damage to the blood-brain barrier. However, the literature also demonstrates that the level of evidence is weak,[518] and each issue remains controversial. More research is required and the OCEEH Hub can provide the leadership to network with other international projects in order to develop and promote the required studies,[519] [520] such as developing a working definition of electromagnetic field hypersensitivity (EHS), developing and validating a diagnostic tool (questionnaire) to characterize subjects with purported EHS, identifying subjects, who may be more at risk for testing, performing double-blind exposure challenges (applying the specific frequencies to which each of the participants report reactions), and developing management and treatment tools for patients who identify symptom provocation with EMF proximity.

Like those with ME/CFS and FM, more women are affected with ES/MCS than men. Of those affected with ES/MCS, 70 to 80% are women.[521] [522]

One common denominator of these three conditions is limbic system sensitization. There are sex differences in how the limbic system responds. Functional brain scans reveal that, when challenged, men and women activate different limbic structures following the same provocative stimuli.[523] There are sensory differences which are related to limbic system function. Women have a higher prevalence of several pain-related conditions, including migraine headaches, temporomandibular joint disorders, carpal tunnel syndrome, Raynaud's disease, chronic widespread pain, osteoarthritis (OA), irritable bowel syndrome and pain related to autoimmune disorders (rheumatoid arthritis and other collagen vascular diseases).[524] [525] On average, women are more responsive to painful stimuli,[526] and women also tend to have a heightened inflammatory response compared to men.[527]

Statistics gleaned from the National Health and Nutrition Environmental Survey (NHANES) in the US suggests that environmental pollution exposures affect women more than men.[528] [529] [530] Women biologically handle chemicals differently compared to men. The enzyme systems for

detoxification are more active than men.[531] [532] [533] Normal kidney clearance of chemicals is lower in females compared to males.[534] [535] [536] [537] Also, women retain more inhaled volatile organic compounds than men.[538] [539] This is likely because women have a higher percentage of body fat,[540] which affects the distribution of chemicals that are not easily eradicated.[541] [542] [543]

Given the higher domestic responsibilities relative to men, women also have greater exposure to chemical cleaners, detergents and fabric softeners. Women also use more cosmetics, skin care and scented products.

In summary, the prevalence of environmentally linked illnesses, as seen particularly well in ES/MCS, are more common in women because they are more responsive to their environment via both the limbic and immune systems, have a greater body burden of chemical exposures and less efficient detoxification systems compared to men.

Children, from embryo to the completion of adolescence, are often at a different and increased risk from environmental contaminants compared to adults because of differences in behavior and physiology.[544] They have greater exposures relative to adults, immature detoxification systems, and still-maturing organ systems.[545] [546]

There has been a significant rise in chronic complex conditions in childhood. The number of children with developmental disabilities has increased by 17% over the last decade so that now one child in six is being diagnosed with one of attention deficit hyperactivity disorder (ADHD), cerebral palsy, autistic spectrum disorder, seizures, stammering or stuttering, mental retardation, moderate to profound hearing loss, blindness or learning disorders.[547]

The Environmental Working Group did two small studies of 10 American, Canadian and Dutch newborn babies in 2005[548] and 2009,[549] in which they measured the chemicals found in cord blood. In both studies, they found well over 200 chemicals in the newborn babies' circulation. More than 400 publications are available in the U.S. National Library of Medicine which confirm the presence of pollutants in newborn children. Sources of contaminants include outdoor and indoor air, food, water and consumer products.

In 2011, the Canadian Environmental Law Association, the Ontario College of Family Physicians and the Environmental Health Institute of Canada published an extensive scoping review of the literature.[550] Their main findings were that there is increasing scientific confirmation for the role of early life (in utero and peri-natal) exposures to environmental contaminants and a lifelong vulnerability to chronic disease.

Children are particularly vulnerable to the effects of outdoor air pollution. Those living in urban areas exhibit higher rates of allergy and asthma compared with those from rural areas.[551] [552] [553] [554] There are several studies showing adverse effects of outdoor air pollutants on lung development in children of all ages.[555] [556] [557] The more time kids spend outdoors and the closer they live to major roadways, the more likely they are to have reduced lung function growth by age 18.[558] [559] Children with a genetic predisposition to poor detoxification are more likely to have their pulmonary function growth affected by air pollution.[560] [561]

Several studies have also associated autism and prenatal and early life exposure to air pollution from traffic.[562] [563] [564] [565] Children with autism have shown a decreased ability to detoxify as well as an elevated body burden of xenobiotics.[566] Furthermore, there may be an epigenetic predisposition inherited from the mother.[567]

- **ES/MCS Diagnostic Criteria**

In the 1980s and 90s various criteria had been proposed for defining a case of MCS, also called environmental sensitivities or hypersensitivities, environmental illness, environmental intolerances, idiopathic environmental intolerances, or toxicant-induced loss of tolerance. There were 9 published definitions. Based on the previous work of Nethercott et al,[568] a list of criteria that reflected an internationally *consistently observed pattern* of symptom presentation was agreed upon by 34 North American clinicians and researchers who collectively had experience with thousands of MCS patients.[569]

Part of the definitional challenge was, and is, related to the fact that symptoms and signs triggered by low level exposures to environmental agents vary among affected individuals and within individuals, depending on inciting agents as well as the doses, timing, and combinations of exposures. Also, while there can be abnormal physical and laboratory findings, the same findings are not *consistently* abnormal in all patients or in individual patients all the time.[570]

The 1999 consensus criteria were subsequently validated using a reproducible questionnaire.[571] A checklist of the criteria is posted on the Ontario College of Family Physicians website for use by practising clinicians.[572] The criteria include:

- symptoms are reproducible with (repeated chemical) exposure
- the condition is chronic
- low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome
- the symptoms improve or resolve when the incitants are removed
- responses occur to multiple chemically unrelated substances
- (added in 1999): symptoms involve multiple organ systems

These criteria were validated by the Ministry of Health-funded Environmental Hypersensitivity Research Unit (EHRU) at the University of Toronto in collaboration with the Environmental Health Clinic at Women's College Hospital. Symptoms which most commonly distinguished patients with ES/MCS from controls were :[573]

- having a stronger sense of smell than others
- difficulty concentrating
- feeling dull or groggy
- feeling spacey

A systematic literature review published in 2005 confirmed that the most frequent system involved in ES/MCS is the central nervous system.[574] It is noteworthy that this same observation was described in the 1985 report to the Ontario Ministry of Health by the Ad Hoc Committee on Environmental Hypersensitivity Disorders,[575] which led to the creation and provincial funding of the Environmental Health Clinic at Women's College Hospital.

- **ES/MCS Pathological Mechanisms**

In animal studies, stimulating the brain with electric currents causes seizures. Stimulating the brain for a few weeks at a very low intensity, too low to cause any type of convulsing (aka seizure or epilepsy), will eventually cause seizures in rats even though only a very low stimulation is applied.[576] Their brains become sensitized to electricity, and the sensitivity lasts for months.[577] [578] This process is called kindling.

Chemicals can cause kindling too. Giving rats repeated low doses of chemicals, which can induce seizures at higher doses, eventually drops the threshold. Giving the rat the previously tolerated low dose would then induce a seizure, without any evidence that the substance had accumulated in the rats.[579] [580] [581] [582] With this discovery, researchers theorized that kindling, as a form of sensitization, provided a biological explanation for the ES/MCS phenomenon.[583] [584] [585]

There is evidence to support the position that sensitization in the brain of rats can be induced by repeated low dose exposures to chemicals. Behavioural or neurochemical alterations can occur from sensitization to solvents, which are toxic at higher doses, such as 1,1,1,trichloroethane,[586] toluene[587] [588] and formaldehyde[589] as well as several different pesticides.[590] [591] [592] [593] [594] Examples in animal experiments demonstrate that sensitization to a chemical leads to increased sensitivity to other, chemically unrelated substances.[595] [596] [597] [598] [599]

Oxidative stress contributes to receptor excitability in kindling.[600] Activating NMDA receptors on the cell membrane of neurons induces kindling.[601] [602] There are other receptors that can be stimulated by oxidative stress, notably the transient receptor potential cation channel subfamily V member 1 **(**TRPV1) receptor, and there is evidence in human studies that these receptors become sensitized in ES/MCS.

TRPV1 receptors are also receptors for capsaicin, which is the pungent ingredient in red-hot chilli peppers. The sensation of heat is created by capsaicin selectively binding to TRPV1 receptors.[603] These receptors are widespread and are found in the brain,[604] eye,[605] lining of the bladder,[606] [607] mast cells,[608] stomach lining,[609] [610] bowels,[611] [612] larynx[613] and bronchial tubes.[614] Because they are found in the pulmonary system, challenging these receptors with inhalations of capsaicin is used to study cough.[615] [616] [617] [618] [619]

The capsaicin inhalation challenge test consists of inhaling different concentrations of capsaicin using a mouthpiece apparatus to control the amount. The total number of coughs provoked is counted over 10 minutes.[620] This test is commonly used in clinical research because it induces cough in a safe, reliable, dose-dependent, and reproducible manner.[621] Well over 100 studies using the capsaicin challenge testing procedure were published over a 20 year period from 1984 to 2004.[622]

ES/MCS patients with respiratory symptoms, even without asthma, are hypersensitive to inhalation of capsaicin, when compared to controls, and this has been demonstrated by double-blind challenges.[623] The ES/MCS patients coughed more and, the higher the dose, the more coughs provoked. Other challenge studies have reproduced the same results, demonstrating TRPV1 receptor hypersensitivity in patients with chemical sensitivities.[624] [625] [626] [627] [628] [629] These

patients also secrete more nerve growth factor (protein which promotes growth of sympathetic and sensory nerve cells) in the nasal secretions after capsaicin provocation challenge.[630]

This hypersensitivity explains how and why ES/MCS patients have multiple symptoms from multiple systems. The TRPV1 receptor is especially active in sensory neurons,[631] [632]and the brain,[633] [634] [635] notably in the limbic system,[636] where it facilitates long lasting sensitization.[637] [638] These receptors drive the excitation of neurons to enhance messaging between them.[639]

Why some people get sensitized to chemicals more easily than others is not clear. There are many factors including genetic susceptibility. There is evidence that ES/MCS patients are genetically predisposed to have inferior enzyme systems for detoxification.[640] [641] Because they are less capable of efficiently detoxifying,[642] oxidative stress occurs in ES/MCS patients.[643] Oxidative stress can sensitize TRPV1 receptors.[644] [645] [646] [647] Although the TRPV1 receptor may be the major target for organic solvents in ES/MCS, there are likely others, such as NMDA receptors.[648] [649] There is also some evidence for systemic inflammation.[650]

Austin Bradford Hill developed the basis of modern epidemiological research, which attempts to establish scientifically valid causal connections between potential disease agents and disease. The Bradford Hill's Criteria of Causation outline conditions he thought were needed to establish the strength of a cause-and-effect relationship between two items.[651] [652] One of the criteria for observing cause, which goes beyond just a statistical association, is whether it makes scientific sense. This is known as the coherence of association. The cause-and effect interpretation of data should not seriously conflict with the generally known facts of the natural history and biology of the disease. Another criterion is plausibility. As stated by Bradford Hill, *"What is biologically plausible depends upon the biological knowledge of the day. In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd."*

Using these cause and effect criteria, it has been argued by some that the etiology of ES/MCS is psychogenic[653] and fails to meet Bradford Hill's criteria as a physical entity.[654] These opinions were published 10 years ago before classical toxicology, i.e. the dose makes the poison, was modernized with recognition of non-monotonic dose responses to many chemicals and the demonstrated model of sensitization. In fact, there are many papers published demonstrating that this classical toxicology model is no longer tenable.

As stated by Bradford Hill: *All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.*

Genetic polymorphisms indicate that people with ES/MCS have more difficulty metabolizing and excreting commonly encountered environmental chemicals and medications in comparison with controls.[655] [656] [657] [658] [659] Even in the absence of an abnormal detoxification polymorphism, oxidative stress occurs in ES/MCS patients.[660]

To summarize, patients with ES/MCS are more likely to have a genetic predisposition to poor detoxification, evidence of oxidative stress and sensitization of TRPV1 receptors. Up-regulation of these receptors occurs secondary to oxidative stress. Studies in animals have demonstrated that central nervous system sensitization to chemicals can occur from repeated and/or strong exposures to individual chemicals. These studies also demonstrated that sensitization to a chemical leads to the increased likelihood of sensitization to other, chemically unrelated substances.

- **ES/MCS Comorbidity**

ES/MCS is frequently comorbid with ME/CFS and FM and they are also frequently comorbid with other common conditions, such as chronic headache, chronic migraine headache, irritable bowel syndrome (IBS), allergies, asthma and autoimmune disorders. See APPENDIX A- Overlapping diagnoses for 23 Chronic Condition Cohorts.

Patients with multimorbid chronic illness face challenges of self-management, with increased adverse events, high health care utilization and poor quality of care.[661] [662] This is no doubt influenced by the fact that medical care has traditionally focused on the prevention, diagnosis and treatment of single diseases.[663]

Most research studies focus on the effectiveness of disease-specific interventions, and patients with comorbidity or complex problems are often excluded from clinical trials.[664] [665] [666] When they are included, it is difficult to know whether the overall effect of a trial can be extrapolated to individuals with comorbidities, i.e. whether the effect of the treatment is different in those with or without comorbidities.

Approximately 40% of people with ME/CFS also have ES/MCS,[667] [668] [669] and 21% were found to have both in the Canadian Community Health Survey 2010. ES/MCS is frequently comorbid with FM,[670] [671] [672] IBS,[673] and major depressive disorder disorder.[674] [675] [676]

- **ES/MCS Management Strategies**

Guidance for treating ES/MCS has come from experience by numerous clinicians internationally, outlined in the ES/MCS Status Report (APPENDIX B- ES/MCE Status Report: Advances in Knowledge and Current Service Gaps).

It is stated the cornerstones in clinical management of ES-MCS are:

- reduction of exposure to each person's unique environmental symptom triggers (e.g. some perfumes, cat dander) and toxins (e.g. formaldehyde emitted from particleboard, pesticides), once identified via exposure history and observation,
- enhancement of internal processing and elimination of chemicals,
- reduction in body burden of retained chemicals if necessary,
- relief of suffering with symptomatic treatments as needed,
- treatment of co-morbid conditions that can exacerbate or be exacerbated by ES-MCS, and
- encouragement to make changes in habits that would be likely to prevent further illness and promote health.

A survey of support groups and 917 participants was published, which rated the perceived efficacy of 101 treatments, and reported help:harm ratios for these treatments.[677] For example, chemically free living space was rated the most beneficial treatment, with a help:harm ratio of 155:1, followed by chemical avoidance (119:1). Psychotherapy to help cope had a somewhat positive effect (6:1), but psychotherapy for MCS cure provided no help but no harm (1:1). Antianxiety/antidepressant medications worsened symptoms (0.3:1).

- **ES/MCS Disability and Prognosis**

Illness related dysfunction from ES/MCS fluctuates on a continuum from mild to serious. It is an important health care issue because it often includes serious dysfunction, is poorly understood by providers and poses extensive financial and treatment obstacles for those who experience it. This can include loss of job, relationships, public access and personal comfort.[678]

There are many studies which have identified a common theme of lack of accessibility.[679] At best, most patients with ES/MCS have difficulty accessing common community resources that most persons take for granted, including communities of worship, grocery stores, shopping centres, community meetings, public libraries, restaurants, movies, use of public transportation, the homes of extended family members and friends, offices of dentists and medical doctors, public parks, classes at local universities, and most significantly, access to work.[680] [681] [682] [683] [684] [685] [686] (People with ME/CFS and FM may have difficulty with access based on lack of energy and reduced activity levels.)

Others' lack of understanding and refusal to make accommodations in the workplace have denied spatial access to those with ES/MCS.[687] [688] It is also almost impossible for many of those who are significantly impacted by ES/MCS to find suitable housing because buying and creating a place to live that does not provoke symptoms is only possible for those with the financial resources to do so.[689] Reduced financial resources is partially as a result of a combination of reduced income, increased expenses, and lack of financial support from authorities, including difficulties receiving worker's compensation and disability benefits because they had difficulties establishing a medical diagnosis.[690]

There has been reluctance to accept ES/MCS as a pathological disorder. But the history of medicine shows that iconoclastic ideas have occurred with many other medical disorders. They invoke controversy, resistance, and sluggish knowledge translation.[691]

The limited access to medical care because of the physical barriers of chemical exposures is complicated further because physicians are often unfamiliar with and/or do not believe in ES/MCS. They lack experts and resources to rule in or out other conditions. As a result, these patients describe unmet medical needs, delays in correct diagnosis, or treatment for the wrong condition.[692]

Persons with multiple chemical sensitivity seek medical treatment in a variety of contexts. Many hospitals and public facilities have initiated scent free policies,[693] in part as a result of the EHC's work with the Canadian Coalition for Green Health Care. However, there are difficulties with cooperation and enforcing the policy. Healthcare providers need to be better informed to avoid iatrogenic harm due to medical exposures (for example from cleaning products, scented soaps,

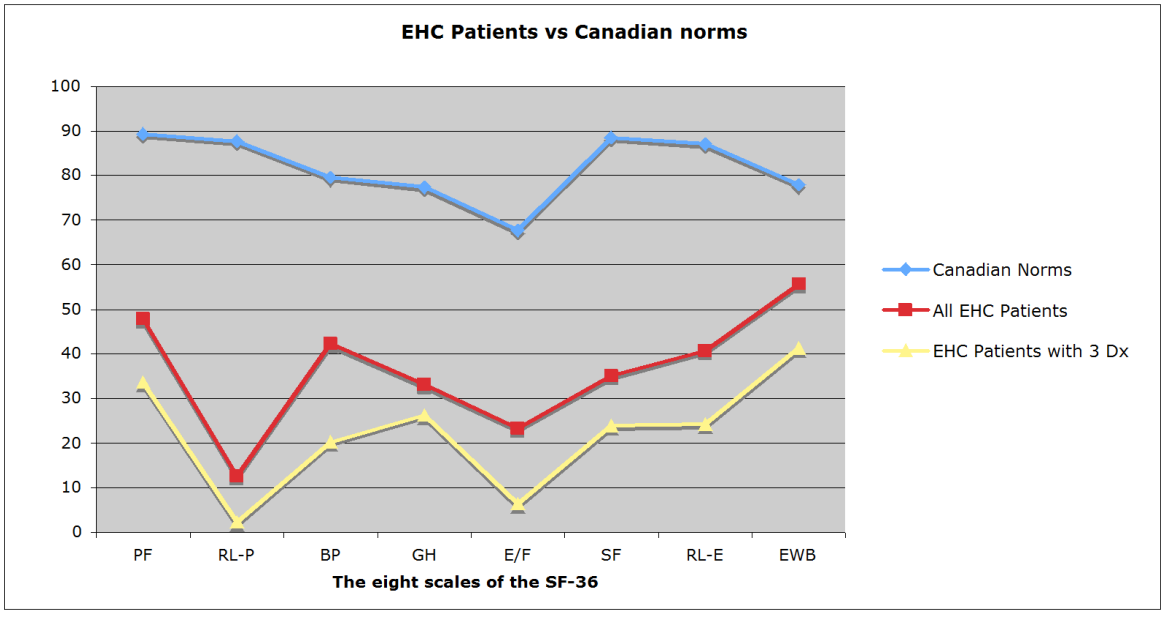
pharmaceuticals, etc.). Preventing reactions not only helps the patient, but saves time and trouble for the staff.

- **Functional Status**

There is substantial comorbidity in patients with any of ME/CFS, FM or ES/MCS. These patients suffer more functional impairment and disability with comorbidity,[694] just like those with other chronic illnesses. Those patients with all three diagnoses experience the greatest amount of disability, as demonstrated by the following graph (Figure 2 below) of 128 consecutive patients seen at the Environmental Health Clinic, Women's College Hospital.[695] This is a graph of scores from the Medical Outcomes Study Short-Form Health Survey (SF-36).

The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It assesses functional status on 8 descriptively named subscales: physical functioning (PF), role limitations due to physical health problems (RL-P), bodily pain (BP), general health perceptions (GH), energy and fatigue (E/F), social functioning (SF), role limitations due to personal or emotional health problems (RL-E), and emotional well-being (EWB).[696] Each has been shown to have high reliability and validity. The SF-36 has been documented in nearly 4,000 publications in articles describing more than 200 diseases and conditions.[697] It has been used in general population surveys of Canadians,[698] [699] in a range of patient populations, including those with CFS,[700] [701] [702] FM,[703] [704] [705] and MCS,[706] as well as in a comparative study of all 3 groups.[707] Scoring results in scale ranges from 0 to 100, with higher values representing better function.

Figure 2 Functional Status (SF-36) of EHC Patients vs Canadian Norms



ES/MCS has been described as a stigmatized condition, both because people affected have to avoid seemingly harmless exposures or wear a mask[708] and because of the psychologization of the condition, whereby they are perceived as liars or hypochondriacs.[709] [710] The veracity,

morality, and accuracy of patient symptom descriptions is questioned. Similarly, psychologization and disbelief are experienced by patients with ME/CFS and fibromyalgia.[711]

- **Psychologization**

Opinion articles still appear in respected medical journals in support of the psychogenesis of ME/CFS, FM and ES/MCS,[712] despite the fact that the citations frequently used to support the argument are outdated.[713]

Significant methodological errors also persist. For example, studies which positively demonstrate the efficacy of graduated exercise for ME/CFS often use case definitions which capture other fatigue-related conditions, such as depression and unexplained chronic fatigue. These latter conditions respond somewhat favorably to pre-programmed exercise, but ME/CFS does not.

ME/CFS patients do have an increased prevalence of current mood disorders, primarily major depression,[714 715 716 717 718] but it is unclear whether the patients had these conditions before or after they became ill with ME/CFS. Some doctors use this fact to insist that ME/CFS is primarily a psychiatric illness.[719 720 721 722 723]

Mood disorder has been added by the Canadian Fibromyalgia Guidelines Committee to the latest diagnostic criteria for FM with scant evidence from a tertiary care sample.

Because there are currently no generally recognized biological markers for ES/MCS and the pattern of sensitivities does not match the traditional toxicology paradigm, psychological theories to explain ES/MCS and psychotherapeutic treatments have been suggested since the 1980s.[724 725] They were roundly criticized for poor methodology.[726] For example, one early study of 50 cases concluded that because at least half the patients were still symptomatic even when avoiding chemical pollutants, ES/MCS cannot exist.[727]

Studies report associations of ES/MCS with panic disorder[728 729] and major depression.[730 731 732] However, association does not mean that there is a cause and effect relationship. In fact, mood disorders are also more likely to be comorbid with other physical diseases such as allergy[733] asthma,[734] diabetes[735] and cardiovascular disease.[736] Nevertheless, the theories of psychogenic etiology due to false attribution, i.e., panic disorder, chemical phobia and agoraphobia, continue to be offered in the medical literature.[737 738 739 740 741 742] Some authors have opined that ES/MCS "is a belief characterized by an over-valued idea of toxic attribution of symptoms and disability, fulfilling criteria for a somatoform disorder and a functional somatic syndrome."[743] These same authors postulate that to work with ES/MCS patients, "one must understand the dynamics of brainwashing, including the effects of iatrogenic influence and the individual's predisposition and susceptibility to it."[744]

Another recently published article refers to these patients as hermits.[745] The authors claimed to have conducted a "literature review" of case reports of ES/MCS and compared their "recluse-like behaviour" resulting from environmental sensitivities to the behaviour of ancient hermits. The bias in this report is reflected by their "literature review", which only searched media articles, blog posts, and online books and forums in order to generate the following quotes: "This is not a

lifestyle I choose", "I have no choice", "Nobody would live like this if they had a choice", and, "Do you think I would have given up a satisfying life … if I had a choice?" Unfortunately, the authors used these quotes to conclude, without any substantiation, that ES/MCS patients have a compulsion to flee, like hermits. What was actually expressed in these case reports is the absence of choice due to symptom provocation in certain environments, and the subsequent negative impact on quality of life in order to maintain health.

If one wishes to study how individuals experience their own problems in the life situation in which they find themselves, interviews can offer a method to obtain such information. They are used as a means of understanding how people experience their world and to gain insight into their perceptions, experiences and emotions. However, the goal of the interview is to obtain nuanced descriptions of various aspects of the interviewee's life-world, and to analyze the data according to qualitative research protocols. Qualitative content analysis of interview data should follow a set procedure: (a) audio review, (b) reading through transcriptions, (c) discussions among investigators regarding key elements of participants' perceptions, (d) determination of conceptual themes, and (e) assignment of relevant responses to appropriate thematic constructs.[746]

In comparison to the lack of science and open bias apparent in the above article comparing ES/MCS patients to hermits, consider the results of a published interview study, in which ES/MCS subjects were first identified objectively by capsaicin inhalation challenge. The interviews were analyzed using qualitative content analysis, which revealed the following themes and suitable quotes:[747]

Limitations in one's life situation

- *I simply can't enter that shop, my eyes smart …I have to leave immediately.*
- *We have someone who uses … it's the smell that makes me feel so bad and I avoid her ever since she got that perfume.*
- *We have relaxation exercises in that room in the morning and it ended up with me leaving; I couldn't take part because we were supposed to lie down on the wall-to-wall carpet and my throat started to catch and I felt bad.*

Lack of understanding from others

- *You can be sitting at a meeting where people reek of strong perfume and an undertone of sweat. And it attracts a bit of attention when you have to inhale and all that and, well...I know that people have thought that I was being fussy.*
- *The staff come back from their breaks and smell of smoke and coffee and what-not and it's…I haven't told anyone that they're causing me any problems…you'd just look like a whiner.*

In support of the psychogenic theory is the argument that we have been unable to demonstrate chemical sensitivity with double blind challenge studies. However, blinding the chemical challenge is impossible, without using another chemical to mask it. Nevertheless, a published, systematic review of all the challenge studies concluded that MCS cannot exist.[748] There was no transparency of authors' financial involvements in this systematic review. Furthermore, there was no explanation as to why several previously published challenge studies using capsaicin to demonstrate chemical sensitivity were not considered.

Based on a reductionist, psychogenic model, published suggestions for treatment have included cognitive behavioral therapy, relaxation therapy with deconditioning and psychotherapeutic medications.[749] However, the level of evidence demonstrating any efficacy of these treatments for ES/MCS is almost non-existent since only a few case reports of improvement have been published in the past 30 years.[750] [751] [752] [753] Furthermore, the fact that relaxation therapies may possibly have a biological impact on patients with ES/MCS does not verify that it is a psychiatric illness. These techniques also have a positive effect on biological entities, such as asthma,[754] [755] hypertension and migraine,[756] and can significantly lower blood glucose, cholesterol and hypertension.[757] [758] [759] [760] [761]

While skeptics and proponents often frame the debate in a dualistic or reductionist manner, claiming that chemical intolerance is either completely psychogenic or completely toxicogenic, accumulating data strongly suggests that a multifactorial process underlies these conditions.[762] The Nova Scotia Environmental Health Centre integrates relaxation therapies with avoidance of chemical triggers, elimination diet for food sensitivities, low dose allergen therapy, intravenous therapy, and pacing and energy management strategies when necessary.[763] This is consistent with the systems medicine model.

Although there is no objective evidence of direct psychogenesis, some people disbelieve patients reporting of symptoms of ME/CFS, FM or ES/MCS, diminish the significance of their symptoms and experiences, and dismiss even the possibility of the existence of the conditions.

- **Interventions and Prognosis for ME/CFS, FM and ES/MCS**

Thus far, treatments routinely used for ME/CFS and ES/MCS are consistent with their definitions. Patients with ME/CFS have fatigue that is exacerbated with minimal exertion, with prolonged recovery. Therefore, the patients are instructed how to pace activities with rest, with reported improvement in quality of life.[764] Patients with ES/MCS have symptoms exacerbated by chemical exposures, which are relieved after they are no longer exposed. Treatment is the provision of support and education to maintain environmental control and avoidance, which seems to provide the highest patient satisfaction.[765] There are more treatments available for fibromyalgia, but they are highly variable, and long-term prospective observational studies have found that patient outcomes are typically poor.[766] [767] Almost half the patients with fibromyalgia are likely to be dissatisfied with treatment.[768] [769]

The basic requirements for care of patients with ME/CFS, FM and ES/MCS are the same as those with other chronic diseases; to provide support, relieve symptoms, improve outcome and quality of life, increase function and independence, and decrease their use of the healthcare system other than periodic monitoring. It is not desirable that patients avoid physicians altogether because they may neglect to get timely treatment for other significant treatable conditions.

Many patients with FM and ES/MCS are at least partially disabled and unable to work, as are most patients with ME/CFS. Reduced physical functioning, which is common in all three of these conditions, is a predictor of work disability.[770] The more time missed from work, the greater the likelihood of long-term disability.[771] [772] The present inadequacies in being able to

provide early diagnoses and the paucity of available treatments in the general medical community underline the need for more education and earlier interventions to preserve or even restore the ability to work.[773] Patients with one of these conditions are more likely to develop one or both of the others, increasing disability. Both the number of comorbidities and disability are strongly associated with cost.[774] Earlier diagnosis can reduce referral costs and investigations, and interventions may prevent the onset of comorbidity, all of which can lead to a net savings for the healthcare sector, and a better quality of life for the individual.

- **Summary**

The 2010 Canadian Community Health Survey (CCHS) reported that the number of Canadians stating they had a diagnosis of ME/CFS, FM and ES/MCS by a health professional has increased markedly since 2005. The prevalence of CFS increased by 23%, 13% for FM and 34% for ES/MCS.

ME/CFS affects up to three percent of the population and, although it may improve, it usually does not go away (around 6% recovery rate). Severe, chronic fatigue is the dominating complaint. It is made worse by exertion, is not substantially relieved by rest, and the post-exertion recovery time is prolonged. It affects women six times the rate of men. It also occurs in children.

There are various definitionsfor ME/CFS, which influence guidelines for treatment. Cardiopulmonary exercise testing repeated 24 hours later demonstrates reduction in maximal aerobic capacity, aerobic threshold and increased oxidative stress. There are extensive alterations in gene expression with at least 7 different subtypes of ME/CFS related to genetic upregulation (86 genes) or downregulation (3genes).

There is significant comorbidity, including with FM and ES/MCS. There is a lack of evidence on the comparative effectiveness of therapies alone or in combination with other treatments, and further studies are required to inform the development of effective treatment programs.

FM is a chronic, widespread pain disorder, present for at least 3 months. Prevalence ranges from 2-6 percent, with females six to nine times more commonly affected. In children, it is more common in prepubertal or adolescent girls. The most recent (2012) diagnostic and management guidelines are endorsed by the Canadian Rheumatology Association (CRA) and the Canadian Pain Society, although there is wide international respect for the Canadian Clinical Working Case Definition of FM (2003).

FM is a nervous system disorder, with activation of NMDA and TRPV1 receptors. Genetic abnormalities affecting the catechol-o-methyl transferase enzyme may predispose to FM. There is evidence for oxidative stress, reduced mitochondrial function and systemic inflammation. It is frequently comorbid. Multiple treatments including pregabalin and duloxetine medications and exercise are recommended. There is significant disability, and the majority of those who work do so part-time.

The consensus criteria for the diagnosis of ES/MCS have been validated by the Ministry of Health-funded Environmental Hypersensitivity Research Unit (EHRU) at the University of Toronto in collaboration with the Environmental Health Clinic at Women's College Hospital.

The Minsitry of Health also funded pioneering genetic research. There is evidence that ES/MCS patients are genetically predisposed to have inferior enzyme systems for detoxification. Because they are less capable of efficiently detoxifying, oxidative stress occurs, which can sensitize TRPV1 receptors.

Sensitization of the nervous system to chemicals and subsequent increased sensitivity has been demonstrated in animal models. This is more likely to occur due to oxidative stress, which activates TRPV1 receptors. These TRPV1 receptors are widespread and are found in the brain, eye, bladder lining, mast cells, stomach lining, intestines, larynx and bronchial tubes. They are capsaicin (hot peppers) sensitive. Capsaicin sensitivity has been documented in ES/MCS.

Women are more affected by ES/MCS than men. This may be due to being more responsive to their environment via both the limbic and immune systems, having more exposures and a greater body burden of chemical agents, and having less efficient detoxification systems compared to men. Clinical practitioners report children are affected, but the prevalence is unknown.

ES/MCS patients, because their symptoms are triggered by environmental exposures, have difficulties accessing common community resources that most persons take for granted, including communities of worship, grocery stores, shopping centres, community meetings, public libraries, restaurants, movies, use of public transportation, the homes of extended family members and friends, offices of dentists and medical doctors, public parks, classes at their local universities, and most significantly, access to work. Others' lack of understanding and refusal to make accommodations in the workplace have denied spatial access. People with ME/CFS and FM may have problems with access based on lack of energy and reduced activity levels.

ES/MCS is frequently comorbid with ME/CFS and FM and is also frequently comorbid with other common conditions, such as chronic headache, chronic migraine headache, irritable bowel syndrome (IBS), allergies, asthma and autoimmune disorders. People with multiple conditions and all 3 of these diagnoses experience the greatest amount of disability.

Patients with ME/CFS, FM and ES/MCS are stigmatized by their condition and have difficulty accessing health care. The basic requirements for care of these patients are the same as those with other chronic diseases; to provide support, relieve symptoms, improve outcome and quality of life, increase function and independence, and decrease their use of the healthcare system other than periodic monitoring.

Earlier diagnosis of these three chronic complex conditions, not only may lead to a better quality of life for affected individuals, but also can reduce referral costs and investigations. In addition, interventions may prevent the onset of comorbidity, leading to a net savings for the healthcare sector.

III Need for Environmental Health Education and Government-funded Canadian Environmental Health Clinics

- **Current Medical Education**

In the early 1990s, the Institute of Medicine advised doctors to be prepared to diagnose, prevent and treat environmentally related conditions because public trust in government and industry was declining and physicians were being looked upon by patients and community groups as reliable sources of information on environmental risks. [775] [776] In 1996, 24% of medical schools in the US had no required environmental content in their curriculum. Those schools which did averaged only a total of seven hours of instruction[777] and 70% of the deans of those schools stated that there was minimal emphasis on environmental health.[778] Environmental medicine was rated as an unimportant area of training by medical students[779] and was described by physicians as the least important area in their practice.[780] Even today, many doctors are still uninformed when questioned by their patients on possible environmental health effects.[781]

It is difficult to teach public health effectively within a medical culture that values acute care of individual patients over population-based health protection, health promotion, and disease prevention.[782] Medical students lack interest in public health undergraduate medical training. Many find it a "waste of time" and irrelevant, which is unfortunate because many students feel they are able to function more effectively as clinicians after taking elective public health courses or a combined MD/MPH degree.[783] Public health and preventive medicine need to be incorporated into the medical curriculum and taught by credible clinicians who are key role models and opinion leaders.[784]

A report of a survey, which was sent to 1000 physicians in Virginia, was published in 2011.[785] The response rate was low, but there were 90 responses, most commonly from family practice and internal medicine. Although 97% of the respondents reported having patients with ES/MCS, only 6% had a treatment protocol for the condition. Only 30% had received any training regarding ES/MCS in medical school and it was not determined what type of training they had received. Only 13% reported currently considering chemicals when diagnosing health problems in new patients. These statistics are significant when one considers that some degree of ES/MCS occurs in up to 1 in 5 primary care patients presenting with diverse symptoms, yet it is rarely recognized by clinicians.[786]

There is an absence of education for management of patients with ME/CFS, FM and ES/MCS, except, as far as funding would allow for the staff physicians of the Environmental Health Clinic, for accredited rounds, annual Environmental Health Days, presentations at professional conferences, and the Mainpro-C programs produced for the Ontario College of Family Physicians (OCFP). Most nursing settings do not have an MCS protocol.[787] Although there is elective training in the EHC, there is no formal education for medical students or residents. The criteria for the diagnoses of ME/CFS, FM and ES/MCS are available on the website of the OCFP. However, no other specialty has a particular interest in any of these patients. The majority of rheumatologists in Ontario do not even want to treat patients with FM.[788] And, there are no specialized treatment centres in Ontario for children with these disorders.

- **Jurisdictional Review of Community Health Centres**

In April 2013, a questionnaire developed by this project's Medical Advisory Committee was sent to various community health centres (CHC's) in Ontario. There were 41 respondents, 80% by physicians and 20% by nurse practitioners. There is a clear lack of comfort in ability to diagnose and/or treat environmentally linked conditions. The following is an analysis of the results:

- **Diagnosis:**
  - 73.2% were not comfortable with their ability to diagnose ME/CFS. Only 2.4% of respondents were totally comfortable with their ability to diagnose ME/CFS;
  - 35.7% were not comfortable with their ability to diagnose fibromyalgia. Only 11.9% of respondents were totally comfortable.
  - 92.7% of respondents were not comfortable with their ability to diagnose ES/MCS;
  - 90.5% of respondents were not comfortable with their ability to diagnose sick building syndrome;

- **Treatment:**
  - 23.8% of respondents were totally or somewhat comfortable with treating patients with ME/CFS;
  - 50% of respondents were totally or somewhat comfortable with treating patients with fibromyalgia.
  - 7.3% of respondents were totally or somewhat comfortable treating patients with ES/MCS;
  - 2.6% of respondents were totally or somewhat comfortable treating patients with sick building syndrome; 80.6% were somewhat or very uncomfortable;

It is quite clear that there is a need for further education in the comprehension, diagnosis, treatment, and self-management of these disorders. The observed reluctance to make the diagnoses of these environmentally linked conditions is consistent with the medical literature.[789] [790] [791] [792] An early diagnosis can have a positive effect on severity and the prognosis for disability in ME/CFS and FM,[793] [794] [795] but unfortunately this rarely happens.[796] [797] The jurisdictional review results strongly suggest that these patients' needs are not being met.

Respondents were also asked to indicate which elements of environmental medicine should be included in pursuing further education on these chronic conditions, and to rank the importance as *absolutely*, *perhaps*, or *not interested*. The following results were obtained:

- **Furthering education (answered as 'absolutely'):**

- diagnostic criteria	93%
- effectiveness of various treatments	92%
- self-management strategies	90%
- history/physical manifestations	87%
- expected course of disease progression	83%
- complementary and alternative treatments	76%
- etiology	73%

- prevention strategies 73%
- completion of insurance disability forms 65%
- comorbidities 59%
- impact of social determinants of health 47%

- **Ontario College of Family Physicians Consideration of a Centre of Excellence in Environmental Health**

In 2008, the Ontario College of Family Physicians (OCFP) was funded by the Ministry of Environment (Ontario) to determine the feasibility of establishing a Centre of Excellence in Environmental Health.[798] The project was chaired by Ms. M. Janet Kasperski, who was the Chief Executive Officer of the OCFP.

The following are quotes from that publication:

- *The Ontario College of Family Physicians (OCFP) and our partners firmly believe that now is the time to invest in a comprehensive program to gather and synthesize the research regarding the impact of the environment on health and use the evidence to support healthy public policy and the education of healthcare professionals (family doctors, paediatricians, obstetricians, nurses, nurse practitioners and dieticians) so that they understand the impact that the environment plays in the health of the population.*

- *While it is vitally important for healthcare professionals to be knowledgeable regarding environmental health, policy makers also need to have easy access to credible information on which to base policy decisions. The Ontario College of Family Physicians (OCFP) and our partners have actively used the evidence we have gathered to support policy development. One concrete example relates to the OCFP's Pesticide Review paper that has been used to support Cosmetic Pesticide By-laws all across the country. The second relates to our urban sprawl paper and subsequent brochures that have been used to support the Greenbelt and Places to Grow legislative bills.*

- *Research indicates that family physicians are seen as the most trusted healthcare professionals to address these concerns; however, doctors report that their academic training did not prepare them adequately to answer the questions that their patients pose. The lack of access to peer-reviewed information on the environment and health further decreases their ability to provide the level of support that patients require.*

- *The Environmental Health Clinic at Women's College Hospital has been gathering the evidence regarding the assessment, diagnosis and treatment of environment induced conditions such as fibromyalgia, chemical sensitivities, chronic fatigue syndrome and the like. They have worked hard to develop tools to help family doctors to assess and manage environment induced conditions and have developed a well regarded educational series, as well as summer internships and practice placements to support learners and practising family doctors to gain experience in the treatment of these complex disorders.*

The following are a few quotes from those who contributed to the feasibility study:

- *The current system in Ontario for environmental research and education (knowledge synthesis, translation and transfer) is grossly inadequate to non-existent.*

- *Scientific back-up is absolutely critical. There is already a lot of science behind this kind of medicine. Because the science comes from here and there and another place, somehow, it gets lost. There is not one common voice. There is lots but we have to put Authority behind it to have a positive impact on future generations.*

- *There is a need to change the current way of thinking so that physicians pay more attention to lifestyle and environmental impacts on health.*

- *The time is now. The public understands that the health of themselves and especially that of their children and their children's children depends upon what we do today. The time is right for the establishment of the centre of excellence in environmental health.*

The feasibility study concluded that *"An Environmental Health Centre, adequately funded, is long overdue."*

- **Government-funded Canadian Environmental Health Clinics**

Along with the present Environmental Health Clinic at Women's College Hospital (EHC) in Toronto, there are two other publicly-funded clinics in Canada for patients with environmentally-linked chronic complex conditions.

There is an academic paediatric clinic in Edmonton that also sees children and adolescents with these conditions, but does not have government funding. It is a member of the Pediatric Environmental Health Specialty Units in the United States.[799]

- **Complex Chronic Diseases Program (CCDP) at British Columbia Women's Hospital and Health Centre**

This program was established in fall, 2012 in Vancouver. Dr. Alison Bested, who was a staff physician at the EHC, is the Medical Director. The program is funded by Provincial Health Services Authority (PHSA) to assist persons with Fibromyalgia, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Tick-borne Illnesses e.g. Lyme disease.[800]

The CCDP has a consultative/research/educational model. It offers an integrative care approach, with an interdisciplinary team including: specialty medicine, nursing, social work, physiotherapy, and naturopathy. It will offer patients a variety of group sessions on the topics of: education, pain management, stress management, and family support. The program will create online learning modules for health care professionals about FM, ME/CFS, and Lyme Disease. There will be Mainpro-C accredited modules and the program also anticipates a strong research mandate.

- **Nova Scotia Environmental Health Centre**

The Nova Scotia Environmental Health Centre is now known as the Integrated Chronic Care Service (ICCS). It is the treatment facility in Capital Health for environmental sensitivities and complex chronic conditions.[801] Capital Health is Nova Scotia's largest provider of health services, including hospitals, health centres and community-based programs throughout Halifax Regional Municipality and the western part of Hants County. It provides service for the 400,000 residents of the Halifax region and specialist services to the rest of Nova Scotia, and Atlantic Canada.

The ICCS provides health services for:

- Chronic fatigue syndrome
- Chronic pain conditions
- Chemical intolerance, chemically triggered conditions, asthma, migraines, allergic conditions, building related illness
- Multiple chemical sensitivity
- Fibromyalgia
- Functional neurologic and gastrointestinal syndromes
- Multiple chronic conditions (multi-morbidities)

Their model is based on the premise that chronic disease outcomes are better managed by addressing the needs of the whole person. They integrate the physical and psychosocial needs of individuals by focusing on the person instead of the disease(s) and on improving functional health and quality of life. The care team includes: physicians, occupational therapists, a nurse practitioner, registered nurse, licensed practice nurse, a psychologist, psychotherapist and a dietitian.

Their individual treatments consist of:

- Assessment and treatment of environmental sensitivities
- Management of medication intolerance
- Occupational therapy interventions
- Elimination diet, management of food sensitivities and other dietary interventions
- Treatment for sensory processing disorders
- Psychotherapy
- Mindfulness-based interventions
- Low Dose Allergen Therapy
- Intravenous therapy

Group-based interventions include:

- Mindfulness-based interventions
- Pacing and energy management strategies
- Food sensitivities management
- Biofeedback approaches
- Health lifestyle education

Rehabilitation may also include:

- Support with return to work and workplace accommodation

- Support with family education

They have published studies measuring health outcomes of a multidisciplinary care approach in individuals with chronic environmental conditions, [802] the impact of their approaches on ES/MCS,[803] [804] among others.[805]

- **Environmental Health Clinic- Ontario**

In contrast, the Environmental Health Clinic at Women's College Hospital provides single physician clinical service only four days per week (0.9 FTE, four part-time doctors). In order to accommodate the demand for consultation, patients are restricted to one assessment visit (up to three-hours) and just two follow-up appointments for about one to one and a half hours each. The assessment of the most likely determinants of illness consists of: review of medical consultations accumulated by the referring physician and laboratory data (in response to suggestions by the EHC); complete review of the illness onset and progression, family history, environmental exposure history, chronological systems review and physical exam; provision of diagnosis or diagnoses; education; development of a treatment plan with the patient; and provision of a detailed report to the referring physician (average 5 pages). Besides administrative support, information in terms of websites or printed articles are provided to patients on the waiting list or patients when they visit.

In order to make the overload on patients' defence systems very understandable, and yet less frightening, a teeter totter analogy is used (see Figure 3), so that patients can see that if they reduce the load on their bodies' functions as much as they can, they will return to more balance and better overall functioning (see Figure 4). The way to get there is to plant "SEEDS of health"via a "Weed, SEEDS and Feed" method i.e. to remove stressors (weeds), plant SEEDS (an acronym meaning Sleep, Exercise, Environment, Diet and Support) and slowly but steadily grow a health garden feeding whatever works. Please see ATTACHMENT C, SEEDS of Health.

Figure 3 **Exhaustion** *Marshall L.- used with permission of author*

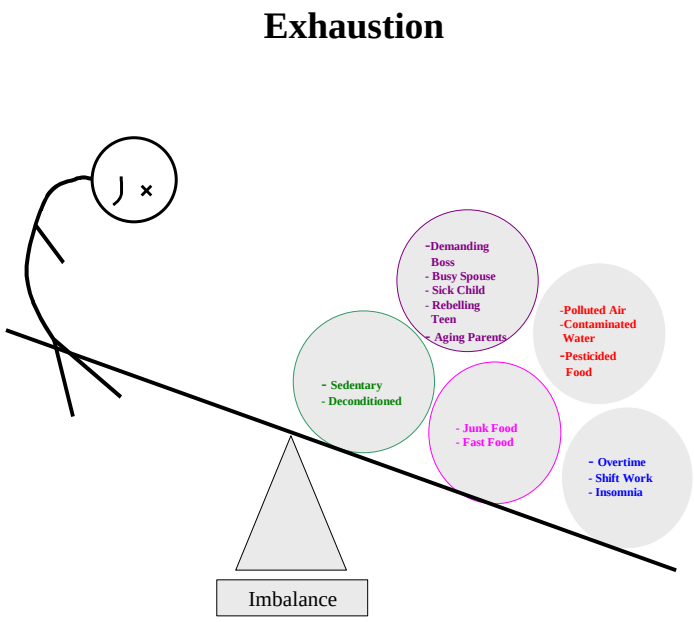
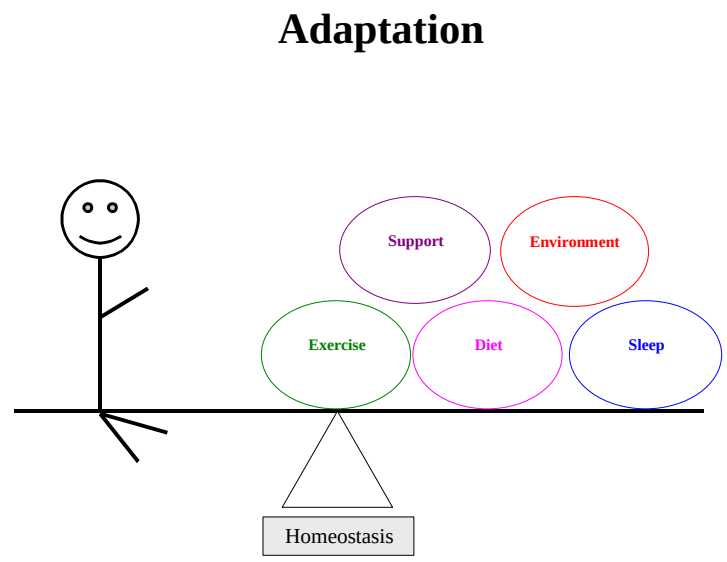


Figure 4 **Adaptation-** *Marshall L.- used with permission of author*



Budget limitations currently prevent the EHC from having a multidisciplinary clinic, although in the past, staff included a nurse, community outreach coordinator, dietitian and psychologist.

An athletic therapist consults upon referral by the EHC physicians, and is deemed very helpful, but consultations with her about exercise are paid by the patients.

- The EHC nurse ensured intake forms were completed fully and would assist patients who were having difficulty. She answered questions and sent resources and tips to patients on the waiting list, completed a cumulative patient profile and some of the physical examination, and liaised with patients by telephone as they required. She compiled a newsletter 3-4 times a year with the assistance of other staff and guest writers. Every year, she taught nursing students from the University of Toronto in the EHC, and supervised their research projects where they reviewed the literature on subjects and designed informative brochures or posters. She started a nurses' discussion group in Canada and wrote an information article for the Canadian Nurse. She served on the hospital "Green Team".

- The EHC Community Outreach Coordinator also served on the hospital "Green Team", where she helped spur the progression to a "Fragrance-free" workplace with attractive signage and presentations to workers and management. She and a physician expanded the program to other willing hospitals through the Canadian Coalition for Green Health Care. She kept in contact with the patient support groups and participated in their programs. She developed power point presentations about Environment and Health and various subjects therein, and was a popular speaker at EHC education events and conferences, and with employers and schools. With the help of the Medical Director, she organized and supervised research projects for medical students as part of their Determinants of Community Health course. She served as Co-chair of the Occupational Working Group of the Toronto Cancer Prevention Coalition, which promoted toxic use reduction.

- Two part-time dietitians were referred patients by the EHC physicians who needed assistance with nutritional sufficiency of their diet, how to do elimination and reingestion challenge tests for suspected food intolerances, and, if necessary, rotate foods. They informed other dietitians of their work and the unique needs of EHC patients.

- The EHC psychologist designed a 10-week educational group "Planning for Health" program for patients that took into account their fatigue and intermittent cognitive difficulties by having freedom of movement within a safe, fragrance-free setting, regular film clips to illustrate the points she was making, and application of breathing and focused attention exercises to relieve pain and improve sleep. An EHC physician who was also trained as a GP psychotherapist atended the groups and saw patients individually as needed. The evaluations of the group and functional status reports were very positive, and patients returned one year after the group ended to review their progress.

- In addition, when she was at the EHC, Dr. Alison Bested wrote a very useful practical book for patients, now in its second edition.[806] She trained in cognitive behavioural therapy for the chronically ill, and ran group programs twice a year, some of them by Ontario Telemedicine Network, which helped expand the educational range.

Accommodating patients in the EHC has challenges. A number of patients with ME/CFS or FM find the duration of the initial appointment long and difficult, due to increasing fatigue and cognitive difficulties. As well, a number of them come from a far distance, and round trip or repeated visits are also difficult. Patients with ES/MCS are not well accommodated physically. Previously, the EHC was in a separate wing of the hospital with terrazzo floors, well off-gased materials and furnishings, and operable windows. Presently, the Environmental Health Clinic (EHC) is situated in a downtown Toronto, mechanically ventilated office building, without any specific retrofitting to improve indoor air quality. Accommodation consists of one portable air filter system in each doctor's office and two large filters in the hall and examining room. The present location is considered temporary due to the reconstruction of Women's College Hospital. However, the EHC staff physicians have expressed concern because there are no specific plans for accommodation to address the environmental needs of patients with ES/MCS when the hospital reconstruction is completed.

The EHC has participated in research projects for the first 10 years with the Ontario Ministry of Health-funded Environmental Hypersensitivity Research Unit at University of Toronto and published six papers, including one validating the survey questionnaire, one determining the best case criteria for ES/MCS, and one outlining genetic susceptibility factors, and the usually normal laboratory tests. Some additional research papers have been prepared by the physicians working in collaboration with colleagues at the University of Toronto, University of Ottawa, the Ontario College of Family Physicians and Health Canada, Transport Canada and the Canadian Human Rights Commission. Dr. Bested, when she worked at the EHC, was a physician member of the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and was selected by Health Canada to serve on the Expert Medical Consensus Panel that developed the Canadian Consensus Criteria and guidelines for diagnosis and treatment of ME/CFS. She also participated in writing the Primer associated with these criteria.

With regard to education and health promotion, the Women's Health Matters website contains several information resources for patients. Physicians are members of the Environmental Health Committee of the Ontario College of Family Physicians and participate in literature review and advocacy reports/brochures for cleaner environments to protect population health. Practice tools are posted on the OCFP website. Medical students and residents, as well as practising physicians have been trained on site, and, while funding allowed, we had a College of Family Physicians of Canada- and Royal College of Physicians and Surgeons of Canada- accredited rounds series, as well as an Environmental Health Fellowship Program with the Department of Family and Community Medicine at the University of Toronto. The physicians were largely responsible for developing a Mainpro-C-accredited 4-module course "Environmental Health through the Lifespan", which is being taught at OCFP and College of Family Physicians of Canada conferences, and on road trips. Two physicians have developed university credit courses, which they have combined to hopefully qualify for a University of Toronto certificate in Environmental Health. The originals were a core curriculum Environmental and Occupational Public Health course in the Master of Public Health program at Lakehead University, and an Environmental Health course for undergraduate science students at the University of Toronto. The EHC clinical staff have been long time environmental health promoters as partners in the Canadian Partnership for Children's Health and Environment and the Canadian Coalition for Green Health

Care. See ATTACHMENT B, ES/MCS Status Report, Advances in Knowledge and Current Service Gaps, Table 6 re partnerships.

- **Summary**

Systems-based medical training, including the environment as a determinant of health, is lacking in medical schools and there is lack of connection to public health. There is an absence of education about ME/CFS, FM and ES/MCS, except for annual OCFP or EHC Environmental Health Days, and presentations and Mainpro-C workshops at professional conferences for practising physicians who choose to attend. The Jurisdictional Review of Community Health Centres revealed that most physicians are not comfortable diagnosing or treating these disorders.

A feasibility study by the OCFP in 2008 concluded that an adequately funded Environmental Health Centre is long overdue. Presently, the Environmental Health Clinic at Women's College Hospital provides much less clinical service than the Nova Scotia Environmental Health Centre and the planned provision of assessment, treatment and research by the newly established Complex Chronic Diseases Program at British Columbia Women's Hospital and Health Centre.

Nevertheless, the EHC has made an important start with clinical programs, resources, education of health professionals, crucial foundational research, and partnerships for health promotion with the Ontario College of Family Physicians, the Canadian Partnership for Children's Health and Environment and the Canadian Coalition for Green Health Care. Please see APPENDIX B- ES/MCS Status Report.

They point out to patients in easy-to-understand language how overload of the body's systems can occur, and employ an innovative "Weed, SEEDS and Feed" framework for organizing complex treatments. Please see APPENDIX C- SEEDS of Health.

IV Ontario Centre of Excellence in Environmental Health- Principles

- **Meaning of Centres of Excellence**

In Canada, Centres of Excellence exist for many different professions, including industry and health, and usually have obtained the designation from federal or provincial governments.[807] [808] There are several Centres of Excellence for health in Ontario, including:

- Ontario Center of Excellence for Child and Youth Mental Health.[809]
- Digital Pathology Centre of Excellence.[810]
- Kensington Eye Institute[811] and Kensington Hospice [812]
- Centre of Excellence for Integrated Senior Services[813]
- Ontario Bariatric Network (4 Centres of Excellence)[814]
  - Hamilton Bariatric Centre of Excellence
    - St. Joseph's Healthcare Hamilton
    - Hamilton Health Sciences Centre (Medical Centre)
  - University of Toronto Collaborative Bariatric Surgery Program
    - Humber River Regional Hospital
    - St. Joseph's Health Centre
    - University Health Network (Toronto Western Hospital, Toronto East General Hospital
    - St. Michaels Hospital
  - Guelph Bariatric Centre of Excellence
    - Guelph General Hospital
  - Ottawa Bariatric Centre of Excellence
    - The Ottawa Hospital
- Mount Sinai Hospital in Toronto lists six Centres of Excellence[815] for:
  - Women's and Infants' Health
  - Surgical Oncology
  - Urgent and Critical Care
  - Inflammatory Bowel Disease
  - Musculoskeletal Disease
  - Biomedical Research
- West Park Healthcare Centre Long-Term Ventilation Centre of Excellence[816]
- Toronto East General Hospital Provincial Weaning Centre of Excellence for Prolonged Ventilation[817]
- Wabano Centre for Aboriginal Health[818]
- Sioux Lookout's Meno Ya Win Health Centre of Excellence for Aboriginal Health Care[819]

There does not appear to be a consistent definition or model for a Centre of Excellence. A review of multiple websites of various Centres of Excellence,[820] [821] including those above, provides some insight into the meaning. A medical centre of excellence (COE) is usually viewed or accredited by a governing agency or third party as a place of research and/or education and/or treatment, and it links with other organizations or Centres of Excellence to enable knowledge transfer and information exchange. Clinically, it should provide the highest quality health care

for specific conditions. Being designated as a COE signifies that the centre has an important and specific expertise for the service that is provided. It delivers or facilitates comprehensive, evidence-based care, that is multidisciplinary, and yields best quality outcomes and high patient satisfaction.

A multidisciplinary approach to delivering care involves a team of healthcare experts working together toward a common goal, with the patients' preferences as the focal point. These healthcare experts should provide the leadership to guide the creation of a multidisciplinary program and set the bar for excellence. This will be a challenge given the multiple systems and symptoms involved in each person's illness. In Phase I of the OCEEH, we hope to have two meetings of experienced clinicians and researchers, 1. to plan the clinical program and GRADE the evidence for various tests and treatments and 2. to set a research agenda, including evaluation strategies, and to discuss priorities.

- **Networks of Centres of Excellence of Canada**

The Networks of Centres of Excellence (NCE) is a Canadian government funding initiative allocated through three federal granting councils: Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council Canada (NSERC), and Social Sciences and Humanities Research Council (SSHRC).[822]

NCE networks are large-scale, academic-led virtual research centers that bring together multi-disciplinary partners from academia, industry, government and not-for-profit organizations to accelerate the creation and application of knowledge.[823] Examples include

- Allergy, Genes and Environment Network (Allergen); McMaster University
- Canadian Arthritis Network (CAN); Mount Sinai Hospital, Toronto
- Canadian Stroke Network (CSN); University of Ottawa
- Neurological Development Network (NeuroDevNet); University of British Columbia
- Stem Cell Network (SCN); University of Ottawa
- Technology Evaluation in the Elderly Network (TVN); Queen's University

As stated on their website, this network obtains funds for collaboration from companies, universities, hospitals, governments and communities to generate knowledge translation into results, such as better health care.

The Ontario Centre of Excellence in Environmental Health (OCEEH) should aspire to be part of this network, because research, while essential to develop strategies for ME/CFS, FM and ES/MCS, is at a very early stage of development. The Ministry of Health made an auspicious start by funding the Environmental Hypersensitivity Research Unit (EHRU) on the recommendation of the Ad Hoc Committee on Environmental Hypersensitivity Disorders (chaired by Judge George Thomson). The EHRU also made an auspicious start by clarifying the diagnostic criteria for ES/MCS and discovering genetic detoxification vulnerabilities. Hopefully, the MoHLTC can encourage the three federal granting councils to fund such research, as ME/CFS, FM, and ES/MCS receive very low research funding.[824] (Please see Table 1, Chapter I-CIHR Funding for Chronic Health Conditions.)

- **Integration of Primary Care and Public Health in the OCEEH**

The OCEEH will utilize and integrate individual and population based approaches:

1. Primary care
2. Preventive medicine
3. Public health

Primary care focuses on providing medical services to individual patients with immediate health needs. Public health focuses on offering a broader array of services across communities and populations that collectively will help people to be healthy. Although primary care and public health share a goal of promoting the health and well-being of all people, these two disciplines historically have operated independently of one another. In 2012, the Institute of Medicine (IOM) in the US called for greater collaboration between public health and primary care because they 'share the common goal of improving population health as well as involving the community in defining and addressing its needs'.[825]

According to the Association of Faculties of Medicine in Canada (AFMC), which represents Canada's 17 faculties of medicine, the integration of public health concepts in clinical practice is essential to providing high quality healthcare.[826]

The University of Toronto's Dalla Lana School of Public Health has recently developed a Division of Clinical Public Health to integrate primary care, preventive medicine and public health. It will foster collaborative research, training and knowledge translation programs within the University of Toronto, associated hospitals and community health centres (CHCs)[827], as well as other primary health centres.

Examples of integrating primary care and public health already exist, funded by the Ontario MoHLTC:

- Living Healthy Champlain coordinates, promotes and facilitates self-management programs across the Champlain Local Health Integration Network (LHIN). They have adapted the Stanford Chronic Disease Self Management Model to provide a centralized program, which focuses on lifestyle change for people with chronic conditions, such as diabetes and chronic pain.[828] As of December 2012, 150 workshop leaders have been trained and over 180 workshops have been held involving 1500 participants. Training is now offered in several languages, including English, French, Mandarin, Arabic, Punjabi and Somali, which reflect the local needs. The workshops have also been offered to Aboriginal groups across the region.[829]
- Southlake Regional Health Centre hosts a Self-Management Initiative for diabetes in the Central LHIN.
- The Central East LHIN hosts a Living a Healthy Life with Chronic Conditions six-week self-management workshop for people with chronic conditions.

Despite the significant role played by environmental exposures in the development and exacerbation of chronic disease, none of the above programs has an environmental health perspective. In the past year, the Ontario College of Family Physicians has developed a 2 day program of 4 Mainpro-C workshops for physicians to integrate environmental health practices

into primary care. These evidence-based programs were developed primarily by the physicians at the Environmental Health Clinic at Women's College Hospital. They teach how to incorporate the fundamentals of systems-based environmental medicine to diagnose and treat patients with environmentally-linked illnesses, such as ME/CFS, FM and ES/MCS. They also teach how to incorporate the use of the environmental exposure history in every day primary care to contribute to the prevention of environmentally linked chronic illnesses from preconception to old age, as well as programs for self management for those who are already chronically ill.

There is increased awareness and interest in prenatal and early exposures by the Canadian Partnership for Children's Health and Environment[830] and a new Ontario Birth Study at Mt. Sinai Hospital, Toronto.[831]

The OCEEH will participate in these and other programs to contribute to the integration of primary care, preventive medicine and public health in individual communities across the province. The primary care focus will be on providing services for those with environmentally linked illnesses, notably ME/CFS, FM and ES/MCS.

Preventive medicine will incorporate the use of systems-based environmental medicine practices into conventional primary care, including the periodic heath examination, from preconception to treatment of the elderly. Most important are the environmental exposure history and education to reduce exposures.

Public health will include community based monitoring, increasing public awareness and promotion of activities to reduce pollutant exposures.

The OCEEH will provide the following services for those with environmentally linked illnesses. Provision of services is to be directed towards individuals (clinical medicine) and the community (public health). This includes:

1. Health services (assessment, diagnosis and treatment)
2. Social services and advocacy
3. Education and Health Promotion
4. Research
5. Policy development

- **Evidence-based Practice of Medicine**

A central role of the OCEEH is to provide evidence-based or evidence-informed assessment, diagnosis and treatment primarily focused for patients with ME/CFS, FM and ES/MCS according to the best available evidence.[832] In order to establish this centre of excellence, recommendations and guidance for the assessment, diagnosis and treatment of these disorders must be developed based on the model of "best" and "promising" practices, and the addition of new practices, when they emerge.

According to the US Institute of Medicine, the best evidence based practice requires the integration of the best research evidence with clinical expertise and patient values.[833] When these

three elements are integrated, clinicians and patients form a diagnostic and therapeutic alliance, which optimizes clinical outcomes and improved quality of life.[834]

As stated by McMaster University's Dr. David Sackett, a Canadian pioneer in evidence-based medicine:[835]

"Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice."

The provision of evidence-based or evidence-informed medicine requires the use of "best" and "promising" practices and the addition of new "emerging" practices. However, there are no precise definitions which delineate them. The following definitions will be used.

- **Best practices**

Best practice is based on the application of the best available evidence to establish a diagnosis and prescribe treatment. According to the highest level of available replicated published literature, there have been positive results linked to outcome from application of specific interventions, and little or no severe side effects. Practices supported by systematic review are considered "best practices". The strength of recommendation is "strong".

- **Promising practices**

There is no consistently applied, precise definition of a promising practice. A promising practice has been described as an approach for which there is documented evidence in at least one setting of its effectiveness in achieving intended health-related results without undue adverse effects.[836] It is usually determined based on expert opinion.[837] Due to accumulating data, the interventions are being used by some centres. The strength of recommendation is "strong" or "weak (conditional/ discretionary)".

- **Emerging practices**

An emerging practice is one of interest, but does not yet have good evaluation data available to demonstrate positive outcomes and safety, when compared to other available practices. The strength of recommendation is "weak".

- **Levels of evidence**[838]:

1. Systematic review - an organized, critical assessment and evaluation of all research studies that address a particular clinical issue. It may include pooling of data from different studies (meta-analysis)
2. Randomized trial - study participants are randomly assigned to one of two groups: the experimental group receiving the intervention that is being tested and a comparison group (controls) which receives a conventional treatment or placebo.
3. Cohort study - individuals with differing exposures to a suspected factor (chemical exposure or lifestyle event such as diet) are identified and then observed for the

occurrence of certain health effects over some period, commonly years rather than weeks or months.

4. Case series - a descriptive report of a group of cases
5. Mechanistic reasoning/expert opinion.

Unfortunately, these levels of evidence do not necessarily provide a definitive judgment about the quality of evidence because there may be variance in design or methodology of the studies reviewed.

In order to develop guidelines to recommend treatment, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading the strength of evidence is recommended.[839] The GRADE system is used widely: Health Quality Ontario[840], the World Health Organization, the American College of Physicians, the American Thoracic Society, UpToDate (an electronic resource widely used in North America, www.uptodate.com), and the Cochrane Collaboration are among the more than 25 organizations that have adopted GRADE. This widespread adoption of GRADE reflects GRADE's success as a methodologically rigorous, user friendly grading system.

To achieve transparency and simplicity, the GRADE system classifies the quality of evidence in one of four levels:

- **High quality** - further research is very unlikely to change our confidence in the estimate of effect
- **Moderate quality** - further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- **Low quality** - further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- **Very low quality** - any estimate of effect is very uncertain

Recommendations to develop guidelines are based on the level of available evidence.[841]

- The strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects. It is determined by:
  - the balance between desirable and undesirable consequences of alternative management strategies
  - quality of evidence
  - variability in values and preferences
  - resource use

- GRADE classifies recommendations as strong or weak
  - **Strong** recommendations mean that most informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly
  - **Weak** recommendations mean that patients' choices will vary according to their values and preferences, and clinicians must ensure that patients' care is in keeping with their values and preferences

The implications of a **strong recommendation** are:

- **For patients**—most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered
- **For clinicians**—most patients should receive the recommended course of action
- **For policy makers**—the recommendation can be adopted as a policy in most situations.

The implications of a **weak recommendation** are:

- **For patients**—most people in the situation would not want the recommended course of action, but many would
- **For clinicians**—should recognize that different choices will be appropriate for different patients and that each patient must be helped to arrive at a management decision consistent with her or his values and preferences
- **For policy makers**—policy making will require substantial debate and involvement of many stakeholders.

The present level of available treatment for ME/CFS, FM and ES/MCS is clearly insufficient to induce significant recovery and reduction of disability for all, especially as measured by ability to return to work. It is beyond the scope of this proposal to rate the quality of evidence available for the assessment, diagnosis and treatment of environmentally linked conditions. It is also beyond the scope of this proposal to develop guidelines for the diagnosis and treatment of these disorders. As a result, at present, the reliance is on recommendations and resources for diagnosis and therapy contained in the Mainpro-C modules, accredited by the College of Family Physicians of Canada.

Developing guidance for the assessment of environmentally linked conditions and for the treatment of these conditions separately and when comorbid will require the participation of the Hub health professionals and other experienced clinicians communicating with researchers utilizing the GRADE system. A forum (preferably 3 days) will afford such an opportunity. Such a Forum is proposed in Section VI, "Building the OCEEH". Since research is obviously needed, a second forum is proposed to set the research agenda, including evaluation criteria, and priorities.

- **Hub and Spokes Model**

The care of patients in the OCEEH will be based on existing and emerging patient and person focused evidence-informed chronic care models. The proposed model for the OCEEH includes a central Hub and Spokes throughout the province. The Spokes will involve health care providers, who will receive specialized education, developed and delivered by the medical experts in the Hub. The Hub will also provide the leadership for the best and promising practices to be available for those patients and families who are assessed, treated and followed in the Spokes, and will provide the necessary continuing medical education to maintain these practices.

Ongoing research will play a key role in the OCEEH. Developing a database, with permission from patients to track long-term outcomes is essential. Collecting and analyzing data on the

patients from before they enter and after completing the clinical pathways will analyze how well the Hub and Spokes model is able to treat patients who have come through the program. Research will help to identify and assess new tools for assessment and treatments, as they are developed and become available. The Hub will also collaborate with the University of Toronto and other research centres on basic research into underlying mechanisms.

Presently, the availability of care required for patients with these disorders is inadequate. The results of the jurisdictional review of the healthcare providers in community health centres demonstrated a clear lack of comfort in the ability to diagnose and/or treat these chronic, complex, environmentally linked conditions.

The purpose of creating the OCEEH Hub and Spoke model is to fill the gap in care for these patients and to make it more accessible across Ontario. The Hub, funding permitting, is positioned to advance science in this area. Individualized care models will come from the available best and promising practices, which are defined by the weight of evidence in the medical literature. Environmental health and systems medicine approaches to care are not currently in the core curriculum of medical or nursing schools. Care will be provided to patients in the meantime, and a goal will be that these elements will be incorporated in all aspects of training in medical and nursing schools, as well as in family practice and specialty residencies.

In considering the best and promising practices, a jurisdictional review of expert centres was also conducted by the Medical Advisory Committee of the Steering Committee for this Business Case Proposal.

- **Jurisdictional Review of Expert Centres**

Reputed experts and expert centres were recommended by members of the Medical Advisory Committee and Patient Consultants and solicited to participate in a Jurisdictional review of diagnostic methodologies, assessments of function and treatment modalities. Of 14 expert centers solicited, only nine responded. One respondent only does research. 100% (8/8) of respondents see patients with ME/CFS and FM. 62.5% (5/8) see patients with ES MCS or sick building syndrome. With respect to diagnostic tests and treatments, there was wide variation in responses. Given the low number of responders, it is regarded as more productive to host a forum where a working group of experts will review and discuss best and promising practices.

- **Patient- and Person-centred Care**

  - **Chronic Care Model**

The traditional model of health care has been that physicians were primarily responsible for managing chronic conditions.[842] This led to patients being passive recipients of medical advice, rather than being active participants in medical decisions.[843] With respect to chronic care treatment, primary care encounters are usually bound by time constraints, such that multiple diagnoses, problems and patient concerns compete with each other for a place on the agenda.[844] Environmental medicine has always depended on close interaction with and feedback from patients, given the lack of definitive diagnostic tests, and the patients' need for assistance in self-management, for example in pacing and avoidance of symptom triggers. However, the

physicians were often underpaid, but the healthcare system is promoting change. For example, enabling physicians to be remunerated for the time spent with patients with these chronic complex conditions (e.g., K037) is helping to encourage the transformation to provision of better healthcare.

The Chronic Care Model (CCM) is based on the concept that when proactive health care teams provide care to informed, activated patients, clinical quality and outcomes should improve.[845] [846] Patient interest and motivation to be involved in care planning and resources to participate in the interventions are central to successful outcomes. Self-management and self-management support are integral components of the CCM.[847] Self-management refers to the way in which people with chronic conditions manage their lives, lifestyles and treatment.

- **Self-management**

Because of the burden of chronic disease on individuals and families, primary care is now shifting from a predominantly medically focused diagnosis and treatment model to patient focused self-management.[848] [849] [850] Self-management refers to the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition. Efficacious self-management encompasses the ability to monitor one's condition and to affect the cognitive, behavioural and emotional responses necessary to maintain satisfactory quality of life. Self-management is a dynamic and continuous process of self-regulation.[851]

Chronic disease prevention and management is founded on patients' inner strengths and their personal expertise about their health/illness experiences, in combination with information given to them by different health professionals. It focuses on supporting the modification of risk factors and encouraging self-management. It does not eliminate the need to be seen by physicians or other personnel periodically for condition-specific advice, as is provided with most other chronic illnesses. It has been shown to be effective in cardiovascular disease,[852] chronic obstructive pulmonary disease,[853] asthma[854] and diabetes,[855] leading to a decrease in the use of health services, and improved functional status and quality of life.

Self-management support by the healthcare team is vital to improving care and outcomes. Providing the information and support to enable patients and families to better care for their illness is essential.[856] Self management programs focus on the patient, encourage collaborative goal setting, and build self-efficacy[857] to enable them to better manage their health in partnership with health-care providers.[858] [859] [860] Achieving success requires an ongoing collaborative process between patients and healthcare professionals.[861] [862] Self-management support is defined as the systematic provision of education and supportive interventions by health care staff to increase patients' skills and confidence in managing their health problems, including regular assessment of progress and problems, goal setting, and problem-solving support.

- **Patients' Needs and Preferences**

Empowering patients to self manage their symptoms using targeted education and support can lead to significant and sustained change. Most definitions of patient empowerment include some conceptualization of personal control and self-efficacy/self-mastery.[863] [864] [865] [866] [867] [868] Empowerment interventions have proven to be clinically useful, especially in the context of chronic disease.[869] [870] [871] [872]

Patient-centered care is not technology centered, doctor centered, hospital centered or disease centered.[873] The hallmark of patient-centered care is to customize treatment suggestions and decision-making at visits in response to the patients' preferences and beliefs. As emphasized by the Institute of Medicine (IOM), patient-centered care with good communication and interaction is an essential component of all quality care.[874] The IOM defines it as the provision of care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions.

Patient-centered care is paying attention to patient needs and circumstances when planning care. It is associated with improved health care outcomes.[875] It helps to facilitate the understanding of the impact of an illness or a treatment effect on the patient`s overall quality of life, and leads to better satisfaction and improved self-management.[876] When patients perceive their physician visit to be patient-centered, i.e., they feel understood and adequately involved in developing their treatment plan, they experience better recovery, better emotional health, and dramatically fewer diagnostic tests and referrals.[877] A focus on patient-centred care can reduce the use of specialists and the number of visits to their primary health care provider by 20%.[878]

- **Ongoing Relationships with Staff**

In addition to patient-centered communication/interaction, the heart of person-centered care is the developing relationship between the client and the frontline staff and the healthcare providers.[879] Person-focused care is based on the gradual, accumulated knowledge of clients. It provides the basis for better recognition of health problems and needs over time, and facilitates appropriate care for these needs in the context of other needs. It specifically focuses on the whole person.

Primary care is whole person-focused care over time, not disease-focused. To be person-focused, it must be accessible, comprehensive (dealing with all problems except those too uncommon to maintain competence), continuous over time, and coordinating when patients have to receive care elsewhere. The essence of person-focus implies a time focus rather than a visit focus. It extends beyond communication and respect for the individual because much of it relies on the knowledge of the patient that accrues over time. It is not specific to disease-oriented episodes. Relationship continuity is a key element in primary care.[880]

Both patient-centered and person-focused care require adequate recognition of health problems experienced by people, but they are different.[881] Care is better when it recognizes that the patient's problems are unique to the person's context, rather than what the diagnosis is.

The Hub is a tertiary centre, and thus the care provided by the Hub will be more patient-centered than person-focused. It will develop individualized multidiscipline treatments for each patient, using the chronic care model. It will rely on a patient-centered focus to inform and promote empowerment and self-management, recognizing as much as possible each person's context. Patients referred from the Spokes will eventually (perhaps as early as 6 months) be returned there or to their primary care provider for their longer term care, in order to make space for new referrals. Hence, a goal is to involve Family Health Teams as well as Community Health Centres

as spokes, and to eventually incorporate education about ME/CFS, FM and ES/MCS in primary care practices across the province.

The continuing care provided in the Spokes (when they are widespread across the province) will be both patient- and person-focused, emphasizing relationship continuity. This is consistent with Health Quality Ontario's bestPATH initiative, which focuses on three key elements of health care delivery:[882]

1. person-centered
2. appropriate
3. timely

- **Interprofessional team**

Patients with chronic, complex health conditions typically require more than one health discipline to address multiple problems. The US Institute of Medicine has suggested that healthcare professionals working in interprofessional teams can best communicate and address these complex and challenging needs.[883] [884] Members of the team have the common goal of restoring and maintaining an individual patient's health. The interprofessional team approach encourages the sharing of expertise and perspectives, and combining resources, which can improve healthcare processes and outcomes.[885]

There are important characteristics that determine team effectiveness, including members seeing their roles as important to the team, open communication, the existence of autonomy, and quality of resources.[886]

- **Interprofessional Collaboration**

According to the Canadian Interprofessional Health Collaborative,[887] collaboration is a partnership between a team of health providers and patient/client in a participatory, collaborative and coordinated approach to share decision-making around health and social issues. It is the process of developing and maintaining effective interprofessional working relationships with learners, practitioners, patients/clients/ families and communities to enable optimal health outcomes. Elements of collaboration include respect, trust, shared decision making, and partnerships.

- **Shared Decision-making**

Shared decision-making is an interactive process in which healthcare providers and consumers collaborate to make healthcare decisions. What the patient brings to the discussion table is his or her own unique experience of illness. People with chronic illness often struggle to juggle the competing demands of their lives, including but not limited to the challenge of managing their health, dealing with the costs of illness, the personal limitations imposed by ill health, and the obstacles faced in negotiating "the system" (medical, legal, third party insurance, etc).[888] [889] [890] All of this is frequently complicated further by multimorbidity.

The essential components involve healthcare providers' and consumers' participation at all stages of the treatment decision-making process, including information exchange, deliberation (discussing treatment options and consumer preferences) and arriving at an agreement on a

decision to implement.[891] It is a core element of patient-centered care.[892] [893] In fact, interprofessional collaboration as well as collaboration between the healthcare professionals and the patient are all vital to the concept of patient-centered care and shared decision-making.[894] [895]

- **Individualized Treatment Program**

Most patients with chronic complex conditions have multimorbidity. Therefore any treatment program must be individually designed according to that patient's needs rather than depend solely on guidelines which do not consider multimorbidity. The existence of multiple chronic conditions can result in atypical clinical presentations, poor diagnostic accuracy of laboratory tests, and conflicting treatment priorities.[896] [897] [898]

The determinants of health for each individual patient also need to be considered when evaluating treatment options. These include the person's social and economic environment, individual characteristics, preferred lifestyle, and his/her own environmental exposure history.

Collaboration between multiple interprofessional team members and the patient and his/her family, with coordination, will assist the decision-making process. This model suggests an increased likelihood of success for patients attending either the Hub or Spoke, as measured by improvement of quality of life and reduction of utilization of the healthcare system.

- **Summary**

A medical centre of excellence focuses on delivering comprehensive, evidence-based or –informed care, which is multidisciplinary, aiming for best quality outcomes and high patient satisfaction. In particular, the OCEEH will utilize and integrate individual and population based approaches- primary care, preventive medicine and public health. It will provide service for complex, chronic environmentally linked illnesses, focused on ME/CFS, FM and ES/MCS, including health services, social services and advocacy, research, education and health promotion, and policy development.

The guidelines for assessment and treatment will be developed based on the level of available evidence and will be provided according to best and promising practices. The quality of evidence will be classified using the GRADE system. The strength of the recommendations will be determined by four key factors: (1) balance between desirable and undesirable effects; (2) quality of evidence; (3) patients' values and preferences and (4) costs.

The present level of available treatment is clearly insufficient to induce significant recovery and reduction of disability, especially as measured by ability to return to work. It is beyond the scope of this proposal to rate the quality of evidence available for the assessment, diagnosis and treatment of these chronic, complex, environmentally linked conditions. It is also beyond the scope of this proposal to develop guidelines for the diagnosis and treatment of these disorders. This will be a prolonged process that evolves as the centre evolves.

As a result, at present, the reliance is on recommendations and resources for diagnosis and therapy that are contained in the Mainpro-C modules, accredited by the College of Family Physicians of Canada. However, it is planned to provide a three-day workshop of experts who

will GRADE the current tests and treatments into best practices (for which there is sufficient evidence), promising practices (where there is consensus they are likely to be helpful with minimal adverse effects, plus agreement to evaluate their use), and emerging practices (which have to be tested by formal research protocol).

The proposed model for the OCEEH includes a central provincial Hub and ever-widening Spokes providing services as close to home as possible. The Spokes will involve health care providers, who will receive specialized education, developed and delivered by the experienced medical staff in the Hub and a few trained community clinicians. Ongoing research will play a key role.

The purpose of creating the OCEEH Hub and Spoke model is to fill the gap in care for these patients, to make it more accessible across Ontario, and to advance the field.

Treatment will be made available according to GRADE recommendations. Emphasis will be on the provision of education and supportive interventions by health care staff to increase patients' skills and confidence in managing their health problems, including regular assessment of progress and problems, goal setting, and problem-solving support, in a patient- and person-centered manner.

Patients will be empowered by person-centered care, developing ongoing relationships with their healthcare team.

Individual care will be delivered by an interprofessional team collaborating with the patient in shared decision-making. Treatment programs will be individualized because of the likelihood of multimorbidity and the uniqueness of each individual's determinants of health.

The OCEEH will also contribute to the integration of primary care, preventive medicine and public health in communities across Ontario.

V Function and Overview of Services in Hub and Spokes

- **Evolution**

The model of the OCEEH contains a central provincial Hub and multiple Spokes distributed throughout the province to provide health and social services as close to home as possible, and to support primary health practitioners in ongoing care for their patients.

To develop this model requires the experience of the environmental health physicians presently working in the Environmental Health Clinic (EHC) at Women's College Hospital in Toronto, as well as a few experienced community physicians, along with building health professional capacity.

Similar to the Ontario Health Technology Advisory Committee's Recommendation on Specialized Multidisciplinary Community- based Care[899] for Chronic Disease,[900] the most effective evaluations will be developed with the assistance of clinical experts and researchers.

The following is what is being currently envisioned, but the function, staffing, equipment and space of the OCEEH Hub and Spokes will necessarily evolve as the Centre develops. At a time of change and new linkages/integrations within the health care system, it is not possible to accurately predict now what will be most suitable in 2020. We will need to re-assess on an ongoing basis.

- **The Hub**

The Hub will be an academic, tertiary healthcare centre, providing specialized investigation and treatment to people referred primarily from primary and secondary healthcare providers, including the physicians in the Spokes. The Hub will build on the scholastic foundations of the present Environmental Health Clinic at Women's College Hospital.

It will provide tertiary level consultations for the most complex patients with ME/CFS, FM and ES/MCS referred from the Spokes and other physicians. It will also provide continuing medical education for the healthcare providers both in and outside the Spokes. It will provide leadership working collaboratively with the Spokes to develop and evolve their individual and group self-management and education programs.

The Hub will design and conduct research studies to study ME/CFS, FM and ES/MCS, in collaboration with partners, such as the Dalla Lana School of Public Health, University of Toronto, as well as other universities, international professional organizations and affiliated teaching hospitals,.

- **Association with a Teaching Hospital**

The Hub must have close and direct affiliation with a teaching hospital, in order to be able to access and work with various specialists. Although the vision for the OCEEH is to be an independent, self-governed organization, this may not be possible until a later stage of development. If the Hub is part of a hospital, its funding needs to be designated according to an

accountability agreement with the MoHLTC or the LHIN. This affiliation of the Hub is mandatory for the creation of a credible, vibrant, creative and influential Centre of Excellence. Collaboration between the Hub and the hospital is necessary to support the following:

1. Multidiscipline medical and other health professional case conferences required for the most difficult and complex cases. Other health professionals include neuropsychologists, physiotherapists, respiratory technicians, etc.
2. Future research will require the use of specialized equipment available in the hospital setting (e.g. cardiopulmonary testing, tilt table, functional brain scans, pulmonary function testing, hyperbaric oxygen etc.).
3. The hospital should have a strong expertise in research. Future research will require collaboration with other medical disciplines (e.g. infectious disease, clinical pharmacology, internal medicine, toxicology, pediatrics)
4. Attracting researchers and Fellows.
5. A small number of ES/MCS patients will require hospitalization electively, primarily for other illnesses/injuries, and provision of in-hospital care in an environmentally controlled, safe room must be an available option. Fot example, a washed down infection control room can be environmentally controlled due to positive pressure To create hospital policy for the proper care and management of environmentally sensitive patients within a hospital setting dictates that the Hub must be closely associated with a hospital. Collaboration between the Hub and the hospital is mandatory in order to develop and manage protocols.
6. An environmentally safe hospital setting for patients with severe chemical sensitivities should include the availability of environmental physicians to consult when their expertise and assistance in management of hospitalized patients is required, preferably on staff at that hospital. Telehealth could be used.
7. When admission to the closest hospital occurs because of urgency, advice from the Hub and hospital guidelines will serve the needs of community hospitals.
8. The knowledge gained from the developed guidelines can be transferred to community hospitals, to remove these barriers to health care for those with ES/MCS.
9. Being a centre of excellence demands credibility. It is the opinion of the patients, the environmental physicians involved in medical legal cases, the Medical Advisory Committee of this Business Case Proposal (BCP), and various other physicians consulted during the process of creating this BCP that a close and specific association with a teaching hospital must be maintained. The credibility of the Environmental Health Clinic to this point in time, assisted by its association with Women's College Hospital, has included the respect of peers and increased ability to provide support for patients experiencing medical legal issues, including obtaining disability support payments from third party insurers, accommodation in the workplace, and travel grants for medical appointments.

A partnership agreement with a teaching hospital, similar to the Canadian Forces Health Care Centre (CFHCC) and Montfort Hospital (MH) in Ottawa, is an example. These two health centres are in close proximity - CFHCC and MH share the same building. The Hub must be in close proximity to the hospital. CFHCC controls the health care services provided to Canadian Forces members, but the provision of laboratory services, diagnostic imaging services and a

number of readily accessible specialist and medical support services can be procured from Montfort when required.[901]

It is recognized that the present financial constraints of hospitals are an obstacle to this partnership, which demands the top-down financial guarantee of designated funding from the MoHLTC and/or the Local Health Integration Network in support of the Hub.

- **Association with Academia**

Given the location of the Hub in the Greater Toronto Area (GTA), provision of education for medical students, family medicine residents and fellowship programs requires an association with the University of Toronto, in particular with the Department of Family and Community Medicine in the Faculty of Medicine, and with the Division of Clinical Public Health in the Dalla Lana School of Public Health.

- **Location**

The location of this Hub should be central and easily accessible via public transportation. Given that the Hub will be located in the GTA, consideration must be given to the air quality impact associated with being close to a major roadway, such as the 401 and the Gardiner Expressway. However, proximity to, or being physically inside, a major teaching hospital is the highest priority, in order to establish a high functioning Hub. The present recommendation for location is in the downtown Toronto area, close to teaching hospitals and the Dalla Lana School of Public Health.

- **Physical Requirements of the Hub**

An environment for the Hub with clean air quality can assist patients with sensitivities to concentrate during history taking, and aids the effective administration of treatments, while avoiding atmospheric confounders in conducting research.

A goal would be that the physical environment of this centre meets the needs of the most environmentally sensitive patients. However, it may take some time, and basic protections have served most patients since the EHC opened in 1996. Building or retrofitting this centre will require the expertise of building engineers, architects and environmental health practitioners, who have relevant expertise and experience in indoor air quality. It will require the most inert building, furnishing and maintenance materials, and ventilation at least 1–2 orders of magnitude above the present guidelines for acceptable indoor air quality. It will also require state-of-the-art filtration (HEPA) for particulate matter, and activated charcoal for volatile and semi-volatile organic compounds. Some teleconferencing or house calls may be necessary until this is achieved.

Given that the Hub will provide multidiscipline assessments for the most complex cases, including those with severe ES/MCS, provision of safe lodging in the vicinity of the Hub will be required. This Lodge will be specific to the Hub and available only for those requiring special accommodations during their visit(s).

- **Responsibilities**

The responsibilities of the Hub include provision of health services, guiding and conducting research, education, knowledge transfer and policy development.

The specific roles of the Hub are to provide:

1. Consultation for difficult, complex cases referred from the Spokes or elsewhere
2. Multidiscipline medical and other health professional case conferences, when indicated.
3. Advanced treatment programs designed for each client.
4. Individual and group programs to encourage self-management.
5. Support and perhaps assessment for patients requiring elective admission to hospital.
6. Development and promotion of hospital guidelines for patients that need emergency admission.
7. Assistance with development of undergraduate medical and nursing education in Ontario, including enhancements to the curricula.
8. Continuing medical education for both medical and other health professionals in the Hub and Spokes, as well as all primary care practitioners, including an introductory course in Environmental Health.
9. Training programs for Fellowship for graduating residents of family practice or specialists, and for practising physicians.
10. Provision of an online certificate course (a minimum of 39 hours) in "Environments, Occupations, Communities and Human Health" from Continuing Education and Professional Development at the University of Toronto (and perhaps in collaboration with different universities e.g. Northern Ontario School of Medicine) to be endorsed by the Environmental Health Committee of the Ontario College of Family Physicians.
11. Provision of four College of Family Physicians of Canada-approved Mainpro-C workshops, rotating through communities or online, that demonstrate management of chronic complex conditions and impacts of environment on health across the lifespan.
12. Generate and conduct research to improve understanding of etiology, and develop and enhance the tools for assessment, diagnosis and treatment of ME/CFS, FM and ES/MCS. This will include conducting data analysis from case series information gathered in the Spokes.
13. Maintenance of existing connections and expansion of collaboration and networking in the professional community.
14. Community health promotion and disease prevention with Public Health and community partners.
15. Policy development and support for patients federally and provincially, including such issues as ODSP and WSIB, and implementation of hospital guidelines.

- **Staff Required for Hub Clinical Services**

The numbers of physicians and other health professionals required daily in the Hub is not yet known. The present 0.9 allocation to the EHC is inadequate. It is recommended that the EHC medical staff be increased to develop the guidance, education and infrastructure required to establish and maintain the clinical components of the Hub and Spoke model.

The staff component may be reviewed after the workshops of experts to establish the grading of available evidence for treatments and to set the research agenda.

The projected future clinical staff needs for the Hub are proposed by MNP consultants (September 20, 2013), based on loose estimates from the MAC.

Hub

Physician (including a Medical Director)	4.0
Nurse Practitioner	3.0
Registered Nurse	1.4
Registered Practical Nurse	1.0
Psychologist	1.2
Other Health Staff (Social Worker and Health Promotion)	2.0
Therapeutic Staff (Dietitian, physiotherapist, occupational therapist, etc.)	5.0
Resident Fellows (PGY3)	2.0

Associated specialty medical staff, required for case conferences and research:

1. Allergy/Immunology
2. Anaesthesia
3. Clinical Pharmacology
4. Ear, Nose and Throat
5. Endocrinology
6. Gastroenterology
7. Genetics
8. Gynecology
9. Haematology
10. Infectious Diseases
11. Neurology
12. Radiology
13. Respirology
14. Rheumatology
15. Sleep Specialist

- **Staff Required for Hub Administrative Support**

Executive Director	1.0
Manager Clinical Services	1.0
Manager Policy and Education	1.0
Manager Laboratory Services	1.0
Manager Research	1.0
Information Technology Support	1.0
Medical Office Assistants	4.0

- **Staff Required for Research**

In order to progress the field, the Hub willl require a qualified Research Director.

- **Assessment, Treatment and Research**

The assessments and treatments in the Hub will be provided by those who are trained and have experience in the concepts of systems-based medicine, including environment as a determinant of health. Given that there is as yet no formalized special interest or specialization program in environmental medicine in Canada, these positions will be filled immediately by the experienced physicians presently working in the Environmental Health Clinic at Women's College Hospital or community clinics, who will work to increase capacity as quickly as possible.

The initial assessment for all patients requires a comprehensive, chronological history, which should include:

1. environmental exposure history
2. chronological functional inquiry

The environmental exposure history documents environmental chemical exposures chronologically. It is limited by its subjective nature and dependency on memory of the patient. Nevertheless, it is beneficial to determine an association of significant chemical exposures with onset of symptoms. It is also useful to begin the data collection to enhance the recently developed concept of the exposome.

Genetic transformation and evolution are not significantly contributing to the rapid and significant changes in health patterns that have recently emerged.[902] Only 15-20% of chronic illness is genetic.[903] [904] The exposome considers everything that is not due to the genome.[905] It is defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health.[906] We do not have the ability to measure the impact of our lifetime chemical and psychosocial exposures from uterus to old age. Developing this ability is key to unravelling the major causes of chronic diseases.[907] As we acquire the markers to measure and follow the exposome through life, we will add to our understanding of the complex interplay between the genome, the epigenome and the environment.[908]

The functional inquiry is the basis of a detailed medical history, which is taught to and practiced by every medical student. In this traditional model, the "history of the present illness" focuses on the primary complaint, which may be pain, fatigue, or heartburn. The functional inquiry acknowledges other symptoms, which are not considered to be significantly associated with the primary complaint. However, in chronic illness, and in particular environmentally linked, complex illnesses, multiple systems are always involved. It is well recognized that there are multiple pathological and environmental pathways to the development of chronic illness and subsequent multimorbidity. Establishing the chronology of all these dysfunctions aids in the understanding of the individual patient's pathology.

- **Specialized Equipment and Space**

Recommendations for equipment and space will be reviewed at the expert workshops that are considering the evidence levels for treatment and setting a research agenda. The equipment and space will be shared when available, as long as clean space is available for patients who are environmentally sensitive.

1. Cardiopulmonary exercise testing for ME/CFS patients (one large room space)
2. Tilt table (one small room)

3. Maxin MA3 device for capsaicin inhalation challenge testing (one small room)
4. Complex carbohydrate challenge breath testing to measure hydrogen and methane (Breath Tracker DP[909]) (one small room)
5. Hyperbaric oxygen chamber; possibly more than one (one large room; oxygen storage tank area; one small room change area)
6. Blood and urine sample collection (one small room with refrigerator)
7. Intravenous therapy (one large room; several cots or reclining chairs; IV poles)
8. Far infrared sauna (one small room and private shower/clothing change area, or multiples)

- **The Spokes**

  - **Responsibilities:**

- to assess, diagnose, and treat clients with ME/CFS, FM and ES/MCS
- to be able to perform functional assessments on those diagnosed with these disorders
- to accept referrals from other medical practitioners in the community to assist in the diagnosis and treatment of those clients with these disorders
- to provide accessible healthcare to those patients with ES/MCS
- until the Spokes expand to adequately reflect the needs in the province, it is expected patients referred to the Spoke will have to be referred back to their primary health practitioner (PHP) (perhaps within 6 months) to make room for new referrals. Hence the primary healthcare practitioners (PHPs) will need to be educated too, and coached/advised as necessary.
- to refer the more complex or difficult cases to the Hub
- to use the same comprehensive chronological history, including the same environmental exposure and chronological functional inquiry questionnaires as the Hub to collect clinical data as well as for research and analysis
- to provide information so that individual patients may reduce chemical pollutant exposures
- to provide educational programs to the community to promote lifestyle changes and reduce environmental chemical exposures
- to provide individual and group chronic care management programs, the training for which is available from the Mainpro-C programs provided by the OCFP and the physicians in the Hub
- to initiate and oversee chronic disease self-management programs (some programs, such as the Stanford model, will require further specific training)
- to use the environmental exposure history whenever appropriate in the family practice setting (e.g. change in illness, such as exacerbation of asthma, moving, change in job)
- to practice preventive medicine by using the environmental exposure history whenever appropriate in the family practice setting (e.g. preconception and prenatal counseling, annual wellness visits, etc.)
- to educate other Ontario primary health providers, so that all will be using the exposure history when applicable in everyday practice
- to obtain and use electronic record keeping for the comprehensive clinical history, environmental exposure history and chronological functional inquiry, to be developed in

the Hub, and, with patients' permission, to store and share data for future research reference

- **Staff Required for Spokes Clinical Support**

The projected clinical staff needs for the Spokes were proposed by MNP consultants (September 20, 2013), on the basis of loose estimates by the MAC.

1. Staff Physician trained in systems-based environmental medicine 1.0
2. 1 Nurse/Nurse Practitioner or Physician Assistant 1.0
3. Physiotherapist 1.0
4. Psychologist/Counselor 1.0
5. Social Worker 1.0
6. Dietician 1.0
7. Community Outreach Coordinator 1.0
8. Compounding Pharmacist in the community 0.25

- **Staff Required for Spokes Administrative Support**

It is proposed that administrative support persons will be required by somewhat lesser numbers for the Spokes. However, there will be requirement for an Administrative director, a Manager Clinical and Laboratory Services, Manager Policy and Education, Manager Research and Information Technology, and medical office assistants.

- **Education of Staff**

Clinicians and other healthcare professionals will be educated in the basic concepts of systems-based medicine, incorporating environment as a determinant of health, and will maintain that level of competency via continuing medical education. The initial education will be based upon the Mainpro-C programs already available from the OCFP, provided by the staff physicians in the Hub and the OCFP Environmental Health Committee.

Health professionals in the Spokes will use the same comprehensive clinical history, environmental exposure history and chronological functional inquiry as that used in the Hub, which will be made available online for all health care practitioners involved in OCEEH patients' care. Healthcare practitioners in the Spokes will be capable of making the diagnoses and initiating recommended treatments for ME/CFS, FM and ES/MCS. Routine lab screening will be obtained to minimize costs for assessment, as recommended by the guidelines to be developed by the Hub.

Spokes clinicians will also be taught to conduct functional assessments, i.e., measure the impact of pain and/or fatigue on quality of life in patients with ME/CFS, FM and ES/MCS. These assessments will be used to follow the outcome of treatments including self-management. These validated measurements will allow the healthcare practitioners to advocate for their clients for disability claims with third party insurance carriers and accommodation at the workplace, when indicated.

The Spokes will provide the following:

1. initiation of fragrance-free and safe cleaning products policies
2. provision of a "safe room" for patients, to be used as required
3. organize and manage patient support groups
    a. gather and provide community-centered information, such as access to resources, e.g., a reference list of local relevant specialty stores, organic farms and farmers markets, specialty restaurants, and lists of products catering to gluten free, dairy free, and other elimination diets
    b. menu planning and cooking classes can be provided
4. develop education tools to reduce chemical exposures for all individuals in the community

- **Physical Requirements**

The physical environment of Spoke centres should evolve according to future research designs or results, with aspirations to meet the needs of most environmentally sensitive patients. Given the difficulty in guaranteeing that every patient/client/visitor to the Spoke will be scent and chemical free, there needs to be a safe, designated area available when required. Building or renovating this designated area will require the expertise of building engineers, architects and environmental health practitioners, who have an expertise and experience in indoor air quality. It will usually require the most inert building and furnishing materials, and appropriate ventilation and filtration for particulate matter, and volatile and semi-volatile organic compounds. Where it is not possible to provide a safe room, home or Ontario Telemedicine Network visits may be necessary. A portion of ME/CFS and FM patients do not have environmental sensitivities, and so the Spokes would be able to meet their needs in a usual fragrance-free patient environment.

- **Integration of Responsibilities of Hub and Spokes**

There are four areas of service provided by the Hub and Spokes:

- health services
- social services and policy enhancement
- education and health promotion
- research

- **Health Services**

The healthcare providers of the Hub will consult on the difficult cases referred from Spokes and other secondary sources. Being available in the hospital setting will allow for providing expert opinion on patients admitted electively. Hub clinical practitioners will consult with other specialties as required in case conferences, which may be required for the most difficult cases.

The primary healthcare providers in the Spokes will provide assessment, diagnosis, treatment and support for patients with a focus on ME/CFS, FM and ES/MCS and other environmentally linked conditions. These providers receive specialized education, developed and delivered by the those with clinical experience in the Hub. They will integrate the concepts of systems-based environmental medicine, public health and preventive medicine into clinical practice. Because they will have the training and expertise, the healthcare providers in the ever-expanding Spokes

will also provide consultation (by telephone or telehealth) on request from other local primary care providers.

They will promote individual self-management, which is patient- and person- centered. They will also be able to provide group education and self-management support. They will link with other self-management support groups which are locally available.

- **Social Services and Policy Advancement**

Social service support is frequently necessary for chronic illness, especially for those in lower socioeconomic groups. For example, financial support can be provided to obtain HEPA and/or activated charcoal filtration systems for those with ES/MCS, or those requiring specific elimination diets. Public health can and should be involved in promoting equity.[910]

The healthcare providers can also advocate for workplace accommodation or, if necessary, a request for disability third party insurance coverage.

They can advocate for safe healthcare facilities and housing for those diagnosed with ES/MCS. Furthermore, they can advocate for reduction of pollution exposures in their community, such as promoting the initiation of fragrance free policies in public buildings and local workplace environments.

- **Education**

Education to train fellows, primary caregivers in the Spokes, residents, medical students and nurses will initially be provided in the Hub setting by presentations in person, or by telehealth. Individual education will be maintained by regularly scheduled case presentations and/or journal clubs. Knowledge transfer will also occur via networking with other centres of excellence and should help to inform government policy development.

The education of patients is mandatory for chronic patient-centered care. These programs need to be further developed. The Spokes must also contribute to educating the community at large with respect to lifestyle change and reduction of pollutant exposures.

- **Research**

Research is required to develop etiological understanding, diagnostic markers and treatments. Research design and use of specialized medical technology and equipment (e.g. 2-day cardiopulmonary exercise tests, tilt table, capsaicin challenge tests, functional scans, etc.) will be provided by the Hub. Sharing of space and equipment will take place when available, provided safety for patients with special needs is maintained.

The Spokes will participate with data collection, including demographics, symptoms and function. Treatments can be evaluated with continuing case studies or under research protocols, depending on the level of available evidence.

- **Assessments**

  - **Introduction**

The driving force behind this Business Case Proposal is the patients' need, for more effective treatment and increased capability to self-manage these disorders with better support, and the need for research into etiology, assessment and treatment. Presently, there is an absence of identified biological markers and most tests performed clinically are used to rule out other known biological entities that could explain the symptoms of ME/CFS, FM and ES/MCS. There are tests available in the United States, which aid in understanding the pathophysiology of these conditions. However, there is a clear need for better, evidence-based tools for the assessment and treatment of chronic, complex environmentally linked conditions, including ME/CFS, FM and ES/MCS.

The following section provides a list of tools used for assessment and treatment for ME/CFS, FM and ES/MCS. They were obtained from the medical literature and the jurisdictional review of expert centres.

  - **Laboratory Assessments**

Presently, the following tests are obtained routinely by the Environmental Health Clinic at Women's College Hospital, prior to attendance, to screen for readily treatable problems that may be contributing to symptoms:

- Complete blood count with differential (CBC)
- Erythrocyte sedimentation rate (ESR)
- Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase
- Total Protein, Albumin, Globulin
- Calcium, ionized, Phosphorus
- Glucose
- Electrolytes
- Creatinine
- Thyroid stimulating hormone (TSH)
- Antinuclear antibody (ANA)
- Cholesterol/lipid screen
- Immunoelectrophoresis
- Vitamin B 12
- Ferritin
- Urinalysis

Most of these tests are recommendations for screening patients with potential ME/CFS; to rule out other causes for chronic fatigue.[911] According to the 2012 Guidelines for Fibromyalgia, testing to screen patients should be limited to simple blood testing including a CBC, ESR and TSH as above, plus C-reactive protein (CRP) and creatine kinase (CK).[912] The diagnosis is established as a clinical construct.

- **Additional Laboratory Tests**

Additional laboratory tests have been suggested particularly for ME/CFS, to rule out other conditions known to cause fatigue:[913]

- Infectious Screen: Hep B&C, Lyme, Epstein-Barr virus (EBV), Venereal Disease Research Laboratory tests for syphilis (VDRL), Human Immunodeficiency virus (HIV), tuberculosis (TB)
- Urine/blood for mycoplasma/ureaplasma
- Protein/Immuno-electrophoresis, complement (C3, C4)
- Rheumatoid factor, anti-ds-DNA, anti-thyroid antibodies
- Celiac profile
- RBC Magnesium, Folic Acid, Vitamin D,
- Free T3, free T4
- AM/PM Cortisol, ACTH
- Heavy metals (arsenic, cadmium, mercury, lead): blood and 24-hour urine collection
- Flow cytometry T suppressor lymphocyte subsets and function (CD4, CD8, natural killer cells (NK), B-cell)

- **Experts' Opinions**

In the small jurisdictional review by 8 experts, along with the tests reviewed above, the following were also mentioned as possible tests for assessment:

- Sex hormones, estradiol, FSH, prolactin, testosterone
- Stool for Ova & Parasites
- Specific tests for celiac: gliadin and endomysial antibodies (IgG, IgA; serum, stool)
- Lipid screen should include oxidized LDL
- Glomerular filtration rate (GFR)
- ACTH challenge
- Insulin (to measure resistance)
- Infectious screen should include human herpes virus (HHV-6, HHV-7), cytomegalovirus (CMV)
- Western Blot (Lyme) for Borrelia burgdorferi (and other Borrelia-(afzelii, garinii, sensu stricto), and other related tests
- Candida antibodies; intradermal testing
- Urine mycotoxins
- NK cytotoxic activity
- Other lymphocytes CD56, $CD16^-$
- Cytokines
- Xenobiotic and heavy metal testing (blood, urine, sweat)
  - Heavy metal screening should include:
    - RBC levels
    - Hair analysis
- Test Phase 1 and Phase 2 detoxification
- Oxidative stress markers
- Mitochondrial function testing

Numerous tests have been proposed for the determination of oxidative stress in clinical situations, but there are problems with establishing reference values.[914 915 916 917 918] Case-control studies are needed. Oxidative stress can be measured in numerous ways,[919 920 921] including the following in Table 4- Oxidative Stress Biomarkers.

Development of clinically available markers of oxidative stress that are sensitive, specific, reliable, and accurate in reflecting underlying oxidative stress states is essential. It will enable clinicians to be able to assess therapy and predict risks in chronic illness, including increased morbidity and risk from environmental exposures. Patients who meet the criteria for environmentally linked illnesses, can be assessed for oxidative stress and compared to control groups, which would likely be those healthy individuals identified from the environmental exposure history as also having lower pollutant exposures.

Methods to probe mitochondrial function *in vivo* are being developed, using near infrared and magnetic resonance spectroscopies.[922 923 924]

Table 4

Oxidative Stress Biomarkers

DNA/RNA Oxidation:
- 8-hydroxyguanosine (8-OHG)
- 8-hydroxydeoxyguanosine (8-OHdG)

Protein Oxidation:
- Protein carbonyls

Lipid Peroxidation:
- 8-iso-Prostaglandin F2alpha (8-isoprostane)
- Malondialdehyde (MDA)
- Thiobarbituric acid reactive substances (TBARS)
- Oxidized low density lipoprotein

Non-enzymatic Antioxidants
- **Lipid soluble**
  - α-tocopherol (vitamin E)
  - Carotenoids
    - α-carotene
    - β-carotene
  - lycopene
  - Retinol (vitamin A)
- **Water soluble**
  - Ascorbic acid (Vitamin C)
  - Glutathione
  - Total antioxidant status

Enzymatic Antioxidants
- Catalase activity
- Glutathione peroxidase
- Superoxide dismutase

It is beyond the scope of this review to do an appropriate literature review to categorize which tests for assessment are best, promising, emerging or not indicated. It is recommended that, for now, the tests obtained routinely by the Environmental Health Clinic at Women's College Hospital, prior to attendance (see above), is an appropriate screen for readily treatable problems that may be contributing to symptoms. However, further discussion is recommended in an experts' forum to assign the above and other proposed tests to the aforementioned designations of best, promising and emerging practices that will allow for more specific analysis, i.e., case series or more rigorous research protocols.

- **Assessments of Function**

There are no global, generally available, or cheap biomarkers of fatigue,[925] which is difficult to define but even more difficult to measure. Fatigue perception is most frequently measured by application of self-report scales, many of which have demonstrated reliability, validity, ability to detect change, and clinical and research usability.[926]

Like fatigue, the assessment of the widespread pain of fibromyalgia is challenging because there are no biomarkers. The Fibromyalgia Impact Questionnaire (FIQ) was developed to meet the need for comprehensive fibromyalgia patient evaluation. It is a validated questionnaire,[927] which has been used to assess people in the community who have chronic pain,[928] to determine the impact of fibromyalgia on everyday life[929] and to measure disability[930] as well as outcomes in drug studies, exercise treatment, multidisciplinary approaches and treatment program evaluation. It is an instrument designed to quantify the overall impact of fibromyalgia over many dimensions using visual analog scales (e.g. function, pain level, fatigue, sleep disturbance, psychological distress etc.).

The FIQ and Fibromyalgia Impact Questionnaire Revised (FIQR) are useful assessment tools in fibromyalgia because they evaluate the total spectrum of problems related to fibromyalgia, including functional impairment, overall impact, and fibromyalgia-related symptoms. The FIQ total score has proved to be a useful outcome measure in key clinical trials of fibromyalgia.[931] Currently, the FIQ is considered among the best measures of self-reported function and work disability in fibromyalgia.[932]

The FIQR[933] has the same 3 domains as the FIQ: function, overall impact and symptoms. It differs from the FIQ in having modified function questions and the inclusion of questions on memory, tenderness, balance and environmental sensitivity. It has sound psychometric properties, discriminates between fibromyalgia patients and patients with rheumatoid arthritis, lupus, and major depression disorder, takes just over one minute to complete, is easy to score, and can be used in online surveys. The FIQR has a good correlation with the original FIQ.

The FIQ and FIQR should be used to initially assess and follow all the patients with chronic fibromyalgia.

The Short Form (RAND)-36 Health Status Inventory (SF-36), comprising 36 questions, is a validated questionnaire which has been used in countless health outcome studies, health care financing studies, and clinical practice evaluations. It is a multidimensional, general health status patient-reported outcome measure containing subscales for 8 domains. It assesses functional

status on 8 descriptively named subscales: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, energy and fatigue, social functioning, role limitations due to personal or emotional health problems, and emotional well-being.[934] Each has been shown to have high reliability and validity. The SF-36 has been used in general population surveys of Canadians,[935 936] in a range of patient populations, including those with ME/CFS, [937 938 939] fibromyalgia,[940 941 942] or ES/MCS,[943] as well as in a comparative study of all 3 groups.[944]

The SF-36 is an evaluation tool employed at every patient encounter in the Environmental Health Clinic at Women's College Hospital. It should continue to be utilized to assess and follow all patients with environmentally linked conditions.

Other tests which are suggested for consideration to be used to assess function include:

- Multidimensional Fatigue Inventory
- Multidimensional Assessment of Fatigue
- Activity Log
- Functional Capacity Scale[945]
- Karnofsky Energy Rating Scale[946]
- Central Sensitization Inventory Scale
- Pain Catastrophising Scale
- Quick Environmental Exposure and Sensitivity Inventory (QEESI)
- Chronic Pain Coping Questionnaire
- Beck Depression Inventory
- General Anxiety Disorder Scale
- Neuropsychological testing:

-Neuropsychological testing

Objective measures of neuropsychological performance have not consistently yielded evidence of neuropsychological dysfunction. However, most studies support the observations that patients with ME/CFS have decrements in cognitive performance. Impairments have been measured in verbal fluency, memory, motor speed, sustained attention, speed of cognitive processing, and deficits in verbal and nonverbal memory tasks.[947 948 949]

Similarly, a review of the literature reveals that patients who have fibromyalgia seem especially sensitive to distraction, and the cognitive mechanisms most affected in fibromyalgia are working memory, episodic memory, and semantic memory.[950]

In validating the case criteria for the diagnosis of ES/MCS, the Environmental Hypersensitivity Research Unit at the University of Toronto found that the symptoms of difficulty concentrating, feeling dull or groggy, and feeling spacey also distinguish patients with ES/MCS from controls.[951]

> More research is required to determine which battery of neuropsychological tests best discriminate environmentally linked conditions from controls and, in particular, whether this testing can discriminate between ME/CFS, FM and ES/MCS.

- **Other Medical Tests**

Other tests mentioned in the jurisdictional review include:

- Skin prick testing for allergies
- Intradermal serial dilution endpoint titration testing for natural inhalant and food allergies and sensitivities
- IgG food testing (ELISA, RAST)
- Pedometer
- Functional brain scan
  - -fMRI
  - -SPECT
- Heart rate variability testing
- Tilt table
- Overnight polysomnogram
- Venous pO2
- Complex carbohydrate challenge breath testing
- Patch testing for chemicals

- **Potential diagnostic tests**

- Capsaicin inhalation challenge for ES/MCS
- Repeat cardiopulmonary exercise tests (24 hours) for ME/CFS

- **Treatment**

- **Present Guidelines and Treatment**

Guidelines for ME/CFS remain controversial. The recommendation of exercise in some of these guidelines[952] must be tempered by the fact that the most prominent characteristic of ME/CFS is that minimal exertion exacerbates the fatigue, recovery is prolonged, and it significantly increases oxidative stress.

Given the fact that many patients with fibromyalgia also have comorbid ME/CFS, there is conflict regarding recommendations for exercise, emphasizing the need to develop the appropriate guidelines for comorbidity.

According to the 2012 Fibromyalgia Guidelines, ideal management includes both non-pharmacologic and pharmacologic treatments in a multimodal approach, with active patient participation fostered by a strong patient-centered locus of control. The essence of the evidence is that there is no "gold standard" of treatment; with responses mostly modest at best. These 2012 Guidelines note that, in a meta-analysis of 49 outcome studies published 14 years ago, non-pharmacologic treatments appeared more effective than pharmacological interventions.[953] They state that non-pharmacologic treatments have a positive effect with improvements in self-reported outcome measures including physical status, fibromyalgia symptoms, psychological status and daily functioning, but also state that many of the studies have been poorly executed.

Pharmacological treatments are those used for chronic pain disorders and include antiseizure and antidepressant medications. Antiseizure medications consist of those that dampen incoming ascending pain signals and those that augment descending pain inhibitory mechanisms.[954] The

descending pathways may be affected by antidepressant drugs that increase the level of the transmitters serotonin and norepinephrine at the synapse.[955] Medications in the opioid and cannabinoid classes act at many levels in the nervous system, affecting both the sensory and emotional components of pain.

With respect to antidepressants, amitriptyline has been a first-line treatment for neuropathic pain for many years. However, a Cochrane systematic review reveals that there is no supportive, unbiased evidence for a beneficial effect. The authors' recommendation was to balance this against decades of observed improvement in many patients with neuropathic pain or fibromyalgia. There is no good evidence of a lack of effect either; but concern for overestimation of treatment effect.[956]

However, in a British review of the evidence of efficacy for antidepressants prescribed for nonpsychiatric conditions in primary care,[957] it was opined that tricyclic antidepressants (TCA) did show some evidence for effectiveness, and two selective norepinephrine reuptake inhibitors (SNRIs) were recommended for fibromyalgia: milnacipran, which is not available in Canada, and duloxetine. It was opined that venlafaxine could be prescribed but selective serotonin reuptake inhibitors (SSRIs) were not recommended.

A European systematic review and meta-analysis determined that the TCA amitriptyline and the SNRIs duloxetine and milnacipran, along with pregabalin (antiseizure medication), are first-line options for the treatment of fibromyalgia patients.[958] However, only a small number of patients experience substantial symptom relief with no or minor adverse effects and overall, the incremental benefit over placebo is small. Most studies that show benefit report only a greater than 30% reduction of pain, and the studies are short term (6 months).[959] A remarkable number of patients drop out of therapy because of intolerable adverse effects or because they experience only a small relief of symptoms. Medications provide only modest relief at best, with doses often lower than suggested, and drug combinations being used according to clinical judgment.[960]

Systematic reviews have also demonstrated the efficacy of aerobic exercise, balneotherapy and multicomponent therapy for fibromyalgia. [961] [962] [963] Inhaled glutathione is also purported to be of help.[964]

The best known treatment for ES/MCS is consistent with the case criteria and what clinicians observe; environmental control and reduction of exposures to known triggers. In a review of self-reported perceived treatment efficacy by 917 persons with self-reported ES/MCS,[965] creating a chemical-free living space and chemical avoidance were rated by 95% of respondents as helpful. This review identified more than 100 treatments tried by ES/MCS patients, including environmental medicine techniques, holistic therapies, individual nutritional supplements, detoxification techniques, body therapies, Eastern-origin techniques, prescription items, thyroid supplements, herbs and others. Results observed by these patients for most therapies, apart from exposure avoidance itself and prayer (focused attention/meditation), were mixed.

- **Future Guidance**

Presently, treatment is directed towards the specific clinical defining characteristics of ME/CFS, FM and ES/MCS. Given the fact that 70% of these patients have multimorbidity, treatment must

take a multidiscipline, systems medicine approach and consider the underlying common denominators, frequently found in patients with these disorders:[966 967]

- Organ dysfunction
  - Central nervous system
    - central sensitization
    - limbic system dysfunction
  - Gastrointestinal system (IBS/GERD)
    - imbalance of microbiota
    - small intestine bacterial overgrowth (SIBO)
  - Immune system
    - allergies
    - food intolerance
    - systemic inflammation
  - Endocrine system
    - hormonal deficits
    - elevated BMI
- Cell dysfunction
  - TRPV1 sensitization
  - NMDA activation
  - mitochondrial dysfunction
  - oxidative stress

  These therapies deserve literature review and discussion by experts, and recommendations will necessarily evolve as the OCEEH evolves.

- **Organ Dysfunction**
  - **Central Nervous System**

The systems medicine approach to treating the CNS component of these disorders is to reduce the total load, i.e. to reduce the impact of all factors which could be influencing the hypervigilance of the limbic system. This includes reducing the sensory impact of pain, sleep disturbance and chemical exposures, and the influence of the other organ systems, including the gastrointestinal, immune and endocrine systems. It should also include the treatment of psychosocial issues, when indicated.

Stabilization of the limbic system can also be enhanced by the practice of various stress management techniques including:

- meditation
- mindfulness
- relaxation therapies
- Tai chi
- Qigong
- biofeedback, including neural biofeedback

- Biofeedback

  Biofeedback is a treatment technique in which people are trained to improve their health by using signals from their own bodies. It is a patient-guided treatment, which uses a monitoring device to measure physiological

information, of which the patient is normally unaware. The name biofeedback refers to the biological signals that are fed back, or returned, to the patient in order for the patient to develop the techniques to manipulate them.

Using this information, an individual can be taught through relaxation, visualization, and other techniques to actively influence muscle tension, pain, body temperature, brain waves, and other bodily functions and processes. For example, one commonly used type of machine, picks up electrical signals in the muscles. It translates these signals into a form that patients can detect, such that every time muscles grow more tense, the signals trigger a flashing light or activate a beeper. If patients want to relax tense muscles, they try to slow down the flashing or beeping.

Biofeedback is primarily used to treat high blood pressure, tension and migraine headache, and chronic pain. Voluntary control of brain systems is possible. Early studies demonstrated that human subjects can exert voluntary control over certain EEG characteristics.[968] [969]

- Neural Biofeedback

Functional magnetic resonance imaging (fMRI) has revolutionized the study of the human brain over the last 20 years, since it allows high-resolution non-invasive recordings of the blood oxygen level dependent (BOLD) response as an indirect measure of neuroelectric activity.[970] In most fMRI studies results become available to the researcher after a delay of hours or days. But, with additional software,[971] real-time fMRI (rtfMRI) processes images as fast as they are acquired.[972]

Using rtfMRI allows a person to watch and regulate the functional fMRI signal from his or her own brain.[973] Biofeedback using rtfMRI has a unique advantage in that it can precisely localize neurophysiological activity. In particular, it can be used to control neurophysiological activity in various parts of the limbic system.[974] [975] [976] [977] [978] [979] [980]

Numerous studies indicate rtfMRI feedback assisted control over specific brain areas can be applied to pain management.[981] [982] Given the evidence for central sensitization and limbic system dysfunction, rtfMRI biofeedback appears to be a promising therapy for ES/MCS as well as fibromyalgia.

- **Gastrointestinal System**

The brain-gut axis is a bidirectional communication system, comprised of neural pathways, including the limbic system,[983] [984] [985] and humoral pathways, which include cytokines, hormones, and neuropeptides as signaling molecules.[986] The intestinal microbiota, which are often abnormal in IBS, can activate neural pathways in the CNS signaling systems.[987] [988] Treatments which might be beneficial include:

- Elimination (and rechallenge) diet, based on tests for food sensitivities (including gluten) and evidence for flora imbalance

- Hydrochloric acid
- Pancreatic enzyme therapy
- Probiotics
- Antibiotic therapy for small intestine bacterial overgrowth (SIBO)

- **Immune system**

The CNS is the organ system most often involved in patients with ME/CFS, FM, and ES/MCS, but it does not act alone. Psychoneuroimmunology is the study of the well established, bidirectional communication between the brain and the immune system, in which the limbic system plays an important role.[989] [990] [991] [992] Numerous studies of ME/CFS and fibromyalgia have demonstrated involvement of the immune system, although these findings are inconsistent.[993] [994]

Multiple studies of ME/CFS have sought evidence for ongoing, active infection with or reactivation of a variety of viral infections, most notably herpes virus, Epstein-Barr virus and cytomegalovirus.[995] [996] [997] [998] However, the question still remains whether virus reactivation triggers ME/CFS in a subset of patients or viral infection reactivation is yet another outcome of a ME/CFS episode triggered by other agents.[999] Patients with ME/CFS appear to have a variety of immunological abnormalities, which suggest they may have an infection, and that the immune system is chronically activated in response.[1000]

Similarly, patients with fibromyalgia also demonstrate involvement of the immune system.[1001] Different types of autoantibodies, such as antinuclear antibodies (ANA) and anti-thyroid antibodies, are more likely to be found in fibromyalgia patients.[1002] [1003] Moreover, there is a relationship with fibromyalgia and autoimmune disease.[1004] [1005] [1006] [1007]

Many of these patients also have allergies and food sensitivities, suggesting that therapy can have a positive influence on the outcome of these disorders.[1008] Assessments include:

- Skin prick testing (inhalants and foods, when indicated)
- Intradermal serial dilution titration (inhalants and foods, when indicated)
- Patch testing
- Assessment of cytokines

Treatments include:

- Environmental control and avoidance of identified triggers (e.g. mould, dust mites etc. and non-tolerated foods)
- Desensitization
    - subcutaneous standard or optimal dose
    - low dose antigen therapy
    - sublingual

One of the postulates in the 1990s to explain ES/MCS was neurogenic inflammation. This is a well-defined physiological mechanism by which mediators are directly released from sensory nerves to produce-vasodilatation, edema, and other manifestations of inflammation.[1009] Particulate matter can induce neurogenic inflammation via TRPV1 receptors, which lends some support that it occurs in ES/MCS.[1010] However, little is known about the role of airway

neurogenic inflammation in human diseases, although it has been studied in detail in laboratory animal models.[1011]

In one study of patients with contact allergy, there did not appear to be a relationship with their skin and respiratory symptoms and positive skin prick tests for proteins.[1012] On the other hand, there was an association of respiratory reactions to chemicals, such as perfumes, with cutaneous reactions based on positive patch tests in patients reporting chemical sensitivity. The mechanism responsible for positive patch tests to chemicals appears to involve the innate inflammatory immune response, involving reactive T helper 1 and CD8 T cells,[1013] and it appears to be induced by oxidative stress.[1014] Consideration must be given to patch testing patients with ES/MCS as a potential aid in identifying specific chemical sensitivities.

- **Endocrine system**
  -Hormonal Deficits
  Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been linked to the pathophysiology of ME/CFS and fibromyalgia.[1015] Several studies have reported the results of unstimulated plasma and salivary cortisol levels in patients with ME/CFS. Some, but not all, reported significantly lower blood cortisol levels compared with healthy controls. However, meta-analysis of the data published from the mid-1960s to 2010 reveals that patients with ME/CFS have significant hypocortisolism, but the reduction is more modest when not stimulated.[1016] Women have more marked reductions. There can also be a flattening of the diurnal rhythm.[1017] [1018]

  When challenge tests are used to assess the hormone reserve capacity of the HPA axis, the majority of published tests on ME/CFS patients demonstrate a blunted response to challenge.[1019] Similarly, these challenge tests demonstrate hypocortisolism in women with fibromyalgia.[1020] [1021]

  Cortisol exerts negative feedback control on corticotrophin-releasing hormone and adrenocorticotrophic hormone (ACTH) secretion via the glucocorticoid and mineralocorticoid receptors in the hippocampus, the hypothalamus and the pituitary gland. Since the levels of cortisol are low in patients with ME/CFS, one of the suggested mechanisms underlying the chronic hypocortisolism is hyper-responsiveness of these corticosteroid receptors, leading to an enhanced negative feedback mechanism. In fact, this has been demonstrated by several suppression tests.[1022] [1023] [1024] ME/CFS patients with comorbid depression have more suppression.[1025]

  Unfortunately. the evidence of benefit in patients with ME/CFS from low dose steroid use is weak.[1026] Changes in the HPA axis in patients with ME/CFS is likely an epiphenomenon of the illness rather than of particular etiological significance.[1027] Nevertheless, it has been observed that those patients with low cortisol levels or flattened diurnal variation respond more poorly to treatment.[1028] [1029] [1030] These tests might help to determine prognosis.

- Body Mass Index

There is an association with ME/CFS, and high waist circumference and metabolic syndrome.[1031] The number of metabolic syndrome factors is also significantly correlated with worse fatigue. People who are overweight are more likely to have fibromyalgia.[1032] Overweight and obese individuals with ME/CFS demonstrate poorer functioning.[1033] In fibromyalgia, the symptoms are more severe if the BMI is higher,[1034] [1035] [1036] and there is a positive correlation with the number of tender points.[1037]

An abnormal BMI is seen in two studies of children with ME/CFS. However, the results are conflicting; either low[1038] or high.[1039]

Patients with ME/CFS and/or fibromyalgia with an elevated BMI should be encouraged to lose weight. Given the evidence for oxidative stress, they should be informed about a calorie sparse, nutrient (antioxidants) dense diet. Options include vegan[1040] [1041] [1042] paleolithic[1043] [1044] and Mediterranean diets.[1045]

- **Treatment on a cellular level**

As already reviewed, environmentally linked conditions, including ME/CFS, FM, and ES/MCS, are associated with pollution exposure, poor detoxification, oxidative stress with cell dysfunction, including changes in mitochondrial function and upregulation of receptors. This primarily affects different organ systems according to genetic susceptibility or other, as yet unclear factors. There should be stabilization at least by lowering the total load on body defence mechanisms i.e. avoidance of toxins/symptom triggers.

Presently, pollution exposure can only be reduced via education and lifestyle changes to enhance avoidance. The body burden of exposures also can be reduced by detoxification, presently limited to exercise followed by heat depuration. Heat therapy reduces oxidative stress.[1046] [1047] [1048] [1049] Levels of heavy metals can be reduced by chelation,[1050] especially with antioxidant support.[1051] Whether the cell dysfunction due to the damage from oxidative stress can be at all reversed is not clear. Evidence to date suggests that diet, detoxification and antioxidant supplementation may be beneficial, but thus far, the evidence is low.

Treatment requires providing patient education, and multidiscipline, multiple treatments, individually developed for each patient, using the patient focused model of chronic care. Guidance needs to be developed by the medical leaders in the Hub in collaboration with experts from other centres, which will expand as research expands. When considering ME/CFS, FM or ES/MCS individually, the following assessments and treatments should be considered.

- **Specifics for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**

Measurements of the fatigue can be performed using the Multidimensional Fatigue Inventory scale, the Multidimensional Assessment of Fatigue and a pedometer.

The most important parameter for treatment appears to be pacing, consistent with the characteristic of the fatigue. There is conflicting evidence for graduated exercise, which may in part be dependent upon the severity of the illness.

The goal is self-management of usable energy, which can be guided with the use of an activity log. Mild graduated exercise may be prescribed, when appropriate. Patients need to be taught to monitor their exertion, which can be guided by appropriate pulse measurement, calculated by 60% Vmax or by 24 hour repeat cardiopulmonary stress testing.

One potential future treatment specific for ME/CFS is anti-B cell therapy using Rituximab. B cell immunophenotyping in these patients demonstrates abnormal proportions, with a greater number of naïve and transitional B cell subsets.[1052] Treatment with anti-B cell therapy using Rituximab has shown benefit in one randomized controlled trial of 30 patients.[1053] None of the participants in the Jurisdictional review had any experience with this treatment option.

- **Specifics for Fibromyalgia**

The diagnosis is made by the description of unexplained, widespread pain. Some objective evidence to support the diagnosis can be found in the physical examination (11/18 fibromyalgia tender points) and occasionally from an overnight polysomnogram demonstrating sleep abnormality. There is evidence for prolonged sleep latencies, low sleep efficiency and an increased amount of stage I non-rapid eye movement (non-REM) sleep, reduction in slow wave sleep and in REM sleep percentages, and increased number of arousals and restless leg movements. In particular, there are a number of reports describing the presence of alpha electroencephalographic (EEG) activity during non-REM sleep (phasic alpha activity, or "alpha wave intrusion").[1054]

<u>Ruling out other disorders</u>:
Fibromyalgia physical assessment screen for primary care[1055]
1. Tender point assessment (bilateral)
2. Joint evaluation (bilateral swollen or boggy joints on palpation)
3. Muscle strength evaluation for proximal muscle weakness
    - Deltoid
    - Biceps
    - Triceps
    - Hip flexors
4. Connective tissue signs
    - Alopecia
    - Rash (malar, photosensitive, or discoid)
    - Oral or nasal ulcers
    - Digital pits or ulcers
5. Multiple sclerosis (MS) signs or symptoms
    - Visual changes (unilateral partial or complete loss, double vision)
    - Ascending numbness in a leg or band-like truncal numbness
    - Slurred speech (dysarthria)
6. Screen laboratory tests
    - For all patients: comprehensive metabolic panel, complete blood count (CBC), thyroid-stimulating hormone (TSH), erythrocyte sedimentation rate (ESR)
    - Consider:
        - If any bilateral swollen joints: check rheumatoid factor (RF)

- If any connective tissue signs: check antinuclear antibody (ANA)
- If any proximal muscle weakness: check creatine phosphokinase (CPK)
- If any risk factor for hepatitis: check hepatitis C antibody
- If any sign or symptom of MS: consider further MS workup

Treatment

Quantification of the severity of pain plus its impact on function should be performed prior to treatment, in order to assess efficacy. This is best performed using the FIQ or FIQR.

Present recommendations for treatment of chronic pain:

- Exercise (aerobic, strength training, pool, Pilates and multi-component)
- Stretching/yoga
- Medication
  - Antiseizure medication
  - Antidepressant medication
    - SSRI/SNRI
  - Cannabinoids
  - Analgesics
- Treatment of sleep disturbance
  - medication
  - sleep hygiene

Presently, there is some evidence for the effectiveness of**:**

- Waon sauna therapy[1056]
- Hydrotherapy, which includes spa- and balneotherapy[1057 1058 1059 1060]
- IV therapy, thus far consists of one study using Myer's cocktail[1061] (which consists of vitamins B and C, magnesium and calcium[1062]). There is significant clinical observational evidence.
- Hyperbaric oxygen therapy[1063 1064 1065]
- Repetitive transcranial magnetic stimulation (rTMS)[1066 1067]
- Brain biofeedback, including transcranial magnetic stimulation (TMS), electroencephalography (EEG) neurofeedback and real-time functional MRI feedback[1068]
- Acupuncture evidence of effectiveness is mixed.[1069 1070 1071]
- Meditative movement therapies (qi gong, tai chi, yoga) are strongly recommended by the German S3 guidelines on fibromyalgia syndrome.[1072]
- Mind-body therapies (mindfulness)[1073 1074]
- Low Dose Naltrexone Therapy[1075]

- **Specifics for Environmental Sensitivities/Multiple Chemical Sensitivity**

The diagnosis is established by the history. One promising objective measure as a biomarker for the disorder is the capsaicin inhalation challenge, although caution with dosage will be required. Treatment consists of:

- Providing advice and education to create a chemical-free living space
- Environmental control - avoidance of inhalant incitants and food intolerances

- Support accommodation in the workplace
- Activated charcoal filter masks (e.g., N95-OV with activated charcoal)

Clinical observational evidence exists for the use of:

- oral supplements
- IV nutritional therapy
- daily oxygen therapy
- oxygen to treat reactions
- alkali salts

o Lowering the Xenobiotic Load

Various methods exist which may lower the xenobiotic load in humans. The question remains as to whether this could significantly improve detoxification, reduce oxidative stress, enhance cell function including the promotion of mitochondrial biogenesis, create measurable change in function in patients with environmentally linked conditions such as ME/CFS, FM, or ES/MCS, or have a positive impact on chronic diseases linked to the environment, including prevention of the development of multimorbidity.

However, there are many purported detoxification remedies with varying, including low or no scientific validation, 18 of which are reviewed by Stephen Genuis.[1076] On the other hand, supportive animal and case studies include interference with the enterohepatic circulation of organochlorine compounds and their metabolites[1077] [1078] [1079] using bile acid sequestrants (e.g., cholestyramine)[1080] [1081] [1082] or a non-absorbable dietary fat substitute (olestra).[1083] [1084] [1085] [1086] Fibre also interferes with enterohepatic circulation.[1087]

There are two old observational studies using sweat (heat depuration) to detoxify mercury[1088] and lead[1089] (available only in Russian) using sauna. The idea is based on finding drugs in sweat[1090] [1091] [1092] [1093] and enhancing their elimination via sweat induction (sauna).[1094] Physical exercise mobilizes lipids,[1095] [1096] which will also mobilize persistent organic pollutants,[1097] and uncontrolled and controlled small trials and observational studies demonstrate that subsequent sweating after exercise can reduce the xenobiotic load and/or reduce symptoms associated with known exposures.[1098] [1099] [1100] [1101] [1102] [1103] Several protocols have been described[1104] but not compared.

▪ Summary

The model of the OCEEH contains a central Hub and multiple Spokes, expanding across the province to provide access to care as close to home as possible.

The Hub will be an academic, tertiary healthcare center, providing specialized investigation and treatment to people referred primarily from primary and secondary healthcare providers, including the physicians in the Spokes. It will be responsible for the provision of health services through a range of tests and treatments, guiding and conducting research on etiological mechanisms, diagnostic tests and treatments, and effective health promotion techniques. It will be involved in developing education of health care professionals, patients and the public, as well as knowledge transfer resources and policy development. The Hub must have close and direct affiliation with a teaching hospital. It must be associated with academia. Multiple specialized

medical and other clinical staff as well as specialized equipment and space (which cannot be shared) will be required.

Physical requirements include being accessible to those patients with ES/MCS, knowing that special arrangements will need to be made for those who are severely sensitive.

Health professionals in the Spokes will utilize the environmental exposure history and chronological functional inquiry and will be capable of making the diagnoses and initiating recommended treatments for ME/CFS, FM and ES/MCS. The Spokes will provide generally safe facilities (having a fragrance-free policy and utilizing non-toxic cleaning and laundry products) and aim to provide a "safe room" for severely environmentally sensitive patients or contingencies. They will make use of the environmental exposure history in everyday practice to identify patients at risk for developing chronic conditions linked to the environment. They will work with the Hub to engage in innovative research, including evaluating assessment and treatment tools, to provide education programs and service in collaboration with Department of Clinical Public Health at the Dalla Lana School of Public Health, University of Toronto, and other universities.

The Hub and Spokes will integrate the responsibilities of individual and public health services, social services and policy enhancement, research, education and health promotion.

VI Building the OCEEH

- **Introduction and Steps Required**

The Hub must be built before the spokes, although collaboration with interested spokes should begin as soon as possible. The Hub must increase trained health professional capacity, update the tools presently being used, such as the clinical intake history and the environmental exposure history, and make them available online. It must further develop the present guidance for treatment in collaboration with experts from other centres. It must refine the teaching program for the Spokes, including all that is required for both medical and support staff. Once these are established, knowledge transfer to the Spokes can begin.

The allocation of responsibilities between the Hub and Spokes will be an ongoing and evolving process. There is a significant need for treatments to be made available in the Spokes model in various communities around the province. Therefore, best practices should be made available as soon as possible in the Spokes. Thus, the Hub should begin to develop this guidance for dissemination.

If the Hub hosts a forum of clinicians and researchers experienced in the assessment and treatment of people with ME/CFS, FM and ES/MCS, they may agree that promising practices could be made available in the Hub and Spokes and evaluated as case series with close attention to benefit, adverse effects, and help:harm ratio. Emerging practices can be evaluated in the Hub and Spokes under research protocols with external funding.

However, some emerging practices will require specific expertise and/or equipment and will therefore be restricted to the Hub location. For example, 24 hour repeat cardiopulmonary exercise testing must be studied further to determine if it is reliable and necessary to design individual exercise and pacing programs for patients with ME\CFS. If so, the recommended protocol can be transferred to community hospitals with suitably trained personnel, and made accessible to local Spokes, by referral.

If other treatments are found to be efficacious, such as specific intravenous (IV) therapies, transferring this knowledge directly to the Spokes and other practising physicians will make these treatments more available to patients in each local community. This knowledge transfer can occur via medical conference, grand rounds, Ontario Telemedicine Network, and publications. Thus, guidelines for the assessment, diagnosis and treatment for ME/CFS, FM and ES/MCS will continue to be updated by the Hub.

The OCEEH must provide the highest quality of healthcare for ME/CFS, FM and ES/MCS. The designation of centre of excellence mandates that the expertise and care it provides is comprehensive and evidence-based or -informed. It must yield the best quality outcomes and high patient satisfaction. It will involve teams of healthcare professionals with the primary goal of meeting patients' needs and preferences. The approach to delivering care will be multidisciplinary; medical, other clinical and social. The OCEEH will pursue policy discussions to make services more accessible e.g. home care, ODSP etc.

The experts will set the bar for excellence and provide the leadership to guide the creation of the OCEEH, as follows. It is estimated that it will take up to two years to create and exapand the foundation, and then initiation of programing, maintenance and expansion could be rolled out over the next three years and thereafter.

- **Create the Foundation**

  - **Increase EHC Clinical Staff**

Immediately increase the EHC medical staff from 0.9 FTE to 4 FTEs physicians, including a Medical director, and restore other clinical staff. Presently, the wait list for consultation at the EHC is 13 months. Moreover, there is an immediate and significant demand for more physician time required to develop the foundation and programs for the OCEEH, which is extra challenging considering the early stages of this field.

  - **Begin training of Fellows**

Three quarters of the present staff at the EHC are over 65 years old. There is an urgent need to begin training of new physicians to build physician capacity. If funding can be guaranteed before December 2013, advertising for applications for Fellowship training can begin immediately. If so, training can begin in July 2014, at the onset of the new academic training year.

  - **Organize research projects for Fellows and Clinical Staff**

Organize literature review projects for the Fellows and clinical staff, followed by development and organization of online and paper resources for patients and primary care physicians.

  - **Organize workshop of experts to develop GRADE recommendations**

As reviewed above, provision of new tools for assessment and treatment can be made available as "best" and "promising" practices. Determination of these designations must be made by invited experts in systems-based medicine from national and international centres and organizations, and relevant experts in related fields, using GRADE as a guide for recommendations. This workshop requires expert facilitation, and will likely require at least three full days. It may also consider financial implications and suggest priorities. This would also assist the MoHLTC in projecting possible longer range costs.

  - **Upgrade and refine methods for data gathering**

Prior to the initial assessment at the Environmental Health Clinic at Women's College Hospital (EHC), patients are required to fill out an environmental exposure and comprehensive medical history form. Presently, the EHC uses the environmental exposure history developed more than 10 years ago by Dr. Lynn Marshall[1105], one of the EHC staff physicians. It was recently updated in 2013, but needs to be made electronic so that it can be completed online, and electronic data gathered with the patient’s permission.

The present comprehensive medical history form, which was developed for research and not clinical purposes, is inadequate. While symptoms in the functional enquiry are listed, it is

missing chronology, severity, impact on function, and links to the environment. It needs to be updated, and should be the first priority for the development of the Hub and Spoke model.

Once this form is updated, it needs to be uploaded online. This will allow patients to fill it out online, piecemeal if necessary, or to download it, and fill out various sections when expedient. Given the expected length of the questionnaire, this should ease the burden on patients, especially those with chronic fatigue. Furthermore, having this information returned online in an electronic form will simplify the data collection required for ongoing research, with the patient's consent. A data base registry will be created, using electronic medical records (EMR).

Putting the form online may also be helpful to primary care providers, CHCs, FHTs and public health.

- **Develop specific Hub agreements**

The importance of collaborations/associations to create a credible health provision model worthy of the designation of Center of Excellence have been reviewed above. Specific agreements must be obtained with one or more teaching hospital(s), the University of Toronto, and the Dalla Lana School of Public Health. Most significant is the agreement with a teaching hospital. Because of the costs involved, the importance of guaranteed designated funding from the MoHLTC or LHIN cannot be over emphasized.

- **Prepare education program for Spokes**

Provision of care by health practitioners in the Spokes cannot begin without additional training. Collaboration with Spokes and primary care providers is important to develop the most effective education program, aiming for a consistent quality approach to most aspects of care in both Hub and Spokes.

There are 5 Mainpro-C education modules for health care professionals available from the Ontario College of Family Physicians (OCFP).

One is called "Climate Change and Health: Should we care? Can we make a difference?" This presentation describes the health effects of climate change, including increased heat and smog, waterborne disease and Lyme disease and provides tools for family physicians to deal with clinical cases, as well as reducing the carbon footprints of our medical activities. These tools should be taught to all primary care physicians. Those practicing in the Spokes can take the lead in the dissemination of this knowledge in their medical regions.

The other four Mainpro-C modules were developed by the staff physicians at the EHC and the Environmental Health Committee of the OFCP. They are more specific with respect to the impact of environmental chemical exposures on health and are divided according to the stages in life. They include the following:

1) Pregnancy & Early Childhood Environmental Exposures: Impacts, Prevention, Diagnosis and Management
2) Risks of Environmental Exposures to Child and Adolescent Health and Remedies in Clinical Practice

3) Chronic Pain, Fatigue and Chemical Intolerance Linked to Environment Exposures: Office Assessment and Management
4) Common Chronic Illnesses and the Environment

These four modules were initially developed by different authors to be provided separately. Feedback from attendees at the Continuing Medical Education Mainpro-C program (Environment-linked Illnesses: Prevention, Diagnosis and Management from Preconception to Old Age) in March 2013, which included all 4 modules, indicated that there was overlap in content, which required streamlining. Furthermore, provision of more detail for practical application (e.g. self education and management groups) will also likely be necessary before offering training. It is important to note that these modules begin to address the clinical aspects of multimorbidity.

- **Accreditation in Environmental Health**

Education courses already designed and taught online and in the classroom by physicians in the EHC for Environmental, Occupational and Public Health should be integrated into the required training program for a certificate in Environmental Health granted by the University of Toronto, and possibly by the Northern Ontario School of Medicine (NOSM). Application for special interest designation of Environmental Health in the CFPC should then be sought. Combination of these courses with an MPH program may be possible.

- **Develop updated hospital guidelines**

Patients with ME/CFS, FM or ES/MCS do not often have admissions for their conditions, but they are prone, like everyone else, to need emergency care or admission for injuries or illnesses, or to have elective surgery. Hospital guidelines are required to overcome barriers to safe access for patients with ES/MCS during admission to emergency, day surgery, outpatient clinics, inpatient hospital wards, and intensive care facilities. Several guidelines are available,[1106] [1107] [1108] [1109] but are considered to need updating by the Medical Advisory Committee. They need to be updated by environmental physicians working with hospital administration, pharmacy, anaesthesia, emergency, housekeeping, laundry, engineering and maintenance. They need to be implemented and studied for effectiveness.

Some information is available for ME/CFS patients undergoing surgery.[1110]

Once these guidelines have been established, they can be provided to patients and their physicians planning for elective admissions. Not only will this be good for patient care, but also it will save the hospital staff time and effort. Knowledge transfer to the Ontario Hospital Association will assist in implementing these guidelines in hospitals across Ontario.

These guidelines will be valuable to Community Care Access Centres regarding home care.

- **Expand the Foundation**

- **Begin education of Spoke health care providers**

Training programs provided by the EHC physicians will be initiated for all the healthcare providers involved in the Spokes. Most important, consideration must also be given to

provide shadowing by healthcare practitioners at the EHC and designated community clinics before assessment and treatment programs can be administered in the Spokes.

- **Develop education modules for medical students and residents, and graduate physicians**

Case-based learning and problem-based tutorial programs need to be developed. A start has been made at NOSM, which can be built upon. The ultimate goal would be to include Environmental Health in many aspects of the medical curriculum. All graduating medical students should have developed the skills to take an environmental exposure history, and know when it should be applied clinically.

- **Develop education modules for nursing and other health professionals**

The above-mentioned Mainpro-C modules can be adapted for training other health professionals, including nurses, physiotherapists, occupational therapists, respiratory technicians, dietitians and particularly social workers, who must be able to address housing, diet needs and accommodation issues. A specific education program might be developed to train health coaches re lifestyle.

- **Organize workshop of experts to set research agenda, evaluate criteria and initiate research collaborations**

While the OCEEH must proceed with implementing the very best evidence-based and GRADE-supported approaches to the management of these patients, the base of such evidence is sparse. It is marked by a paucity of well-conducted research on potential fundamental mechanisms of the diseases and trials of therapeutic approaches that are developed based on the understanding of such mechanisms. Thus, research (the development of research faculty, hypotheses, and externally-funded projects) will be critical to coming up with improved strategies for the clinical management of these patients.[1111] The OCEEH, by creating a community of patients and clinicians with a strong relationship with scientists in a leading Division of Clinical Public Health in a top Faculty of Public Health, will be in a strong position to pursue such research.

Initiating this program will involve a workshop (preferably 3 days) of clinician and research experts from Canada and international centres/professional organizations to set the research agenda, including evaluation strategies, and begin collaborations that will lead to submission of research proposals to the three major research funding sources in Canada.

Linkage with one or more academic hospitals interested in research would be helpful as they would have the infrastructure for research and would attract skilled researchers.

- **Develop programs for University Sciences**

Many programs already exist in colleges and universities, which educate students in a variety of areas regarding changes in the environment (e.g. humanities, natural and social science, environmental policy and urban planning). However, none of them teach about the significance of environmental factors on human health, from preconception to old age. Useful small research projects should be incorporated into these programs.

- **Develop education modules for patients**

Environmentally-linked illnesses and conditions are chronic and thus require self-management. Patient education is a major component. Education modules need to be developed and can include oral individual or group sessions, as well as written information supplied by CD, DVD or downloading from the OCEEH future website.

Successful group education programs have been developed already by staff physicians at the EHC. It would be helpful if they were re-established e.g. the group education program models developed by Dr. Alison Bested and by Drs. Annette Lorenz and Lynn Marshall.

- **Develop modules for self-management**

The fourth Mainpro-C module, title Common Chronic Illnesses and the Environment provides information for physicians to help their patients achieve self-management of chronic complex conditions including ME/CFS, FM, and ES/MCS.

Study of the Stanford training program[1112] by Hub clinical staff would be helpful, including training a Hub physician and possibly a social worker to become a Stanford Master Trainer who would become a T-Trainer, who trains master Trainers in Spokes. Training of physicians and other clinical staff in the Spokes will enable the establishment and supervision of sustainable self-management support programs.[1113]

- **Develop safe rooms in Spokes**

Access to primary health care must be available for those with ES/MCS. Exact specifications required are unknown at present. Barriers to care due to exposures to normal indoor air contaminants routinely occur in waiting rooms, at reception, in examining rooms, and public areas containing patient groups (self-management and community outreach). Given the dynamics of indoor air, the quality of "safe rooms" to be provided for patients with severe ES/MCS will be partially dependent on the quality of the indoor environment of the clinic in which they reside.

Enforcing a scent free policy and use of non-toxic, generally well-tolerated cleaning products will be mandatory. Guidelines for lighting, ventilation, air filtration, cleaning and maintenance need to be established. It is strongly recommended that they are developed by a multidiscipline team, including building engineers, architects and health practitioners all of whom should have experience dealing with indoor air quality and people with ES/MCS. Collaboration with the engineering experts at the Material Emissions Testing Facilities of the National Research Council[1114] should also be considered.

- **Create temporary lodging for patients attending the Hub**

Some patients referred to the hub for consultation will likely require extended stays in order to have multiple discipline assessments and case conference(s). Some may be partaking in specific treatment programs. They must be provided with safe lodging during their stay. This is not only necessary for provision of access to care. It is also mandatory in order to eliminate any interference from outside (environmental) sources which may impact on the measured results of assessments to be performed, whether they are functional or physiological.

However, there are no criteria established to ensure a healthy environment.[1115] We do not have guidelines for ventilation to control pollutants at this level. The information to date is experiential and anecdotal. The threshold for sensitivity to chemical pollutants varies individually from day to day and from person to person. Guidelines to accommodate are based on trial and error. The goal is to maximize ventilation, to filter the incoming air, and reduce indoor contamination by choosing materials with low emissions.

A review of the peer-reviewed literature published from 1995 to 2010 found 77 studies that measured chemical pollutants in residences in the United States and in countries with similar lifestyles.[1116] The review considered all chemical contaminants measured in the residential indoor air. There were 267 different pollutants found.

In 1995, the Canada Mortgage and Housing Corporation (CMHC) constructed a prototype research house for environmentally sensitive patients.[1117] They provided low off-gasing building materials and furnishings, ventilation and filtration. However, no studies were published with respect to measurements of indoor air quality. Eventually, this building was sold to the Department of Respirology at the Ottawa Hospital, General Campus, and used as an education library for patients with asthma.

The Environmental Health Center in Dallas, Texas provides lodging for patients.[1118] According to their website, this housing includes:

- a clean and updated HVAC system with environmentally correct components utilizing the most effective filtration media (not described)
- filtered kitchen and shower water
- two Austin or AllerMed air purifiers
- ceramic tile, non-toxic grout floors and non-toxic paint
- organic cotton sheets, towels, mattresses and shower curtains; linens are changed twice a week and rooms are cleaned with non-toxic products twice a week with daily inspections
- all furniture is made from hardwood or metal

It is recommended that an expert group be formed to determine the requirements for the provision of safe rooms and housing for those with ES/MCS. The group should be comprised of building engineers, architects and environmental health practitioners with an expertise and experience in indoor air quality needs for the environmentally sensitive population.

- **Initiate Programming**

    - **Begin provision of care in Spokes**

It is a prominent goal for the OCEEH to provide province-wide state-of-the-art, systems-based healthcare, including environment as a determinant of health, in order to meet the needs of those with ME/CFS, FM and ES/MCS and their families. It is also a key goal to incorporate education/health promotion and social/policy support. The long term success of this model is dependent on first building a solid foundation. It necessitates good bilateral communication between the Spokes and their referral sources, and the Spokes and the Hub.

- **Develop teleconference and e-consultation services for provision of consultations in remote areas**

Waiting for specialist care remains the most important barrier to health care access in Canada,[1119] especially in underserved areas. Telemedicine can improve access to medical expertise and increase care delivery. It can also increase access to professional education, in this case involving the Hub[1120] and spokes across the province. However, it requires specialized and expensive equipment, which makes it inaccessible to most primary care providers.

An electronic consultation (e-consultation) system was recently successfully piloted in the Champlain Local Health Integration Network (LHIN), encompassing Ottawa and its surrounding communities.[1121] It allowed primary care providers to submit patient-specific clinical questions to a specialist, who provided answers or requested additional information before providing advice, within one week. This same service could be provided regionally by the Spokes, with further consultation being passed upwards to the Hub when necessary.

- **Further develop research agenda and research associates**

There are many gaps in knowledge about environmental health and chronic complex conditons. The pathology of ME/CFS, FM and ES/MCS is not well understood. While a strong similarity exists between the three conditions (ME/CFS, FM and ES/MCS) and other chronic diseases, in terms of overlapping symptoms and patient profiles, the upstream etiology and "branches" of mechanistic pathways that ultimately result in the common symptoms remain unclear but is a critical area of research.

The hub will develop associations with other medical disciplines and associated research units and international professional associations, as well as other centres of excellence with links to the environment, and other groups and institutions mandated to seek and transfer knowledge to improve the environment and reduce its impact on health.

The Dean of the Dalla Lana School of Public Health has expressed interest in being a partner in this effort, particularly in relation to creating and executing a research agenda, recognizing that any research requiring significant resources will need to be supported by additional grant applications.[1122]

- **Apply for research funding**

Once the research agenda and foundation is in place, applications can begin for funding defined research projects by three federal granting councils: Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council (SSHRC). Hopefully, the MoHLTC will encourage these funding councils and other agencies to fund worthy OCEEH grant applications.

- **Initiate research programs**

With the agreement of experts in the field, clinical case series can be initiated in the Hub and Spokes for “promising” practices, and the Hub plans to submit formal research protocols for “emerging” practices. Collaboration of the OCEEH with the Division of Clinical Public

Health in the Dalla Lana School of Public Health and the Department of Family and Community Medicine in the Faculty of Medicine at the University of Toronto will enhance this initiative. Being closely linked with an academic health sciences centre could be helpful in attracting researchers in other areas, such as genetics, and would assist in providing research infrastructure. Other resources and collaborations will be sought.

This is an important field that has been neglected with almost no funds (please see Table 1, Chapter I), and research in this area may have important impacts on understanding etiology, management of ME/CFS, FM and ES/MCS and other chronic complex conditions, perhaps preventing multimorbidity. Preventing multimorbidity would help manage these conditions, sustain the health care system and enhance the patient experience.

The Networks of Centres of Excellence is a Canadian government funding initiative allocated through the three federal granting councils. As stated on their website, this network obtains funds for collaboration between companies, universities, hospitals, governments and communities to generate knowledge translation into results, such as better health care. The Ontario Centre of Excellence in Environmental Health (OCEEH) should explore being a part of this network, which could also increase the likelihood of obtaining research funds.

- **Create an OCEEH website**

An attractive website needs to be built to promote the OCEEH, provide resources for patients, researchers, and the public, as well as linking to other associated sites.

- **Maintenance and expansion**

The following list speaks to the future of the OCEEH and its commitment to excellence.

1. Gather research data
2. Refine assessments and treatment protocols
3. Disseminate knowledge
4. Network
5. Continue research in Hub and Spokes with academic collaborators
6. Expand Spoke availability in Ontario

There is an obvious need and great potential to create a first-class Centre of Excellence in Environmental Health in the Province of Ontario. It is important to carefully build it and maximize patients' access, equity, choice, value and quality in health and social services.[1123]

- **Summary**

In order to provide the highest quality of health care for people with ME/CFS, FM and ES/MCS, the Hub must be built before the Spokes, although collaboration with interested spokes should take place as soon as possible. The Spokes may be in Community Health Centres or Family Hrealth Teams and will eventually spread to other primary health care practitioners around the province.
The Hub must update the tools presently being used, develop guidance for treatment, and refine and provide the teaching program for the Spokes. Building the OCEEH requires the first steps

oulined in Table 5 to create and expand the foundation, and the next steps outlined in Table 6 to initiate, maintain and expand the program.

Table 5 First Steps to Building the OCEEH

Create the Foundation	Expand the Foundation
Immediate increase of EHC medical staff to 4 FTEs, including a Medical Director	Begin education of Spoke health care providers, starting with an introductory course
Begin training of Fellows to expand medical staff	Develop education modules and case-based training for medical students, residents, Spoke providers and primary care providers
Organize research projects for Fellows and clinical staff	Develop education modules for nursing and other health professionals
Organize workshop (preferably 3 days) of clinical and research experts to develop GRADE recommendations, and advise re "promising" practices	Organize workshop (preferably 3 days) of clinical and research experts to set research agenda, including evaluation strategies, and initiate research collaborations
Upgrade and refine methods for data gathering	Develop programs for University Sciences (humanities, natural and social science, environmental policy and urban planning)
Develop specific Hub agreements with the university(ies) and teaching hospital(s)	Develop education modules for patients
Prepare education program for Spokes	Develop modules for self-management
Develop university certificate in Environmental Health, and apply for CFPC special practice designation	Develop safe rooms in Spokes
Develop updated hospital guidelines	Create temporary lodging for patients attending the Hub

Table 6 Next Steps in Building the OCEEH

Initiate Programming	Maintenance and Expansion
Begin provision of care in Spokes, and provide support consultations	Gather research data
Develop teleconference and e-consultation service for provision of consultations in remote areas by Hub and Spokes	Refine assessments and treatment protocols
Further develop Research Agenda and Research Associates	Disseminate knowledge
Initiate research programs; case studies and research protocols	Network
Apply for Research Funding	Continue research in Hub and Spokes
Create a website	Expand Spoke availability in Ontario

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Note: To save space, only the primary author is named. Most of these citations are readily available in Medline.

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- Leaders Teach / Facilitate community workshops for people with chronic diseases;
- Master Trainers In addition to what Leaders do, Master Trainers train Leaders
- T-Trainers In addition to what Master Trainers do, T-Trainers train Master Trainers

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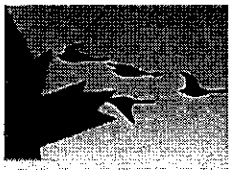
APPENDIX A



Overlapping diagnoses
For 23 Chronic Condition Cohorts
Source: Canadian Community Health Survey 2005

The Canadian Community Health Survey (CCHS) is an important source of information about health issues in Canada. Statistics Canada released survey results for 2005 in database format on a "Public Use Micro-data File". Data have been extracted from this file .

The target population of CCHS 2005 was Canadians age 12 and up, with several exclusions:

- persons living on Indian Reserves
- residents of institutions
- full time members of Canadian Armed Forces
- residents of certain remote regions.

Overall, there were 27,126,165 Canadians in the target population. This is about 98% of Canadians age 12 and up.

Statistics Canada interviewed 132,221 Canadians (about 1 in every 200 members of the target population). Respondents were asked a series of health related questions. Their responses were weighted to arrive at estimates for the target population.

Respondents were asked about chronic health conditions as follows:

"Now I'd like to ask you about certain chronic health conditions which you may have. We are interested in long term conditions, which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional. Do you have .....".

Respondents were read a list of chronic health conditions and asked to respond to each one. Possible answers include yes, no, don't know, refuse, and not stated. The chronic condition cohorts in this fact-sheet include only those people who responded "yes" to that condition. The same individual may be included in several chronic condition cohorts.

It is very important to remember that CCHS data is based on self-reporting of diagnosis. The data may or may not reflect how many people actually have the chronic condition. Note also that the statistics are based on sampling and therefore are only estimates.

CCHS was not conducted in 2006. It was conducted in 2007, 2008 and 2009 but the questions on Chronic Fatigue Syndrome, Fibromyalgia and Multiple Chemical Sensitivities were omitted.

The National ME/FM Action Network represents Canadians with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Fibromyalgia. Ms Parlor worked as a professional data analyst for many years.

Prepared by Margaret Parlor, President, National ME/FM Action Network www.mefmaction.net
2009-02

National ME/FM Action Network

	% of people with MCS having this additional diagnosis	% of people with CFS having this additional diagnosis	% of people with FM having this additional diagnosis	% of target population having this diagnosis
Food Allergies	27.3	16.2	19.4	7.2
Other allergies (not food)	61.1	42.8	51.0	26.6
Asthma	25.7	21.3	21.2	8.3
Fibromyalgia	10.0	28.5	n/a	1.4
Arthritis/rheumatism	38.5	47.1	58.8	16.4
Other back problem (not arthritis or FM)	39.7	51.9	50.4	18.8
High blood pressure	24.5	28.3	30.6	14.9
Migraine headache	26.3	32.7	28.0	10.5
Chronic Bronchitis	11.4	11.5	9.3	2.5
Diabetes	6.9	11.6	11.0	4.9
Epilepsy	1.3	2.1	1.4	0.6
Heart disease	9.8	14.9	10.5	4.7
Cancer	2.3	4.4	3.5	1.4
Stomach/Intestinal ulcers	8.9	14.6	12.3	3.1
Effects of stroke	2.5	5.4	3.6	1.1
Bowel disorder	13.1	19.7	23.7	3.9
Cataracts	9.1	10.5	10.3	4.2
Glaucoma	3.9	3.5	3.1	1.5
Thyroid condition	13.8	20.0	17.0	5.6
Chronic Fatigue Syndrome	9.9	n/a	24.4	1.2
Multiple Chemical Sensitivities	n/a	17.7	15.4	2.2
Mood disorder	15.9	34.4	22.3	5.6
Anxiety Disorder	14.5	24.5	15.5	4.4

	People with MCS are roughly x-times more likely than the target population to have this diagnosis	People with CFS are roughly x-times more likely than the target population to have this diagnosis	People with FM are roughly x-times more likely than the target population to have this diagnosis
Food Allergies	4	2	3
Other allergies (not food)	2	2	2
Asthma	3	3	3
Fibromyalgia	7	20	n/a
Arthritis/rheumatism	2	3	4
Other back problem (not arthritis (	2	3	3
High blood pressure	2	2	2
Migraine headache	3	3	3
Chronic Bronchitis	5	5	4
Diabetes	1	2	2
Epilepsy	2	4	2
Heart disease	2	3	2
Cancer	2	3	3
Stomach/Intestinal ulcers	3	5	4
Effects of stroke	2	5	3
Bowel disorder	3	5	6
Cataracts	2	3	2
Glaucoma	3	2	2
Thyroid condition	2	4	3
Chronic Fatigue Syndrome	8	n/a	20
Multiple Chemical Sensitivities	n/a	8	7
Mood disorder	3	6	4
Anxiety Disorder	3	6	4

APPENDIX B

WOMEN'S COLLEGE HOSPITAL
Health care for women | REVOLUTIONIZED

Environmental Sensitivities-Multiple Chemical Sensitivities Status Report

Advances in Knowledge, and Current Service Gaps

Environmental Health Clinic
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October 31, 2010
Updated February 17, June 2, August 10, 2011

Environmental Sensitivities-Multiple Chemical Sensitivities (ES-MCS) Status Report Advances in Knowledge, and Current Service Gaps

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Environmental Sensitivities-Multiple Chemical Sensitivities (ES-MCS) Status Report Advances in Knowledge, and Current Service Gaps

Executive Summary:

There have been many advances in understanding of ES-MCS since the mid-1990's, including validation of consensus case criteria and refinement thereof, funded by the Ontario Ministry of Health; proposal and evolution of testing of etiological hypotheses; prevalence, co-morbidity and disability data from the U.S. and Canada; and development of diagnostic, therapeutic, education and health promotion strategies. Academically-affiliated, Ministry of Health-funded referral clinics have been established in Ontario and Nova Scotia, and a Paediatric Environmental Health Specialty Unit integrated into academically-affiliated paediatric services in Alberta. MCS has been recognized as a disability requiring accommodation by the Ontario (2000) and Canadian (2007) Human Rights Commissions.

While the causes and underlying mechanisms of MCS are still not fully understood, there has been increased recognition of the large number of ubiquitous chemicals to which we are all exposed in varying amounts and combinations. Their potential impacts on body defence mechanisms and the contributions of genetic and epigenetic susceptibility factors and metabolic consequences have been hypothesized and are slowly being tested. The science of toxicology has evolved substantially and there is a move away from "physical" versus "psychological" models of disease/illness to the multiple determinants of health model utilized by the World Health Organization (WHO). There is also increasing understanding of unique responses to low doses.

Prevalence surveys have now been conducted in several of the United States for both physician-diagnosed and self-reported MCS. The Canadian Community Health Survey has reported health professional-diagnosed MCS in those over the age of twelve in Canada (2.4% in adults, 3.4% in women and in those with the lowest household income), and has shed light on demographics, functional impacts, and the influence of poverty as well as of co-morbid conditions. In spite of high prevalence and morbidity, there are significant gaps in health, social and housing services.

Diagnosis of MCS in both the provincial Environmental Health Clinic in Ontario and the Nova Scotia Environmental Health Centre is accomplished by ruling out or carefully treating other conditions that could account for or contribute to the presenting symptoms, by assessing each individual's exposures, and by determining whether or not the person's pattern of symptoms fits validated consensus criteria. A few objective tests are helpful in assessing body burden of various chemicals, functional status, co-morbid allergies, and diminished blood flow to the brain.

There being a duty to provide care and not abandon patients with newly reported complex clinical conditions to their own devices, treatment for ES-MCS has evolved based upon approximately 50 years of international clinical case reports and case series, supported by treatment surveys. It is empirically evidence-informed best practice; individualized, holistic and person-centred. It focuses on assisting patients at the earliest possible opportunity to reduce their exposures to their unique symptom triggers and known hazardous chemicals, optimizing their internal processing and elimination of such chemicals through nutrition and dietary fibre, and reducing body burdens when necessary and possible. If co-morbid allergies are not relieved by environmental controls, ventilation or filtration at home or in the workplace, they may be helped by individualized desensitization or medications to relieve symptoms. Dysbiosis (imbalanced microflora in the gastrointestinal tract) may be helped by probiotics and stabilization of pH. Patients are encouraged and supported to take control and self-manage, instituting and nurturing elements of good health. While early diagnosis and prompt treatment can significantly improve individual functioning/quality of life and reduce healthcare utilization, primary prevention through partnering and health promotion is the ultimate goal.

Background:

In response to the Environmental Health Association of Ontario's request for more information on the available scientific evidence underpinning current assessment and management of ES-MCS, this Status Report was developed by the provincial Environmental Health Clinic (EHC) physicians as an explanatory review of the evolution of knowledge of ES-MCS. Although EHC physicians have previously participated in systematic literature reviews on environmental health topics, the financial resources were not available to conduct such a review on ES-MCS at this time. None of the contributors to this report received any remuneration.

Ongoing input on issues included in this report has been provided by members of the Environmental Health Association of Ontario, Myalgic Encephalomyelitis Association of Ontario, and the National ME-FM Action Network, as well as our partners in the Canadian Coalition for Green Health Care, Canadian Partnership for Children's Health and the Environment, and Toronto Cancer Prevention Coalition. Consumer advisors to the EHC, Eleanor Johnston, Varda Burstyn and Lin Grist, as well as EHC Manager Lynn Carter and researcher Dr. Margaret Sears, were consulted and their suggestions to improve structure and clarity of language were gratefully received.

Overview of Efforts with regard to ES-MCS:

With emerging conditions such as ES-MCS, there are many research questions to be answered, including about description, definition, etiological contributors/mechanisms, assessment, diagnosis, prevalence, functional status, and health care utilization, while providing increasingly targeted treatments as evidence evolves. There have been advances in validation of consensus ES-MCS case criteria and in assembling pieces of the etiological puzzle in Ontario Ministry of Health-funded research, in compilation of prevalence data by Statistics Canada via Canadian Community Health Surveys, and in determining functional status and healthcare utilization while providing clinical care in government-funded clinics in Ontario and Nova Scotia. ES-MCS has now been recognized as a disability requiring accommodation through avoidance of symptom-triggering exposures and toxin reduction by the Canadian and Ontario Human Rights Commissions, but there remain many gaps in primary care and specialty health services, income/other social supports, and safe, affordable housing**.**

In order for multi-centre research to provide the most useful ever-developing picture of a condition, it is important that there be agreement on the definition/case criteria for what is being studied, as outlined below. Patients' needs cannot ethically be ignored while answers to the many research questions slowly accrue, with some uncertainty almost always remaining. Health, social, and housing services need to continually improve, not only to meet immediate patient needs, but also to protect all citizens from health impacts of known or suspected environmental hazards. An ounce of protection can truly prevent a pound of costs- to individuals, the health/social service systems, and the economy.

Case Criteria Development

- In the 1980s and 90s various criteria had been proposed for defining a case of MCS, also called environmental sensitivities, hypersensitivities, illness, intolerances, or toxicant-induced loss of tolerance, names which were inclusive of a broader range of environmental agents. Based on the previous work of Nethercott et al (Nethercott JR, Davidoff LL, Curbow B, et al. Multiple chemical sensitivities syndrome: toward a working case definition. Arch Environ Health 1993;48:19-26), a list of criteria that reflected an internationally *consistently observed pattern* of symptom presentation was agreed upon by 34 North American clinicians and researchers who collectively had experience with thousands of MCS patients (Bartha et al. Multiple Chemical Sensitivity: a 1999 consensus. Archives of Environmental Health, May/June 1999; 54(3): 147-9).

- Part of the definitional challenge was, and is, related to the fact that symptoms and signs triggered by low level exposures to environmental agents vary among affected individuals and within individuals depending on inciting agents as well as the doses, timing, and combinations of exposures. Also, while there can be abnormal physical and laboratory findings, the same findings are not *consistently* abnormal in all patients or in individual patients all the time (Thomson GM, Day JH, Evers S, et al. Report of the Ad Hoc Committee on Environmental Hypersensitivity Disorders. Ontario Ministry of Health, 1985:17-18).

- The 1999 consensus criteria were subsequently validated using a reproducible questionnaire (McKeown-Eyssen Gail E., Sokoloff Ellen R., Jazmaji Vartouhi, Marshall Lynn M., Baines Cornelia J. Reproducibility of the University of Toronto self-administered questionnaire used to assess Environmental Sensitivity, American J. of Epidemiology, 2000; 151 (12): 1216-22). In addition, four *specific* neurological symptoms were found to discriminate between most patients and controls in a study by the Ministry of Health-funded Environmental Hypersensitivity Research Unit at the University of Toronto (McKeown-Eyssen GE, Baines CJ, Marshall LM, et al. Multiple Chemical Sensitivity: Discriminant validity of case definitions; Arch Environ Health, 2001; 56(5):406–12) (**Table 1**). A checklist of the criteria is posted on the Ontario College of Family Physicians website for use by practising clinicians (http://www.ocfp.on.ca, → Environmental Health Committee).

Table 1:

Multiple Chemical Sensitivity Case Criteria

Multiple Chemical Sensitivity: A 1999 Consensus Bartha et al. Archives of Environmental Health, May/June 1999; 54(3): 147-9; Based on: Nethercott JR, Davidoff LL, Curbow B, et al. Multiple chemical sensitivities syndrome: toward a working case definition. Arch Environ Health 1993;48:19-26
▪ The symptoms are reproducible with [repeated chemical] exposure. ▪ The condition is chronic. ▪ Low levels of exposure [lower than previously or commonly tolerated] result in manifestations of the syndrome. ▪ The symptoms improve or resolve when the incitants are removed. ▪ Responses occur to multiple chemically unrelated substances. ▪ [Added in 1999]: Symptoms involve multiple organ systems.
Multiple Chemical Sensitivity: Discriminant Validity of Case Definitions McKeown-Eyssen GE, Baines CJ, Marshall LM, et al. Arch Environ Health, 2001; 56(5):406–12
▪ Having a stronger sense of smell than most people ▪ Feeling spacey ▪ Feeling dull or groggy ▪ Having difficulty concentrating

- Lacour et al suggested adding non-discriminating non-specific complaints of the central nervous system and functional disturbances in other organ systems to the case definition, but this would decrease discriminative ability. (Lacour M, Zunder T, Schmidtke K, Vaith P, Scheidt C. Multiple chemical sensitivity syndrome (MCS)- suggestions for an extension of the US MCS-case definition, Int J. Hyg. Environ. Health, 2005; 203:141-51).

- Since the validated combined MCS case criteria do not distinguish mild, moderate and severe MCS, functional status measures have been employed clinically as well. Further clarity in research on MCS of varying degrees of severity may be possible using six evaluated domains of questionnaire-based criteria for MCS (Kutsogiannis DJ, Davidoff AL. A multiple center study of multiple chemical sensitivity syndrome, Arch Environ Health, May/June 2001; 56(3):196-207- funded by Ontario Ministry of Health).

- The validated combined 1999 MCS consensus criteria and four specific neurological symptoms were used to select cases in subsequent case control studies funded by the MOH/MOHLTC at the University of Toronto (McKeown-Eyssen G, Baines C, Cole DEC, Riley N, Tyndale RF, Marshall L, Jazmaji V. Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR, Int. J. Epidemiol. July 15, 2004; 33: 1-8; Baines CJ, McKeown-Eyssen GE, Riley N, Cole DE, Marshall L, Loescher B, Jazmaji V. Case-control study of multiple chemical sensitivity, comparing haematology, biochemistry, vitamins, and serum volatile organic compound measures, September 2004; 54 (6):408-18; Baines CJ, McKeown-Eyssen GE, Riley N, Marshall L, Jazmaji V. University of Toronto case-control study of multiple chemical sensitivity-3: intra-erythrocytic mineral levels, Occupational Medicine, published online October 17, 2006) .

- ***Initial Steps toward Addressing Patients' Needs***
  - Those with ES-MCS have long complained about lack of availability of knowledgeable healthcare professionals and effective health services for their condition, borne out by Gibson et al's finding in a U.S. cross-sectional survey of 917 members of MCS support groups that participants had consulted a mean of twelve health care providers, but only found a mean of three helpful (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1499).

  - In Ontario, after carefully reviewing the available evidence on ES-MCS in 1984, both published and revealed in interviews and focus groups, the Ad Hoc Committee on Environmental Hypersensitivity Disorders, appointed by the then Ontario Minister of Health, Keith Norton, and chaired by Judge George M. Thomson (http://www.lsuc.on.ca/media/june1209_georgebio.pdf), concluded that there was sufficient evidence that environmental hypersensitivity was a health problem that needed to be addressed, and recommended funding of a collaborating university research program and academically-affiliated provincial clinic to fill the scientific and service gaps (Thomson GM, Chair. Report of the Ad Hoc Committee on Environmental Hypersensitivity Disorders to the Ontario Ministry of Health, 1985). Health Minister Elinor Caplan appointed a liaison committee, arranged for interested researchers and clinicians to meet to discuss priorities, and funded several research initiatives.

  - In the early 1990's, when Ontario Health Minister Frances Lankin learned that there had been other reports (Ashford NA, Miller CS. Chemical sensitivity: A report to the New Jersey State Department of Health, December, 1989; Health Canada. Environmental Sensitivities Workshop, Chronic Diseases in Canada, Supplement, January, 1991) that had very similar findings and had made similar recommendations as the Thomson Committee, she ordered funding, and the subsequent Health Minister Ruth Grier instituted the Environmental Hypersensitivity Research Unit (EHRU) at the University of Toronto (for a total of $1,500, 000) (McKeown-Eyssen G, Marshall L, Baines C, Rodin G.

Research Initiatives at the University of Toronto Environmental Hypersensitivity Research Unit, Regulatory Toxicology and Pharmacology, 1996; 24: S126-S128). A collaborating Environmental Health Clinic was also established for the province at Women's College Hospital, Toronto. Decisions regarding priorities for clinical services and research studies were effectively guided by a Clinical and Research Advisory Board (CRAB) appointed by the Ontario Ministry of Health in the 1990's.

- Pioneering research was done in the EHRU that validated published MCS case criteria and refined them (McKeown-Eyssen GE, Baines CJ, Marshall LM, et al. Multiple Chemical Sensitivity: Discriminant validity of case definitions; Arch Environ Health, 2001; 56(5):406–12), and that pointed to potential genetic susceptibility factors (McKeown-Eyssen G, Baines C, Cole DEC, Riley N, Tyndale RF, Marshall L, Jazmaji V. Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR, Int. J. Epidemiol. July 15, 2004; 33: 1-8), as well as investigating other potential etiological factors and diagnostic test possibilities. However, the EHRU funding ended before further studies on etiology, diagnosis and treatment could be mounted.

- The enduring provincial Environmental Health Clinic (EHC) at Women's College Hospital, with a total annual budget of $408,000, essentially static since 1998, employs 0.9 of a full time equivalent (FTE) physician, shared among 5 physicians, supplemented somewhat for clinical work by the Ontario Health Insurance Plan and recently for teaching by a hospital family practice group alternate funding plan. It also employs one full time Nurse Educator, 0.8 FTE Community Outreach Coordinator, 0.8 FTE receptionist/dictatypist, and approximately 0.3 FTE shared manager. The clinic provides comprehensive assessments and treatment advice to ongoing care physicians, and self management advice to physician-referred patients from a provincial population base of over 13 million (http://www.ontario.ca/en/about_ontario/EC001035 - accessed August 13, 2010-website last modified May 5, 2010). The EHC has a virtually perpetual six to eight month waiting list, is unable to offer urgent or ongoing treatment, and generally cannot provide consultations for children or out-of-province residents.

- Canada has one paediatric environmental health consulting clinic integrated into a regular multi-function paediatric clinic in Edmonton, Alberta, affiliated with the University of Alberta and a group of Paediatric Environmental Health Specialty Units in the U.S.

- The Nova Scotia Environmental Health Centre (NSEHC) is located in Fall River just outside Halifax, Nova Scotia. The NSEHC is funded by the Capital District Health Authority and is affiliated with Dalhousie University. The NSEHC has been able to offer assessments and ongoing multi-faceted, individualized treatment and psychosocial support to both adults and children in Nova Scotia, with a provincial population of 938,183 (http://www.gov.ns.ca/finance/statistics/agency/default.asp, July 1, 2009), as well as to some out-of-province residents. The NSEHC has an annual budget of $1,410,000 and employs two physicians, two nurses, one licensed practical nurse, one dietician, one psychologist, one psychotherapist, one occupational therapist, one rehabilitation counsellor, one manager/researcher, and five administrative staff (Merritt C, NSEHC. Personal communication with Drs. A. Bested, R. Bray and L. Marshall by telephone and e-mail, October 2010). The average waiting time for referred patients in Nova Scotia is approximately four months, but eight months if from out of province.

- It has been extremely challenging to assist EHC patients in Ontario to obtain adequate ongoing care in their communities when primary care physicians, specialists, and other local healthcare/homecare professionals have had little training in environmental health. The provincial EHC in Ontario has leveraged its resources by collaborating with multiple partners (**Table 6**) for education/training, research, community support, and health promotion with regard to ES-MCS and other environment-associated conditions.

- There is currently no Ontario Health Insurance Plan diagnostic code for ES-MCS, and no time-based complex case code to pay physicians for the extra time required for them to assess and treat those with ES-MCS. Hence, although Ontarians' needs are great, it is difficult to attract new physicians, given this reality.

- ***Cost Implications and Recognition of the Need to Accommodate***
  - Health care utilization costs for patients referred to the Nova Scotia Environmental Health Centre between 1998 and 2000, who were diagnosed with MCS by NSEHC physicians, were almost twice the provincial average. However, a NSEHC cohort study combining chart review and medical insurance records revealed reduced healthcare utilization by NSEHC patients subsequent to treatment, resulting in significant health care system savings. The largest reduction in health system utilization occurred in those who were initially most severely ill (Fox RA, Joffres MR, Sampalli T, Casey J. The impact of a multidisciplinary, holistic approach to management of patients diagnosed with multiple chemical sensitivity on health care utilization costs: An observational study, The Journal of Alternative and Complementary Medicine, 2007; 13(2):223-9).

  - A chart review study in the provincial Environmental Health Clinic in Ontario of 128 consecutive patients diagnosed with one or more of MCS, chronic fatigue syndrome, or fibromyalgia revealed that the mean number of visits to a family physician in the twelve months before completion of the intake questionnaire was 10.7 (SD 8.7; n=123), and to other physicians was 13.7 (SD 18.2; n=123). This was far higher than for the general population in Canada where the mean numbers of visits were 2.9 (SD 4.3) and 0.79 (SD 2.0) respectively. Furthermore, most (68.8%) had stopped work, on average about three years after symptom onset, and had "markedly lower functional scores than population average values" (Lavergne MR, Cole DC, Kerr K, Marshall LM. Functional impairment in chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity, Canadian Family Physician, February 2010; 56: e60-1).

  - Although some of the basic steps to fill scientific and service gaps have been taken as suggested by Thomson et al (Thomson GM, Chair. Report of the Ad Hoc Committee on Environmental Hypersensitivity Disorders to the Ontario Ministry of Health, 1985), there is unfortunately still a disturbing lack of recognition of the many challenges for those with ES-MCS in accessing knowledgeable health care (both urgent and ongoing) in safe facilities, adequate nutrition, supportive dietetic and community services, workplace accommodation, and safe healthy housing (Canada Mortgage and Housing Corporation. Research House for the environmentally sensitive, 1994, reprinted 1995, 1998, 2002, Cat. No. NH15-90/1994E; http://journals.lww.com/jphmp/toc/2010/09001#-1750774083; Building materials for the environmentally hypersensitive 61089, 1995, revised 2005, www.cmhc-schl.gc.ca/; http://journals.lww.com/jphmp/toc/2010/09001#-1750774083 J of Public Health Management and Practice, September/October 2010 16 (E-Supplement 5): S1-S93).

- In 2006, having received many complaints from Canadians with ES-MCS about the lack of health and financial support services and dismissal or trivialization of their health problems, the Canadian Human Rights Commission (CHRC) ordered a scientific literature review on environmental sensitivities (Sears M. The Medical Perspective on Environmental Sensitivities. Canadian Human Rights Commission, 2007, http://www.chrc-ccdp.ca/pdf/envsensitivity_en.pdf). The CHRC subsequently declared the condition to be a disability requiring accommodation under the *Canadian Human Rights Act* (the policy is posted at: http://www.chrc-ccdp.ca/legislation_policies/policy_environ_politique-en.asp) .

- The Department for Transport Energy and Infrastructure in South Australia has also specified a detailed disability accommodation policy for those with MCS in government buildings: http://www.sacfs.asn.au/download/SA%20Gov%20Access%20Assement%20%20guide%20version%20SBF%20final%20DTEI%202007_30_11.pdf

- Environmental sensitivities were included as "non-evident disabilities" in the Ontario Human Rights Commission's *Policy and Guidelines on the Duty to Accommodate* in 2000, and are also specifically mentioned when defining disabilities that must be accommodated under the Ontario *Human Rights Code* http://www.ohrc.on.ca/en/issues/disability.

- The Ontario Accessible Built Environment Standards Development Committee under the *Accessibility for Ontarians with Disabilities Act, 2005* has appointed the Environmental Health Clinic's Community Outreach Coordinator to represent those with environmental sensitivities.

- The Public Service Alliance of Canada (PSAC) has a policy statement on scent-free environments (Chemical Sensitivities - Environmental Disabilities) on their website that includes the PSAC Awareness Kit on Scent-Free Environments, January 2006 http://psac.com/documents/what/scent-free-kit-feb2006-e.pdf .

- The Canadian Centre for Occupational Health and Safety has information on its website on how to establish a "Scent-Free Policy for the Workplace" (www.ccohs.ca/oshanswers/hsprograms/scent_free.html) , as does National Defence and the Canadian Forces. (Environmental sensitivities, Safety Digest, Edition 6/2010, reproduced from the Safety, Emergency and Security Management Division of Treasury Board; retrieved August 27, 2010. http://www.vcds-vcemd.forces.gc.ca/dsafeg-dsg/pi/sd-dsg/6-10/article-07-eng.asp.)

- The Ontario provincial Environmental Health Clinic team, other Women's College Hospital staff and consumer support groups have collaborated with the Canadian Society for Environmental Medicine on information for hospital staff to enable accommodation of those with allergies or sensitivities (Marshall LM, Maclennan JG. Environmental health in hospital: A practical guide for hospital staff. Part I Pollution prevention, Part II Environment-sensitive care, Canadian Society for Environmental Medicine, 1993, revised editions 2001, www.mcscanadian.org/hospital.html)

- Through participation in the Canadian Coalition for Green Health Care (www.greenhealthcare.ca), the provincial Environmental Health Clinic in Ontario has been a leader in promoting fragrance/scent-free programs and policies in health care facilities across the country, with the assistance of an Ontario Trillium Foundation grant.

Etiology:

While the causes and underlying mechanisms of ES-MCS are still not fully understood, progress has been made over the past 15 or so years. There has been increased recognition of the large number of ubiquitous chemicals to which we are all exposed in varying amounts and combinations. Their potential impacts on body defence mechanisms and the contributions of genetic and epigenetic susceptibility factors and metabolic consequences have been hypothesized and are slowly being tested. The science of toxicology has evolved substantially and there is a move away from "physical" versus "psychological" dualistic models of disease/illness to the multiple determinants of health model utilized by the World Health Organization (WHO).

- ***Increased Chemical Exposure***
  - More than 80,000 potentially toxic chemicals have been introduced into commerce in North America mostly since World War II (Grossman E. What the EPA's "Chemicals of Concern" plans really mean, Scientific American, January 11, 2010), and 23,000 in Canada (Health Canada. Assessing Chemicals in Canada for Risk: Protecting the Health of Canadians and their Environment. Health Canada. Dec. 15, 2006. March 27, 2009 http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/brochure/index-eng.php) , to which Canadians are virtually all regularly exposed (Genuis SJ. Nowhere to hide: chemical toxicants and the unborn child, Reprod Toxicology, 2009; 28:115-6).

  - Some patients began reporting a variety of symptoms linked with intermittent exposure to synthetic chemicals in the 1950's and 60's, and their physicians reported the phenomenon to colleagues (e.g. Randolph T.G. Human ecology and susceptibility to the chemical environment. Springfield, IL: Charles C Thomas, 1962), but little notice seemed to be taken initially- perhaps not surprising since the effects of chemical sensitivities are usually not visible to others, and it can be hard to believe that chemicals at levels not bothering most people could be adversely affecting some.

  - In the 1970's, in the wake of an oil embargo in the Middle East, buildings were "tightened" to prevent heat loss, trapping chemicals indoors, at the same time as regulated ventilation rates were lowered to save energy. Reports of symptoms in multiple body systems occurring "with increased frequency in buildings with indoor climate problems" were recognized by the World Health Organization as a clinical phenomenon called "Sick Building Syndrome" (WHO, Indoor Air Quality Research. Euro-Reports and Studies. Copenhagen, No. 103. 1984).

  - ES-MCS was reported more in the 1980's and 90's - a similar phenomenon to Sick Building Syndrome occurring in a broader range of locations and circumstances. Symptoms were triggered by 'everyday' exposures, often after a recognizable initiating event, usually of a pronounced chemical exposure, such as a chemical spill at work, pesticide application or building renovation, or by a combination of chemical exposures in the stressful context of war (Cullen, MR. The worker with multiple chemical sensitivities: an overview. Occup. Med. 1987; 2:655-661; Ashford NA, Miller CS. Chemical sensitivity: a report to the New Jersey State Department of Health, December, 1989; Ashford NA, Miller CS. Chemical exposures, low levels and high stakes, Van

Nostrand Reinhold, New York, 1991, and 2nd Edition, John Wiley & Sons Inc., 1998; Ross GH. History and clinical presentation of the chemically sensitive patient. Toxicol. Ind. Health. 1992; 8, 21-28; Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch. Environ. Health, 1995; 50, 119-129; Haley RW, Billecke S, La Du BN. Association of low PON1 type Q (type A) arylesterase activity with neurologic symptom complexes in Gulf War veterans, Toxicol Appl Pharmacol 1999;157:227-233; Gulf War and Health, Vol. 8: Health Effects of Serving in the Gulf War Update 2009 , National Academies Press, 2010, http://www.nap.edu).

- Early on, the most common symptom-triggering agents, reported by occupants of sick buildings and those with ES-MCS, were usually not recognized as containing potentially harmful ingredients (e.g. the unlabeled volatile organic compounds (VOC's) being emitted from many common building and furnishing materials, cleaning, laundry, and personal care products), or exposures were considered to be at levels too low to be harmful. While reports of chronic conditions in children, such as asthma and neurocognitive difficulties, were increasing, they were not necessarily seen as related (McKeown D. Toronto Public Health. Environmental threats to children: Understanding the risks, enabling prevention, September 2005; Grandjean P, Landrigan JP. Developmental neurotoxicity of industrial chemicals, doi:10.1016/S0140-6736(06)69665-7, 2006).

- In the first decade of the 21st century, as uses of electrical appliances/equipment and radiofrequency telecommunications have expanded, there have been reports of a condition with a pattern like MCS of multisystem symptoms occurring in relation to exposures to everyday levels of electromagnetic radiation (Huss A, Roosli M. Consultations in primary care for symptoms attributed to electromagnetic fields- a survey among general practitioners, BMC Public Health, Oct. 30 2006;6:267). An international committee of scientists have examined and reported on the evidence to date (The Bioinitiative Working Group. Bioinitiative report: A rationale for a biologically-based public exposure standard for electromagnetic fields, 2006, last updated 24 May 2010; www.bioinitiative.org). Although there is still much uncertainty, in response to public enquiries, Toronto Public Health has developed fact sheets (Toronto Public Health. Electromagnetic fields-Fact sheet, http://www.toronto.ca/health/emfs.htm, last updated February 2011; Toronto Public Health, Cell Phone Use and Human Health, last updated January, 2011, http://www.toronto.ca/health/hphe/pdf/factsheet_cellphone.pdf. In addition, Health Canada outlines risk reduction measures on its webpage on the Safety of Cell Phones and Cell Phone Towers- http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/prod/cell-eng.php, last updated May 2009.

- It may be that people in many industrialized nations reporting the pattern of ES-MCS from the 1950s on are the '*canaries*' for the general population with respect to responses to the multitude of chemicals introduced into our air, food, water, soil, and consumer products since World War II, as well as to increasing exposure to electromagnetic radiation.

Overwhelmed Body Defence Mechanisms

- Fortunately, the body may normally utilize many mechanisms and combinations thereof to defend against foreign biological, chemical or physical agents, or rapidly dividing cancer cells. However, defence mechanisms can become overwhelmed and individuals may become more sensitive to a variety of chemicals at everyday dosages, for example patients with cirrhosis of the liver, or undergoing chemotherapy for cancer.

- Primary body defence mechanisms include the following (simplified):
  - Surface barriers: Inhaled particles and chemicals may be breathed out or trapped in mucus in the nose and sneezed out, or in the bronchi and lungs and coughed out. The gastrointestinal tract wall and mucus can block absorption of ingested hazardous substances. Substances may be brushed or washed off the skin before they are absorbed.

  - Cellular Immune Responses: immune cells, including neutrophils, monocytes and lymphocytes e.g. B cells, T cells and Natural Killer cells, are found in the blood and throughout the body in organs such as the lungs, liver, spleen and brain. When viruses, bacteria or other foreign proteins enter the body, the immune cells become activated to release chemical mediators to 'chew' them up (Klaasen CD. Casarett and Doull's Toxicology, the basic science of poisons, 7th Edition, 2008, McGraw-Hill Inc.; Guyton AC, Hall JE. Textbook of Medical Physiology, 11th Edition, Saunders, July 2005).

    Immune responses are powerful mechanisms in the body, with potential to cause harm (e.g. anaphylaxis or autoimmune disease). Danish researchers have demonstrated dose response-related increased histamine release from the basophils of patients with asthma and perfume contact allergy, in comparison with controls, on exposure to perfume (Elberling J, Skov PS, Mosbech H, Holst H, Dirksen A, Johansen JD. Increased release of histamine in patients with respiratory symptoms related to perfume, Clin and Experim Allergy, 2007; 37:1676-1680).

  - Humoral Non-Cellular Immunity: there are many different humoral immune pathways where the body produces or reacts with large complicated proteins such as immunoglobulins (antibodies), complex proteins and enzymes for the coagulation or clotting system and the complement system, or reactive proteins such as cytokines or other chemicals that are produced in response to what the body identifies as foreign: bacteria, viruses, fungi, cancer cells, radiation and chemicals. The proteins and chemicals travel through Phase I and Phase II biotransformation pathways that occur mainly in the liver (Klaasen CD. Casarett and Doull's Toxicology, the basic science of poisons, 7th Edition, 2008, McGraw-Hill Inc.; Guyton AC, Hall JE. Textbook of Medical Physiology, 11th Edition, Saunders, July 2005, 1152 pgs).

  - Phase I and Phase II Biotransformation, followed by Phase III Excretion: the Phase I (Cytochrome P-450) enzyme system prepares (bioactivates) the parent substance via various mechanisms, so that it can connect (conjugate) with another substance in a Phase II pathway to make the compound water soluble in order that it may be excreted more easily in Phase III. The rate at which Phase I produces activated intermediates must be balanced by the rate at which Phase II conjugates and Phase III excretes toxins in the urine via the kidneys, in the bile and stool via the bowel, and to some degree in sweat. Otherwise, there can be a build up of the parent substance and its active intermediate metabolites, which, in some cases can be more toxic than the parent.

    Many drugs are P-450 enzyme inhibitors which may result in accumulation of medications and foreign chemicals (xenobiotics) with increased side effects and toxicity. Examples are cimetidine, ciprofloxacin, diltiazem, erythromycin,

ketoconazole, verapamil, and a number of selective serotonin reuptake inhibitors (SSRIs).

There are essentially six Phase II conjugation pathways:
-Glutathione conjugation
-Amino acid conjugation
-Methylation
-Sulfation
-Acetylation
-Glucuronidation

There must be adequate nutrients available for efficient operation of Phase I and II biotransformation pathways, in particular, high intake of highly-coloured vegetables, ascorbate, anti-oxidants, glutathione precursors provided by adequate protein, niacin and cobalamin, as well as balanced essential fatty acid intake and phosphatidyl choline, along with high fibre to enhance GI transit function in Phase III and sufficient fluid to assist excretion via kidneys. (Burford-Mason A. What foods need to deliver, Nutrition for Docs, Dalla Lana School of Public Health, University of Toronto, Syllabus, April 17-18, 2010).

- ***Genetic Susceptibility Factors***
  - From 1990-2003, the human genome was categorized (http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml). Genetic polymorphisms have been found in those with ES-MCS in comparison with controls that seem to indicate that people with ES-MCS may have more difficulty than the majority of the population metabolizing and excreting commonly encountered environmental chemicals and medications (La Du BN, Billecke S, Hsu C, Haley RW, Broomfield CA. Serum paraoxonase (PON1) isozymes: the quantitative analysis of isozymes affecting individual sensitivity to environmental chemicals. Drug Metab Dispos. 2001;29:566-9; McKeown-Eyssen G, Baines C, Cole DEC, Riley N, Tyndale RF, Marshall L, Jazmaji V. Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR, International Journal of Epidemiology 2004; 33:1–8 [funded by the Ontario Ministry of Health]; Furlong CE, Cole TB, Jarvik GP et al. Role of paraoxonase (PON1) status in pesticide sensitivity: genetic and temporal determinants, Neuotoxicology 2005;26:651-9; Schnakenberg E, Fabig KR, Stanulla M et al. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug metabolizing enzymes. Environ Health. 2007; 6:6 ; Muller KE, Schnakenberg E. Die Bedeutung der Glukuronidierung bei umweltmedizinischen Erkrankungen am Beispiel der UDP-Glukuronosyltransferase 1A1. Umwelt Medizin Gesellschaft, 2008; 21(4): 295-300).

  - The science of epigenetics and how environmental stimuli influence genes to turn on and off their expression of metabolic enzymes is in its infancy and is evolving rapidly (Anway MD, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors, Endocrinology 2006, Vol. 147, No. 6 s43-s49; Crews D, McLachlan JA. Epigenetics, evolution, endocrine disruption, health and disease, Endocrinology, 2006, Vol. 147, No. 6 s43-s49; Korkina L, Scordo MG, Deeva T, Cesareo E, De Luca C. The chemical defensive system in the pathobiology of idiopathic environment-associated diseases, Current Drug Metabolism, 2008; 10:914-31). Genuis noted “Just as a loaded gun needs to be triggered to unload destruction, epigenetic research confirms that disease is often

the result of vulnerable genes being triggered by specific determinants. Mounting evidence suggests that without activation, some disease processes will not develop, and removal of the initiating trigger may allow developing illness to abate or subside." (Genuis SJ. Medical practice and community health care in the 21st century: A time of change, Public Health, 2008; 122:671-80).

- In a recent Italian study comparing diagnosed or suspected MCS patients with healthy controls, even though some measured genes were not noted to be different in the combined 'case' population, it was found that several key metabolizing enzymes were. The authors concluded, "Altered redox and cytokine patterns suggest inhibition of expression/activity of metabolizing and antioxidant enzymes in MCS. Metabolic parameters indicating accelerated lipid oxidation, increased nitric oxide production, and glutathione depletion in combination with increased plasma inflammatory cytokines should be considered in biological definition and diagnosis of MCS" (De Luca C, Scordo MG, Cesareo E, Pastore S, et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes, Toxicology and Applied Pharmacology, 2010, doi:10,1016/j.taap.2010.04.017).

- ***Metabolic Vicious Cycle***
  - Human metabolic systems, identical in all cells, are responsible for conversion of matter into the energy of adenosine triphosphate (ATP) to perform life- and health-necessary functions. Humans are equipped with alternate pathways to maintain or restore normal levels of bio-energetic potential, even with genetic and environmental insult (Strohman R. Manoevering in the complex path from genotype to phenotype, Science, 26 April 2002;296(5568):701-3). A comprehensive catalogue of human metabolic pathways is now readily accessible (http://www.genome.jp/kegg/pathway.html).

  - Plausible biochemical vicious cycle mechanisms (the nitric oxide-peroxynitrite or NO-ONOO cycle) in MCS and other commonly overlapping complex chronic conditions such as myalgic encephalomyelitis/chronic fatigue syndrome have been proposed and partially tested (Pall ML, Satterlee J. Elevated nitric oxide/peroxynitrite mechanism for the common etiology of multiple chemical sensitivity, chronic fatigue syndrome, and post traumatic stress disorder, Ann NY Acad Sci 2001; 933:323-9; Pall ML. Elevated Nitric Oxide/Peroxynitrite theory of Multiple Chemical Sensitivity: Central role of *N*-Methyl-D-Aspartate Receptors in the Sensitivity Mechanism, EHP, September 2003; 111(12):1461-4; Pall ML, Anderson JH. The vanilloid receptor as a putative target of diverse chemicals in multiple chemical sensitivity, Arch Environ Health, July 2004; 59(7):363-75; Pall ML. Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms, Part 8, Environmental and Ecotoxicology, 92, in General and Applied Toxicology, 6 volume set, 3rd Edition. Editors: Ballantyne B, Marrs T, and Syversen T. November 2009, John Wiley & Sons Inc., 3940 pages).

  - Pall proposed that cases of Multiple Chemical Sensitivity may be initiated by seven classes of chemicals, each acting along a specific pathway in the body, stimulating the *N*-Methyl-D-Aspartate (NMDA) cell membrane receptors. The chemical stimulation produces increased NMDA cell membrane receptor activity in mammals that can be measured, and toxic effects, which are diminished by giving NMDA antagonists. The NMDA receptors are found on the surface of cell membranes throughout the body including in the brain, the peripheral nervous system, the bronchi and the gut. Hence, the

NMDA cell membrane receptors can become sensitized by chemical contaminants, become over-active and trigger sensitivity responses in MCS patients. Further support for these metabolic mechanisms has come recently from an Italian study (De Luca C, Scordo MG, Cesareo E, Pastore S, et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes, Toxicology and Applied Pharmacology, 2010, doi:10,1016/j.taap.2010.04.017).

- Pall has been able to relate the NO-ONOO vicious cycle to previously published MCS etiological hypotheses (Bell I, Miller C, Schwartz G. An olfactory limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders, Biol Psychiatry, 1992:32:218-42; Meggs WJ. Neurogenic inflammation and sensitivity to environmental chemicals, Environ Health Perspect, 1993; 101:234-38; Meggs WJ. Neurogenic switching: A hypothesis for a mechanism for shifting the site of inflammation in allergy and chemical sensitivity, Environ Health Perspect, 1995; 103(1):54-56; Miller CS. Toxicant-induced loss of tolerance- an emerging theory of disease? Environ Health Perspect March 1997; 105S:445-53).

- ***Sensory Hypersensitivity***
  - Capsaicin is the heat producing ingredient in hot peppers and is a well known cough inducer when inhaled, by stimulating vanilloid-sensitive receptors in the bronchial tubes. There are several double-blind capsaicin inhalation challenge studies which demonstrate hypersensitivity in those with MCS when compared to controls, even when asthma has been ruled out (Terneston-Hasseus E. Increased capsaicin cough sensitivity in patients with multiple chemical sensitivity. J Occup Environ Med. 2002 Nov; 44(11):1012-7; Nogami H. Capsaicin provocation test as a diagnostic method for determining multiple chemical sensitivity. Allergology Int 2004 53(2):153-157(155).

  - Challenge studies in those with atopy, and upper and lower airway symptoms have produced the same results, demonstrating neural receptor hypersensitivity to chemicals (Millqvist E. Cough provocation with capsaicin is an objective way to test sensory hyperreactivity in patients with asthma-like symptoms, Allergy, June 2000; 55(6):546-50; Millqvist E. Relationship of airway symptoms from chemicals to capsaicin cough sensitivity in atopic subjects, Clin Exp Allergy, April 2004; 34(4):619-23; Millqvist E. Changes in levels of nerve growth factor in nasal secretions after capsaicin inhalation in patients with airway symptoms from scents and chemicals, Environ Health Perspective, July 2005; 113(7):849-52).

  - Patients with capsaicin sensitivity have faster CNS processing of other chemosomatosensory substances as well (Andersson L. On the relation between capsaicin sensitivity and responsiveness to CO2: detection sensitivity and event-related brain potentials. Arch Environ Health, February 2009; 82(3):285-90).

  - Given that vanilloid receptors are involved in pain perception, it is perhaps not surprising that MCS patients are also more likely to have fibromyalgia (Ziem G. Profile of patients with chemical injury and sensitivity, Environ Health Perspect, March 1997; 105 Suppl 2:417-36; Rainville P. Representation of acute and persistent pain in the human CNS: potential implications for chemical intolerance, Ann NY Acad Sci, March 2001; 933:130-41; Black DW. The Iowa follow-up of chemically sensitive persons. Ann NY Acad Sci, March 2001; 933:48-56).

- ***Evolving Toxicology***
  - The science of toxicology has only recently evolved to understand concepts such as quasi-persistence and chronic toxicity of substances to which there is frequent or continuous exposure, even at low levels (Genuis SJ. Elimination of persistent toxicants from the human body, Hum Exp ToxicolOnlineFirst, April 16, 2010; doi:10.1177/0960327110368417) (particularly relevant for those with MCS who may not be able to metabolize and excrete xenobiotics as readily as most adults and for vulnerable fetuses and children whose metabolic capacities are still under development (Furlong CE, Cole TB, Jarvik GP et al. Role of paraoxonase (PON1) status in pesticide sensitivity: genetic and temporal determinants. Neurotoxicology. 2005; 26:651-659; McKeown D. Environmental threats to children: Understanding the risks, enabling prevention, Toronto Public Health, September, 2005).

  - It was also not until recently considered that dose response curves could be non-monotonic, and that some substances encountered at exceedingly low levels could adversely affect the endocrine and immune systems (American Chemical Society. http://portal.acs.org/portal/PublicWebSite/policy/publicpolicies/promote/endocrinedisruptors/CNBP_023441; Martin OV, Lester JN, Voulvoulis N, Boobis AR. Human health and endocrine disruption: A simple multicriteria framework for the qualitative assessment of end point-specific risks in a context of scientific uncertainty, Toxicological Sciences, 2007; 98(2):332-48; www.ourstolenfuture.org -->Does the dose make the poison?; Vogel SA. The politics of plastics: The making and unmaking of Bisphenol A "safety", Amer J Pub Health, 2009 99(S3):S559-66; American Chemical Society. Testing for Endocrine Disruption. Public Policy Statement 2009-2010. http://portal.acs.org/portal/PublicWebSite/policy/publicpolicies/promote/endocrinedisruptors/CNBP_023441).

  - It has recently been realized that there might be no safe threshold of exposure below which there would be no adverse health effects for some substances, such as lead (American Academy of Pediatrics, Committee on Environmental Health. Lead exposure, including: prevention, detection and management, Pediatrics, Oct. 2005,116(4):1036-46; Abelsohn AR, Sanborn M. Lead and children, clinical management for family physicians, Canadian Family Physician, June 2010:531-5). High dose laboratory animal experimental "no observable adverse effect levels" (NOAELs) are typically relied upon to estimate regulatory exposure limits, with somewhat arbitrary 'safety' factors applied to protect those more vulnerable.

- ***Central Nervous System Hypoperfusion***
  - Baseline and post-chemical challenge brain perfusion decreases have been noted in MCS patients compared with controls on single photon emission computed tomography (SPECT) brain scans. Decreased perfusion correlated with psychometric test results of decreased quality of life and neurocognitive function in cases at baseline, and neurocognitive worsening after chemical exposure "at non-toxic concentrations" (Orriols R, Costa R, Cuberas G, Jacas C, Castell J, Sunyer J. Brain dysfunction in multiple chemical sensitivity, Journal of the Neurological Sciences, 2009; 287:72-8).

- ***'Physical' vs 'Psychological' and Consequences, or Multiple Determinants***
  - Since the time of French philosopher Rene Descartes (1596-1650), the mechanistic concept of separation of mind and body has persisted in medicine (Gold J. Cartesian dualism and

the current crisis in medicine- a plea for a philosophical approach: discussion paper, J of the Royal Soc of Med, August 1985; 78: 663-6), in spite of ongoing evidence of mutual influence of each on the other (e.g. Choi J, Fauce SR, Effros RB. Reduced telomerase activity in human T lymphocytes exposed to cortisol, Brain, Behavior and Immunity, May, 2008; 22(4): 600-605). There has correspondingly been a tendency to categorize ES-MCS etiological factors as *either* physical *or* psychological. This reductionist dichotomous view and ensuing discordant medial debate about 'physical' versus 'psychological' origins for ES-MCS has lead to public confusion and misunderstandings, since society looks to the medical community for information and guidance. The Thomson Committee commented "We believe that confidence in the health care system is eroded when productive dialogue between different medical specialties disappears or is replaced by acrimonious debate before a confused public" (Thomson GM, Day JH, Evers S, et al. Report of the Ad Hoc Committee on Environmental Hypersensitivity Disorders. Ontario Ministry of Health, 1985:266-70).

- Since consistently abnormal objective physical findings and laboratory test results are presently not established to 'prove' a physical origin for ES-MCS, the dichotomous view can lead to an assumption of psychogenic etiology, with a tendency for this assumption to be favoured by industry, insurers and government agencies, as discussed by Ziem and Spencer and Schur (Ziem G. Multiple chemical sensitivity: Treatment and follow up with avoidance and control of chemical exposures, Toxicol Ind Health July 1, 1992; 8(4):73-86; Spencer TR, Schur PM. The challenge of multiple chemical sensitivity. J Environ Health 2008, 70(10):24-7).

- Although there is no objective evidence of psychogenesis, some people disbelieve patients reporting ES-MCS, diminish the significance of symptoms and experiences, and dismiss even the possibility of the condition. Also, Genuis has noted the tendency of some authors to have "disregard for recent laboratory and animal evidence" and to categorize sensitivity-related illness as a "psychogenic confabulation" (Genuis SJ. Sensitivity-related illness: The escalating pandemic of allergy, food intolerance and chemical sensitivity, Science of the Total Environment, 2010; 408: 6047-61; 6057). For instance, Staudenmayer et al concluded that "idiopathic environmental intolerance" "is a belief characterised by an over-valued idea of toxic attribution of symptoms and disability, fulfilling criteria for a somatoform disorder and a functional somatic syndrome" (Staudenmayer H, Binkley KE, Leznoff A, Phillips S. Idiopathic Environmental Intolerance, Toxicol Rev 2003;22(4):247-61). Even psychiatrists can tend to hold patients responsible for "psychological" illnesses (Miresco MJ, Kirmayer LJ. The persistence of mind-brain dualism in psychiatric reasoning about clinical scenarios, Am J Psychiatry, May, 2006, 163:913-18).

- Studies supporting MCS psychogenesis, when critically reviewed, had various methodological problems and were often subject to selection biases (Davidoff AL, Fogarty L. Psychogenic origins of multiple chemical sensitivities syndrome: a critical review of the research literature, Archives of Environmental Health, 1994; 49(5):316-25).

- In contrast, in a 2001 multi-center cross-sectional survey of 1,166 patients who visited outpatient occupational, otolaryngology, allergy and clinical ecological/environmental clinics, the authors found that the majority (60-79%) of those who met the criteria for MCS did not report treatment for anxiety, depression, or distress/adjustment problems,

and 73% reported "good" or "excellent" health during their first 30 years of life which they thought was "not supportive of the idea that MCS syndrome is primarily a psychiatric or psychosomatic condition". However, they reported that MCS patients were 5-6 times more likely than controls to seek treatment for psychological concerns secondary to chemical sensitivity "congruent with the hypothesis that much of the psychopathology seen in MCS syndrome is secondary to feeling ill" (Kutsogiannis DJ, Davidoff AL. A multiple center study of multiple chemical sensitivity syndrome, Arch Environ Health, May/June 2001, 56(3):196-207).

- Also, a 2003 population-based survey (N=1582) revealed that few of 199 individuals reporting MCS (1.4%) had a history of prior emotional problems, whereas a substantial number (37.7%) developed such problems after the onset of physical symptoms associated with chemical exposures (Caress SM, Steinemann AC A review of a two-phase study of multiple chemical sensitivities, Environ. Health Perspect. 2003, 111(12), 1490).

- Furthermore, Gibson et al found that the 917 persons with self-reported MCS who participated in their treatment survey reported a higher help-harm ratio for "psychotherapy to cope with MCS" and "support group" than for "psychotherapy to cure MCS". Psychotropic medications were consistently rated more likely to harm than to help (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1501-2).

- Disbelief, diminishment and/or dismissal lead to stigmatization and a lack of appropriate emergency or ongoing medical care for sufferers, as well as barriers to obtaining workplace and housing accommodation and income support. Being marginalized and impoverished can in turn lead to increased illness and disability (Lipson JG. Multiple chemical sensitivities: Stigma and social experiences, Medical Anthropology Quarterly, 2004;18(2):200–213). Das-Munshi et al noted that those with MCS were frequently refused Workers' Compensation "on the grounds it is psychological" (Das-Munshi J, Rubin GJ, Wessely S. Multiple chemical sensitivity: Review, Current Opinion in Otolaryngology Head Neck Surgery, 2007; 15:274-80).

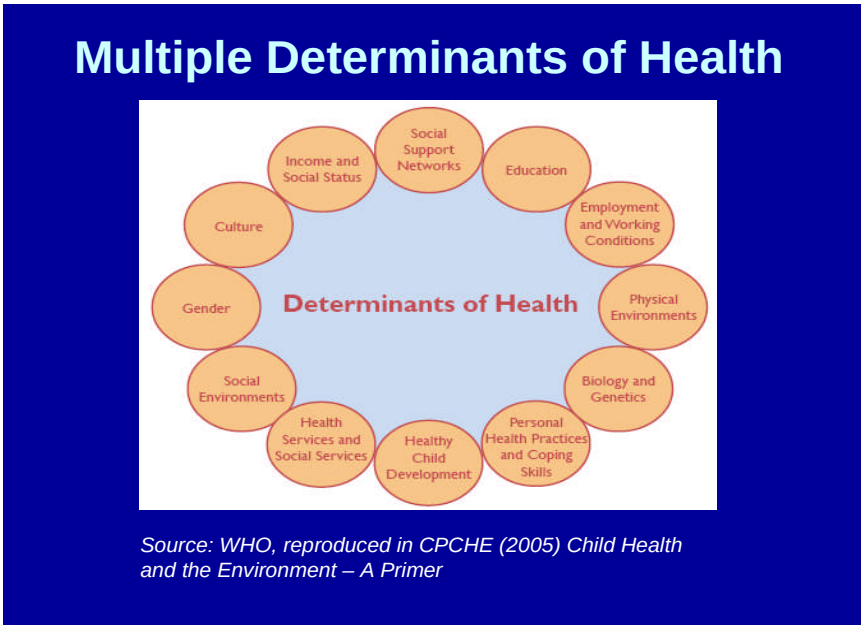
- Delegitimizing those with ES-MCS, who may be warning us all of the need for toxics reduction, also tends to impede development of practical, precautionary, potentially preventive and cost-saving public health strategies.

- Trivialization and disparagement of ES-MCS as a legitimate medical condition, and of ES-MCS patients, has also extended to their physicians, prompting the Thomson Committee's Recommendation 8: "We recommend that the fee schedule permit an enlargement of the fee to be charged if added time is required to obtain good histories, to counsel a patient on avoidance procedures and to monitor the patient's performance" (Thomson GM, Day JH, Evers S, et al. Report of the Ad Hoc Committee on Environmental Hypersensitivity Disorders. Ontario Ministry of Health, 1985:280). Recommendation 33 of a May 24, 1990 Health and Welfare Canada Workshop on environmental sensitivities stated: "Physicians who show interest in the field should not be stigmatized and should be adequately compensated for the time they spend with patients with complicated illnesses" (Health and Welfare Canada. Environmental sensitivities workshop, Chronic Diseases in Canada, Supplement, January 1991, ISSN-0228-8699). Unfortunately, the

situations leading to these recommendations have not changed, and so few physicians are attracted to the field of environmental health, and research progress is hampered.

- The World Health Organization (WHO) describes multiple determinants of health (**Figure 1**), which may be addressed for each ill individual, allowing many more treatment options. A "multifactorial model" for MCS was suggested by Das-Munshi et al, although psychological-behavioural treatment approaches were, perhaps not surprisingly, favoured by the psychiatrist and psychologist authors (Das–Munshi J, Rubin GJ, Wessely S. Multiple chemical sensitivities: review, Curr Opin Otolaryngol Head Neck Surg 2007, 15(4): 274-80).

Figure 1: World Health Organization's Multiple Determinants of Health
(Child Health and the Environment- A Primer, Canadian Partnership for Children's Health and the Environment, August 2005, www.healthyenvironmentforkids.ca)



Prevalence:

Prevalence surveys have now been conducted in several of the United States for both physician-diagnosed and self-reported MCS. The Canadian Community Health Survey has reported health professional-diagnosed MCS in those over the age of twelve in Canada, and has shed light on demographics, functional impacts, influence of poverty and co-morbid conditions. There is no available incidence data nor are there prevalence statistics for children under twelve.

- ***Diagnosis by a Health Professional***
  - In a study funded by the Ontario Ministry of Health, Kutsogiannis and Davidoff noted that several statewide surveys in the U.S. found that 3.1-6.3 percent of the American population reported diagnosis of MCS by a physician (Kutsogiannis DJ, Davidoff AL. A multiple center study of multiple chemical sensitivity syndrome, Arch Environ Health, May/June 2001, 56(3):196-207). Also, the 2002 and 2003 Canadian Community Health Surveys (CCHS) revealed that 2-3 % of Canadians reported being diagnosed with MCS

by a health professional (Park J, Knudson s. Medically unexplained physical symptoms, Health Reports, Statistics Canada Catalogue 82-003, February 2007, 18(1):43-7).

- We believe it is important to recognize the significant reporting of MCS compared with a few other well known "long term conditions" in the Canadian Community Health Survey (2000-2003) that are "expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional" (**Table 2**).

Table 2:

Prevalence of Multiple Chemical Sensitivity and Other Long Term Conditions
(From online Statistics Canada-based prevalence reports, 13/08/2010, compiled by L. Marshall)

Long Term Health Condition	Prevalence over age 12 or 15 (CCHS, 2000-2003)
Multiple Sclerosis	0.24%
AIDS	0.4%
Breast Cancer	1%
All cancers	2.6%
Multiple Chemical Sensitivity	**2.4% (1.4% men, 3.4 % women)**
Type 2 Diabetes	3-4%
Heart Disease	5.4% men, 4.6% women
Arthritis/Rheumatism	16% (2/3 women)

- In the 2005 Canadian Community Health Survey, 2.5% of adult Ontarians had been diagnosed by a health professional with MCS, with prevalence increasing with age, peaking at 5.8% in women between the ages of 60 and 64 years (**Table 3**).

- The provincial Environmental Health Clinic in Ontario recently reported considerably decreased functional status of our MCS patients relative to the Canadian population on the eight functional status scales of the well-validated Short Form-36 (Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). 1. Conceptual framework and item selection, Med Care 1992, 30(6):473-83), and markedly increased health care utilization rates (Lavergne MR, Cole DC, Kerr K, Marshall LM. Functional impairment in chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity, Canadian Family Physician, February 2010; 56: e57-65).

Table 3:

Prevalence of Multiple Chemical Sensitivity (MCS) by Age and Gender in a Target Population*

(From the 2005 Public Use Microdata File of the Canadian Community Health Survey, Statistics Canada.10-10-2007, compiled by Margaret Parlor, BA, LLB, Statistical Analyst)

	% of population* with MCS	% of males with MCS	% of females with MCS
Total age 12 y and over	2.2	1.2%	3.1%
12 to 14 years	0.8	0.6	1.0
15 to 17 years	0.7	0.4	1.0
18 to 19 years	0.9	0.8	0.9
20 to 24 years	0.9	0.5	1.2
25 to 29 years	1.4	1.1	1.7
30 to 34 years	1.6	1.0	2.1
35 to 39 years	1.7	1.2	2.2
40 to 44 years	2.4	1.7	3.0
45 to 49 years	2.9	1.3	4.4
50 to 54 years	3.3	1.7	4.9
55 to 59 years	3.6	1.7	5.5
60 to 64 years	3.6	1.4	5.8
65 to 69 years	3.3	1.8	4.6
70 to 74 years	2.9	1.9	3.8
75 to 79 years	3.2	1.6	4.5
80 years plus	1.9	1.1	2.3

*Target population: citizens aged 12 and over, excluding Canadians living in institutions, native Canadians living on reserves, full time members of the armed forces, and Canadians living in remote regions

- ***Self-reported MCS***
  - Like almost any medical condition, people may be mildly, moderately or severely affected, and those more mildly affected may not present for medical care. Also, it takes time for educational programs for healthcare professionals to be developed after a relatively newly observed illness has been reported, and so diagnoses may be less frequently made and the condition under-reported. Researchers in three U.S. states therefore also asked randomly selected adults if they thought themselves to be "unusually" or "especially" sensitive and if they felt ill on exposure to low-level everyday chemicals. In California and New Mexico, 16% said yes (Kreutzer R, Neutra RR, Lashuay N. Prevalence of people reporting sensitivities to chemicals in a population-based survey. Am J Epidemiol 1999, 150:1-12; Voorhees RE. Memorandum from New

Mexico Deputy State Epidemiologist to Joe Thompson, Special counsel, Office of the Goveror, 13 March 1998). In North Carolina, 33 % of randomly selected adults, and in Arizona, 33 % of college students answered affirmatively (Meggs WJ, Dunn KA, Bloch Rm et al. Prevalence and nature of allergy and chemical sensitivity in a general population,Arch Environ Health, 1996,51:275-82; Bell IR, Schwartz Ge, Peterson JM et al. Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures, Arch Environ Health, 1993, 48:6-13). High prevalence rates found in workers studied after occupational overexposures were cited in a study funded by the Ontario Ministry of Health (Kutsogiannis DJ, Davidoff AL. A multiple center study of multiple chemical sensitivity syndrome, Arch Environ Health, May/June 2001, 56(3):196-207).

- The 2005 National Survey of the Work and Health of Nurses revealed that 3.6% of all Canadian nurses, predominantly women, experienced chemical sensitivities (N=18,676). Of nurses younger than 35 years, 1.4% reported chemical sensitivities, which increased to 3.7% in nurses 35-44 years old, and 4.3% and 4.8% in successive decades (Statistics Canada www.statcan.ca → Publications, electronic format catalogue no. 83-003-XIE; print version 83-003-XPE)..

Poverty Influence

- In the 2002 and 2003 CCHS, MCS prevalence was higher in those of the lowest socioeconomic status, who are known to have higher exposures to hazardous environmental agents, generally poorer nutrition, and more psychosocial stress, all known vulnerability factors for chronic health problems. In addition, these surveys found that 22% of those with MCS were "dependent in instrumental activities of daily living" (Statistics Canada. Canadian Community Health Survey 2003, reported by Park J, Knudson S, Health Reports, Catalogue 82-003, February 2007, 18(1):45).

- Of a random sample of 1,582 individuals from Atlanta, Georgia, 12.6% reported hypersensitivity to common chemicals, and 13.5 % of these (1.8% of the entire sample) reported loss of employment due to their hypersensitivity (Caress SM, Steinemann AC. A review of a two-phase population study of multiple chemical sensitivities, Environ Health Perspect. 2003, 111:1490-7).

- ***Prevalence in Childhood and Incidence***
  The prevalence of MCS in children under age 12 has never been studied, but we at the EHC think there is cause for concern, given that fetuses and children are known to be the most vulnerable to health impacts from exposure to environmental toxins, and exposure during key developmental stages can have lifelong consequences (McKeown D, Toronto Public Health, Environmental Threats to Children, Understanding the Risks, Enabling Prevention, September 2005). Certainly, the rapid rise in childhood asthma, learning and neurobehavioural disorders and disabilities has been linked with increased exposure to various environmental chemicals (Canadian Partnership for Children's Health and the Environment. Child health and the environment-A primer, August 2005:33-40; www.healthyenvironmentforkids.ca).

- To our knowledge, no studies of incidence of MCS at any age have yet been published, and so it is unknown if the condition is increasing or not.

- ***Co-morbid Conditions***
  Much overlap has been noted in the U.S. between prevalence of allergies and chemical sensitivities (Meggs WJ, Dunn KA, Bloch RM, Goodman PE, Davidoff AL. Prevalence and nature of allergy and chemical sensitivity in a general population, Arch Environ Health, 1996, 51:275-82), and between asthma and chemical sensitivities (Caress SM, Steinemann AC. National prevalence of asthma and chemical hypersensitivity: an examination of potential overlap, J Occup Environ Med, 2005, 47:518-22).

- Allergies and asthma commonly overlap with MCS in Canada too, and the prevalence of several other underlying or co-morbid chronic conditions affecting multiple body systems is greater in the MCS population compared to the general Canadian 'target population' (Statistics Canada, CCHS, 2005) (**Table 4**) Medical care for many of the listed chronic conditions on their own is provided in medical specialty clinics, although patients with myalgic encephalomyelitis/chronic fatigue syndrome and some with fibromyalgia are chronically underserved by specialty clinics in Ontario and are commonly referred to the provincial Environmental Health Clinic by their primary care physicians. If specialists are not knowledgeable about how chemical sensitivity reactions can mimic or trigger many of the problems that they treat, patients with ES-MCS who go to such specialists are not likely to receive effective treatment/support, and may even have treatments recommended that are harmful for them, such as non-tolerated medications. Because of stigmatization of ES-MCS, specialists have not been encouraged to study how the condition impacts their specialty scope.

Table 4:

Frequencies of MCS Co-diagnoses for Canadian Target Population*

(From the 2005 Public Use Microdata File of the Canadian Community Health Survey, Statistics Canada.10-10-2007, compiled by Margaret Parlor, BA, LLB, Statistical Analyst)

Chronic condition	% of people with MCS having this additional diagnosis...	% of target population having this diagnosis...
Other allergies (not food)	61.1	26.6
Other back problems (not arthritis or fibromyalgia)	39.7	18.8
Arthritis/rheumatism	38.5	16.4
Food Allergies	27.3	7.2
Migraine headache	26.3	10.5
Asthma	25.7	8.3
High blood pressure	24.5	14.9
Mood disorder	15.9	5.6
Anxiety Disorder	14.5	4.4
Thyroid condition	13.8	5.6
Bowel disorder	13.1	3.9
Bronchitis	11.4	2.5
Fibromyalgia	10.0	1.4
Chronic Fatigue Syndrome	9.9	1.2
Heart disease	9.8	4.7
Cataracts	9.1	4.2
Stomach/Intestinal ulcers	8.9	3.1
Diabetes	6.9	4.9
Glaucoma	3.9	1.5
Effects of stroke	2.5	1.1
Cancer	2.3	1.4
Epilepsy	1.3	0.6

* Target Population: citizens aged 12 and over, excluding Canadians living in institutions, native Canadians living on reserves, full time members of the armed forces, and Canadians living in remote regions.

Diagnosis:

Diagnosis of ES-MCS is accomplished by ruling out or treating other conditions that could account for, or contribute to the presenting symptoms, by assessing each individual's exposures, and determining whether or not the person's pattern of symptoms fits validated clinical consensus criteria. A few tests are helpful in assessing body burden of various chemicals, functional status, co-morbid allergies, and brain hypoperfusion.

- ***Ruling Out Other Conditions***
  - Given that there are no definitive objective diagnostic tests for ES-MCS, a practical strategy of 'ruling out' other conditions or factors that could be contributing to each patient's symptoms is used initially via comprehensive clinical history, physical examination, and readily available laboratory tests (Sears M. The Medical Perspective on Environmental Sensitivities. Canadian Human Rights Commission, 2007,

http://www.chrc-ccdp.ca/pdf/envsensitivity_en.pdf). If ES-MCS is suspected, but other conditions or potential contributors are found, they are treated, cautiously, with tolerated treatments, often at lower doses than usual, and the patient's symptoms are re-assessed (Marshall Lynn M., Bested Alison C., Bray Riina I. Poorly understood conditions of the 21st century- Chronic Fatigue Syndrome, Fibromyalgia, and Multiple Chemical Sensitivity, invited paper, Canadian Journal of Diagnosis, July 2003: 65-71, based on a presentation for Family Medicine Forum 2002, Montreal, College of Family Physicians of Canada. http://www.stacommunications.com/journals/pdfs/diagnosis/dxjuly03/drmarshallsyndromes%20.pd.pdf and Frequently Asked questions, Poorly understood conditions of the 21st century: Chronic Fatigue syndrome (CFS), Fibromyalgia (FM), and Multiple Chemical Sensitivity:32, and Why do I feel so tired? : 39-42 http://www.stacommunications.com/journals/pdfs/diagnosis/dxjuly03/wydx.pdf). If a patient has both ES-MCS and one or more co-morbid conditions, it can be challenging to find tolerable treatments, and medication side effects can obscure links between symptoms and exposure to other environmental agents.

- ***Exposure Assessment***
  - A systematic method of taking a comprehensive exposure history using a handy mnemonic has been developed (Marshall Lynn, Weir Erica, Abelsohn Alan, Sanborn Margaret D. Identifying and managing adverse environmental health effects: 1. Taking an exposure history. CMAJ Apr. 16, 2002; 166 (8): 1049-55 and Occupational and environmental exposure, response to letter to the editor by Michael Schweigert, CMAJ, Oct. 1, 2002; 167 (7): 744, 746), as well as exposure history forms utilizing this method, which may be downloaded from the Ontario College of Family Physicians website (Marshall Lynn. Taking an Exposure History, 2002, updated 2004 and 2005 after peer review by the provincial Environmental Health Clinic physicians and Ontario College of Family Physicians Environmental Health Committee Members, www.ocfp.ca → Environmental Health Committee and scroll).

  - Blood and 24-hour urine tests for some toxic metals are accessible in Ontario and, for the most part, are funded by the Ontario Health Insurance Plan. However, blood or urine tests or fat biopsies for other retained chemicals must be obtained in the United States at patients' expense. Some of these tests are currently being used in Canada in biomonitoring studies (Canadian Health Measures Survey, Maternal-Infant Research on Environmental Chemicals, accessed August 15, 2010, http://www.chemicalsubstanceschimiques.gc.ca/plan/surveil/bio-initiatives-enquetes-eng.php)

- ***Ruling In MCS***
  - If no other explanation is found for a patient's presenting illness, and their symptom pattern follows that specified in the consensus case criteria (Bartha et al. Multiple Chemical Sensitivity: a 1999 consensus. Archives of Environmental Health, May/June 1999; 54(3): 147-9), and if the patient reports having a stronger sense of smell than most people and two of three discriminating neurological symptoms (McKeown-Eyssen GE, Baines CJ, Marshall LM, et al. "Multiple Chemical Sensitivity: Discriminant Validity of Case Definitions." Arch Environ Health, 2001; 56(5):406–12), this is considered to 'rule in' MCS. The Environmental Health Clinic physicians have created a checklist of these criteria and posted them online for the use of practising physicians (www.ocfp.on.ca →Environmental Health Committee and scroll).

- ***Functional Status***
  - Blood test indicators of various organ functions as well as nutritional status, along with pulmonary function tests and sleep studies are employed to gauge various functions of ES-MCS patients along the severity continuum.

  - The physicians in the provincial Environmental Health Clinic in Ontario also assess functional status of patients referred by Ontario physicians using the Short Form-36 questionnaire (Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). 1. Conceptual framework and item selection, Med Care 1992, 30(6):473-83). A chart review of 128 consecutive patients diagnosed by an EHC physician with one or more of MCS, chronic fatigue syndrome or fibromyalgia revealed substantial functional impairment (Lavergne MR, Cole DC, Kerr K, Marshall LM. Functional impairment in chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity, Canadian Family Physician, February 2010; 56: e57-65). The results supported findings in the United States (Black DW, Doebbeling BN, Voelker MD, Carke WR, Woolson RF, Barrett DH et al. Quality of life and health services utilization in a population-based sample of military personnel reporting multiple chemical sensitivities, J Occup Environ Med, 1999;41(10):928-33; Jason LA, Taylor RR, Kennedy CL. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms, Psychosom Med, 2000; 62(5):655-63).

  - EHC physicians in Ontario have developed an Activity Log and Functional Capacity Scale that may be downloaded from the Ontario College of Family Physicians website (Bested AC, Marshall LM. Activity Log and Functional Capacity Scale, www.ocfp.on.ca → Environmental Health Committee).

- ***Chemical Provocation Tests***
  - In our view, there are ethical concerns with chemical provocation inhalation challenges because in a vulnerable population it is hard to determine challenge dosages without potential for harm.

  - Das-Munshi et al reviewed heterogeneous studies of chemical provocation, in that various chemicals were used in various doses, sometimes with or without nasal clips or face masks, and sometimes with or without chemical masking agents/placebos that were acknowledged to be potentially active (Das-Munshi J., Rubin G.J., and Wessely S. Multiple chemical sensitivities: A systematic review of provocation studies, J Allergy Clin Immunol, December 2006; 118(6):1257-64). In addition, there was an apparent lack of understanding of, and accounting for the confusing impacts on provocation results of habitual versus intermittent exposure to test agents. Coupled with lack of consistent, objective, easily measurable outcomes, it is not surprising to us that results of these studies were inconsistent.

- ***Allergy Tests***
  - As noted previously (Meggs WJ, Dunn KA, Bloch RM, Goodman PE, Davidoff AL. Prevalence and nature of allergy and chemical sensitivity in a general population, Arch Environ Health, 1996, 51:275-82; Parlor M. Frequencies of MCS Co-diagnoses for Canadian Target Population, CCHS Public Use Microdata File, Statistics Canada, 2005), there is a strong overlap of allergies, to both foods and biological inhalants, such as dust mites, animal danders, pollens and moulds. While blood radioallergosorbent (RAST) tests

may be used to identify antibodies to such allergens, the results do not correlate well with symptoms. Skin prick tests may be helpful to screen for inhalant allergens, less so for foods, but, empirically, can provoke significant exacerbation of symptoms for some patients with ES-MCS.

- Serially diluted intradermal or sublingual tests for inhalants with individual formulation of hyposensitization treatments have been empirically helpful in ES-MCS cases with concomitant allergies (Wright ST. Diagnosis and management of inhalant allergens, http://www.utmb.edu/otoref/grnds/Inhalant-allergens-2003-0611/Inhalant-allergens-2003-0611.doc) in Canada, the U.S. and U.K. They were not included in Gibson's U.S. survey. Moreover, since the treatment is unique for each individual, and individuals with ES-MCS are heterogeneous in many respects, they are not amenable to group trials.

- Since skin prick test results for food allergens do not correlate well with symptoms, elimination and re-ingestion challenge tests may be used, except of course if there is a history of known or suspected life-threatening (anaphylactic) reactions. If many foods are suspected to be problematic, rotation of a broader range of foods can help to ferret out intolerances, and then, once discovered, the patient may be able to limit exposure to those foods. In contrast to Das-Munshi et al's interpretation that rotation of foods has "iatrogenic effects" (Das-Munshi J, Rubin GJ, Wessely S. Multiple chemical sensitivities: review, Current Opinion in Otolaryngology & Head and Neck Surgery, 2007; 15:277), Taylor et al found that the more the diet was adhered to, the better the nutritional intake and the fewer and less severe the symptoms (Taylor JP, Krondl MM, Spidel M, Csima AC. Dietary adequacy of the rotary diversified diet as a treatment for 'environmental illness', Canadian Journal of Dietetic Practice and Research, Winter 2002; 63(4):198-201).

SPECT Scans

- Physicians of the internationally consulted Dallas, Texas Environmental Health Center described specific abnormalities of metabolism in the brains of those with MCS with neurocognitive impairment when imaged with single photon emission computed tomography (SPECT). The recurrent patterns consistent with neurotoxicity included a mismatch in tracer uptake between early- and late-phase imaging, multiple hot and cold foci throughout the cortex, temporal asymmetry and increased tracer uptake into the soft tissues and sometimes the basal ganglia. They had previously noted a similar pattern in patients with acute neurotoxic chemical exposures and breast implants, and indicated: "Affective processes such as depression do not, alone, show this pattern". Further they found that controlled challenges to ambient chemicals induced the same specific changes on SPECT imaging in chemically sensitive patients, and that significant improvement on SPECT brain imaging frequently followed detoxification treatment in these patients. (Ross GH, Rea W, Johnson AR, Hickey DC, Simon TR. Neurotoxicity in single photon emission computed tomography brain scans of patients reporting chemical sensitivities, Toxicology and Industrial Health, 1999 April/May;15(3-4):415-20).

- However, controlled studies have been difficult to mount due to challenges in finding controls, ethical issues regarding chemical challenges, and cost. Nevertheless, a recent, well-designed and executed study has confirmed empirical reports and the authors concluded, "Chemical exposure caused neurocognitive impairment and SPECT brain dysfunction, particularly in odour processing areas, thereby suggesting a neurogenic origin

of MCS" (Orriols R, Costa R, Cuberas G, Jacas C, Castell J, Sunyer J. Brain dysfunction in multiple chemical sensitivity, Journal of the Neurological Sciences, 2009; 287:72-8).

- SPECT scans are very expensive and, while they do provide some objective evidence in MCS, they do not generally impact management more than a careful exposure history. They have been used to bolster legal efforts to obtain benefits or accommodation for those seriously ill with MCS.

- ***Etiological Understanding and Diagnosis***
  - As understanding of etiological mechanisms improves, it will hopefully become possible to design readily available and affordable objective diagnostic tests for those with ES-MCS, and any subset populations that are discovered that have unique features. Such tests would aid earlier diagnosis and treatment and likely save much cost for the health care system.

Treatment:

Treatment for ES-MCS is based on evidence-informed principles, is individualized, holistic and person-centred. It focuses on assisting patients to reduce their exposures to their unique symptom triggers and hazardous chemicals, optimizing their internal processing and elimination of chemicals, and reducing chemical body burdens when necessary and achievable. If co-morbid allergies are not relieved by environmental controls at home and in the workplace, they may be helped by increased ventilation, filtration, individualized desensitization or symptom-relieving medications. Dysbiosis (imbalanced microflora in the gastrointestinal tract) may be helped by probiotics and stabilization of pH. Patients are encouraged to take control and self-manage their health, planting a "health garden" using a "weed, SEEDS and feed approach". With the support of their health care professionals, patients learn how to weed out aggravators, and then to institute and nurture elements of good health. [SEEDS is an acronym for Sleep, Exercise (and pacing), Environment, Diet (nutrition), and Support.]

Patients who do not have adequate economic resources to achieve the above measures early in the course of their illnesses, and/or cannot access knowledgeable physicians in safe facilities, and/or who are severely chemically sensitive, and/or have co-morbid infections/other conditions are greatly challenged. For such people, it can be risky to their already compromised health to undertake necessary activities such as shopping in a supermarket or consulting with a physician in an unsafe office, and lack of physician awareness can increase the risk of inappropriate treatment and further deterioration.

- ***Duty to Provide Care***
  - In the 21st century, physicians and other healthcare professionals are frequently consulted by patients suffering with complex conditions such as ES-MCS, who need immediate and ongoing medical assistance. Despite imperfect knowledge of etiology and mechanisms of conditions, and in the absence of definitive laboratory tests, healthcare professionals nevertheless have a responsibility to provide care. Even if there is a dearth of randomized clinical trial evidence for therapies, physicians are duty bound to "Consider first the well-being of the patient" (Canadian Medical Association. Code of ethics, Update 2004, http://policybase.cma.ca/PolicyPDF/PD04-06.pdf). They need to listen to patients' feedback about their observations and pay attention to their own, and then take the time to advise patients using the *available* evidence and their best clinical judgment, so that patients may make informed choices about the lowest risk, highest potential benefit modalities likely to apply to their individual situations. Such a collaborative working relationship avoids abandoning patients to their own devices.

- ***Patient-centred Trend in Health Care***
  - There has been a shift by Canadian healthcare professionals and policymakers towards "patient centredness" in care, which "may be most commonly understood for what it is not-technology centred, doctor centred, hospital centred, disease centred" (Stewart M. Towards a global definition of patient centred care: The patient should be the judge of patient centred care, BMJ, February 24, 2001; 322, 444-5; Stewart M, Brown JB, Weston WW, McWhinney IR, McWilliam CL, Freeman TR. Patient-centred medicine: Transforming the clinical method, 2nd Edition, 2003, Radcliffe Medical Press Ltd, U.K.).

  - In an observational cohort study of 315 patients seen by 39 randomly selected family physicians, patient-centred communication/practice was found to improve health status outcome and decrease health care costs by decreasing diagnostic tests and referrals (Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW, Jordan J. The impact of patient-centred care on outcomes, The Journal of Family Practice, July 4, 2000, http://www.jfponline.com/Pages.asp?AID=2601).

  - An observational study of 865 consecutive patients in the offices of three doctors revealed the key components to patients of a patient-centred model of care (**Table 5**) (Little P, Everitt, H, Williamson I, Warner G, Moore M, Gould C, Ferrier K, Payne S. Preferences of patients for patient centred approach to consultation in primary care: observational study, BMJ, 24 February, 2001; 322:1-7).

Table 5:

Key Components of a Patient Centred Model of Care According to Patients
(Little P, Everitt, H, Williamson I, Warner G, Moore M, Gould C, Ferrier K, Payne S. Preferences of patients for patient centred approach to consultation in primary care: observational study, BMJ, 24 February, 2001; 322:1-7)

"Main domains of model of patient centredness"
"Exploring the experience of disease and illness: patients' ideas about the problem, feelings, expectations for the visit, and effects on function
Understanding the whole person: personal and developmental issues (for example, feeling emotionally understood) and the context (the family and how life has been affected)
Finding common ground (partnership): problems, priorities, goals of treatment, and roles of doctor and patient
Health promotion: health enhancement, risk reduction, early detection of disease
Enhancing the doctor-patient relationship: sharing power, the caring and healing relationship"

- However, as Ball has pointed out, "Politics and power drive the system and the fact is: consumers have no power" (Ball T. Disruptive innovation: Patient/family-focused care, Managing Change, Summer 2010:1-16). He cited Glover: "the principle of individuality creates an interesting problem: a patient-centred system must be inclusive enough to support 34 million personalized health systems that are unique to each Canadian and ultimately managed by him or her". Glover and the Canadian Association for People-centred Health envision that patients

should be able to select and access the most appropriate providers/coaches and support services they need, and that they are collectively willing to pay for in the Canadian health care system (Glover V. Journey to wellness: Designing a people-centred health system; available at www.caph.ca).

- For ES-MCS sufferers the ideal of 'patient-centred care' is currently in stark contrast to realities within the health care system. Knowledgeable healthcare professionals and support workers are so few as to be virtually inaccessible most of the time. For moderately or severely chemically sensitive persons, physicians' offices, clinics and hospitals commonly are unsafe places to wait, consult, or undergo procedures because patients can be exposed to many symptom triggers emitted from furnishings, cleaning and laundry products, disinfectants, and personal care products on staff or other patients, making their conditions worse. Fragrance/scent-free hospital, home care and rehabilitation services are very rarely available, and there are no chemically safe emergency shelters. Consequently, patients with severe chemical sensitivities may avoid seeking care, risking further deterioration and chronicity, thereby being "caught between a rock and a hard place."

- In this time of health professional shortages and increasing demand by an aging population, it is also difficult to get knowledgeable ongoing medical or surgical care for complex multi-system health problems such as ES-MCS, and patients may still be disbelieved and ignored. The results include poor health outcomes and higher health care costs, both for the patient and for the health care system.

- In addition to aspiring towards truly person-centred individual care, the Environmental Health Clinic team consults with consumer representatives from patient support groups on EHC programs. These representatives attend several EHC staff meetings each year, keep the leaders of relevant support groups informed, and consult them for their opinions on environmental health service issues. The EHC team is constantly hearing from the consumer support organizations how Ontarians with ES-MCS are underserved, and how their ongoing care physicians from across the province find it extremely challenging and time-consuming to address the needs of the population of patients with ES-MCS in their own communities. Clearly, with the current level of funding and staffing, the support that the Ontario EHC team has been able to offer to Ontarians with ES-MCS is inadequate.

- ***Empirical Evidence-informed Approaches***
  - The team at the provincial Environmental Health Clinic in Ontario believes, as does the staff at the Nova Scotia Environmental Health Centre (NSEHC), "that there is no need to wait for a full understanding of the pathophysiology of these conditions before we should manage them" (Fox RA, Joffres MR, Sampalli T, Casey J. The impact of a multidisciplinary, holistic approach to management of patients diagnosed with multiple chemical sensitivity on health care utilization costs: An observational study, The Journal of Alternative and Complementary Medicine, 2007; 13(2):223-9). Both clinics assess potential biological, physical environmental, nutritional, psychosocial, and other potential contributors to illness for each patient, and, whenever possible, assist the individual to self manage these factors with their primary care physician's medical support. Our clinical impression, consistent with that of other clinicians, is that generally the earlier actions are taken to address illness factors, the faster and more satisfactory the recovery- and thus the lower the utilization of the health care system.

  - In Gibson et al's study, subjects commented that it was only the combination of treatments that helped them improve. Many reported that it was necessary to do environmental controls, a

correctly tailored program of nutritional supplements, and a number of other interventions that addressed their own unique constellation of symptoms" (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1503).

- Such a multi-faceted, individualized approach to care of heterogeneous ES-MCS patients is not conducive to group randomized controlled trials, and so no specific treatment protocol has been assessed by that method.

- Just as ES-MCS patients have been disparaged, so have the practising physicians who first observed and reported ES-MCS, hypothesized pathological mechanisms, and clinically explored what they thought were rational therapeutic responses (Swoboda DA. Negotiating the diagnostic uncertainty of contested illnesses: physician practices and paradigms, Health (London), October, 2008; 12(4):453-78). Nevertheless, many of their ideas, including reduction of exposure to triggers and toxins, have stood the test of time. Physicians from family medicine and many medical specialties are now recognizing the importance of environment-health links and information about exposure reduction is being made available to the public (http://www.newswire.ca/en/releases/archive/March2007/01/c4421.html; Canadian Liver Foundation, Liver health begins at home; The Lung Association, http://www.lung.ca/protect-protegez/pollution-pollution/indoor-interieur/index_e.php; Reuben SH for the President's Cancer Panel. Reducing environmental cancer risk- What we can do now. U.S. Department of Health and Human Services, April 2010; http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf)).

- The cornerstones in clinical management of ES-MCS are:
  - reduction of exposure to each person's unique environmental symptom triggers (e.g. some perfumes, cat dander) and toxins (e.g. formaldehyde emitted from particleboard, pesticides), once identified via exposure history and observation,
  - enhancement of internal processing and elimination of chemicals,
  - reduction in body burden of retained chemicals if necessary,
  - relief of suffering with symptomatic treatments as needed,
  - treatment of co-morbid conditions that can exacerbate or be exacerbated by ES-MCS, and
  - encouragement to make changes in habits that would be likely to prevent further illness and promote health.

- Unlike the provincial EHC in Ontario, the NSEHC provides ongoing treatment, and there is now evidence of reduced healthcare utilization by NSEHC patients after treatment, resulting in significant health care system savings from reduced physician visits both to general practitioners and specialists, as well as reduced emergency room visits and hospital admissions (Fox RA, Joffres MR, Sampalli T, Casey J. The impact of a multidisciplinary, holistic approach to management of patients diagnosed with multiple chemical sensitivity on health care utilization costs: An observational study, The Journal of Alternative and Complementary Medicine, 2007; 13(2):223-9).

- ***Reduction of Exposure to Triggers and Toxins***
  - By definition, people with MCS have symptoms that "are reproducible with [repeated chemical] exposure" and that "improve or resolve when the incitants are removed" (Bartha et al. Multiple Chemical Sensitivity: a 1999 consensus. Archives of

Environmental Health, May/June 1999; 54(3): 147-9). Most patients who have noted a few such links between their symptoms and exposure to environmental triggers have already avoided them as best they can by the time they come to medical care, with some improvement in acute, intermittent symptoms. However, they may have chronic symptoms and may not have noticed the symptom-exposure links of substances to which they are exposed very frequently, which may be "masked" due to quasi-persistence in the body. It takes time and expertise for physicians to identify the most likely problematic chemicals via a detailed exposure history and observation, to educate patients about where these chemicals are likely to be encountered, and then how to avoid them or reduce exposures, for example by using less-toxic and/or better-tolerated substitutes.

- Since many of the same triggering agents (e.g. pesticides, paints, and perfumes) are repeatedly reported by those with MCS, it often helps to assist patients to focus on reducing their exposure to these substances as well as to their own unique symptom triggers as a precautionary measure if there is no undue hardship. Gibson et al's finding of MCS sufferers' almost universal use and the helpfulness of "chemical avoidance" and "chemical-free living space" is not surprising. Gibson et al also noted that these therapies are "fairly non-invasive and low risk", as respectively these two strategies were rated to be 119 and 155 times more likely to be helpful than harmful. (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1498-1504).

- Avoidance strategies have also been reported to be helpful for those with MCS by many other authors (e.g. Ziem G. Multiple chemical sensitivity: Treatment and follow up with avoidance and control of chemical exposures, Toxicol Ind Health July 1, 1992; 8(4):73-86; Lax, M., Henneberger, P. Patients with Multiple Chemical Sensitivities in an Occupational Health Clinic: Presentation and Follow-up, Archives of Environmental Health, 1995; 50(6):425-31); Ashford NA, Miller CS. Chemical exposures, low levels and high stakes, 2nd Edition, John Wiley & Sons Inc., 1998; Canada Mortgage and Housing Corporation. Research House for the environmentally sensitive, 1994, reprinted 1995, 1998, 2002, Cat. No. NH15-90/1994E; Caress S.M., Steinemann A.C. Prevalence of fragrance sensitivity in the American population. Journal of Environmental Health , 2009; 71(7): 46-50; National Defence and the Canadian Forces. Environmental sensitivities, Safety Digest, Edition 6/2010, reproduced from the Safety, Emergency and Security Management Division of Treasury Board).
- Sadly, treatment of severely ill patients is often less successful than of those identified in primary care and treated early, when often simple modifications such as avoiding pesticide applications and using low VOC (volatile organic compound) paints and unscented cleaning, laundry and personal care products, possibly with minor dietary changes, are enough to return the person to health. They may still experience symptoms when they encounter such substances elsewhere, but if they can keep away from them in their daily diet, home and work environments, the symptoms triggered elsewhere generally become much milder and shorter lasting. However, avoiding many symptom-triggering exposures in air, food, water, and consumer products is not easy, and much less so if the sufferer has limited financial means (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1503).

- If people with ES-MCS are not successful in achieving accommodation in the workplace, it can directly impact their income-earning capacity and financial resources. Gibson et al found that the mean annual personal income for their sample of 917 people was $20,000. 286 (31%) of the 917 had made a worker's compensation claim, 115 had been compensated and 54 were awaiting resolution. Only 211 (23%) were employed outside the home (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1499).

- Finding or creating a safe living space, although medically desirable (Canada Mortgage and Housing Corporation. Research house for the environmentally hypersensitive, 1994, reprinted 1995, 1998, 2002, and Building materials for the environmentally hypersensitive 61089, 1995, revised 2005, www.cmhc-schl.gc.ca/; http://journals.lww.com/jphmp/toc/2010/09001#-1750774083, J of Public Health Management and Practice, September/October 2010 16 (E-Supplement 5): S1-S93) can be very challenging and can lead to considerable expenditures and possibly the need for stopgap measures. For example, in a 1996 survey, Gibson et al found that 66% of their sample of 305 people with MCS had lived in what they described as "unusual conditions", such as in their vehicles, on porches, or in tents at some time during their illness (Gibson PR,Cleavers J, Warren ML. Multiple chemical sensitivity/environmental illness and life disruption, Women Ther, 1996; 19:63-79). In the Canadian climate, such temporary measures are only tenable in mild weather.

- While relatively modest changes at home such as substituting non-fragranced cleaning, laundry and personal care products, de-cluttering, and removing carpets may make significant differences for many of those with ES-MCS, for others, making a truly safe home can involve remodelling/building anew with tolerated building materials or extensive mould remediation. Gibson et al. found that respondents in their 2003 survey had spent a mean of US $57,000 on such expenses from the onset of their illnesses (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1499).

- Homelessness is an extreme, sometimes life-threatening hardship for any person, but especially for someone who is ill. Ontario has no sufficiently environmentally safe emergency shelters, where a person with moderate to severe ES-MCS can get away from acute chemical exposures quickly enough and stay long enough to recover from them in order to avoid health deterioration. The necessary environmental accommodations are not available in the usual continuum of government-supported care and shelter for Ontarians, from urgent to acute to ongoing to assisted living to long term care. Sufficiently environmentally-safe government-supported housing for those with moderate to severe ES-MCS is also as yet virtually unavailable.

- With only a handful of Ontario ES-MCS-knowledgeable physicians, urgent care treatments that have rationales and a long history of empirical benefit, such as intravenous nutrient repletion (Rea W.J. Chemical sensitivity, Volume 4, Lewis Publishers, 1997:2438, 2653-66) and oxygen therapy (Rea WJ. Chemical sensitivity, Volume 4, CRC Lewis Publishers, 1997:2554-63), are generally not obtainable from hospital emergency rooms.

- ***Enhancing Internal Processing and Elimination of Chemicals***
  - It will never be possible to eliminate all hazardous substances in communities, homes and workplaces. Hence, it is important to take steps to help MCS patients to metabolize and excrete the chemicals they inadvertently absorb, whenever possible.

  - Poverty impacts on the ability of the body's defence systems to defend, both directly through increased exposure to environmental chemical and biological hazards, and indirectly through overloading and overwhelming of protective mechanisms. Both direct and indirect impacts can take effect for those with or susceptible to MCS over a prolonged period in poor housing, more so if they do not have access to protective devices such as air and water filters.

  - Besides a highly nutritious, preferably organic, diet, which may be difficult and expensive to maintain, if there are many food intolerances, nutritional supplements are often required by sensitive people in order to be able to metabolize and eliminate toxic chemicals to which they are unavoidably exposed (Burford-Mason A. Nutrition for Docs: Using nutritional supplements in clinical practice, a practical, evidence-based approach, Dalla Lana School of Public Health, University of Toronto, Syllabus, April 17-18, 2010).

  - Tolerated targeted supplements may be cost prohibitive, but if patients do not have adequate nutrition, they may accumulate more and more body burden of hazardous substances and become so overloaded that encountering even minute quantities of avoided chemical triggers will initiate severe symptoms which can be debilitating and last for days or longer. In such circumstances, their symptoms often spread to other body systems and the number of triggering substances expands as well. If they are being continually exposed to triggering agents, they may have chronic "masked" symptoms that affect their ability to function and to defend against infectious organisms (Miller CS. The compelling anomaly of chemical intolerance, Annals of the New York Academy of Sciences, 2001; 933:1-23).

  - A high fibre diet is also a well-accepted and common sense method to enhance bowel transit function and elimination of toxins (Mayo Clinic Staff. Dietary fiber: Essential for a healthy diet, http://www.mayoclinic.com/health/fiber/NU00033, updated July 8, 2010; accessed August 17, 2010).

  - Since thyroid and other hormonal functioning can be disrupted by many commonly encountered environmental chemicals, sometimes at exceedingly low levels (Diamanti-Kandarakis E et al (2009) Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews* 30(4):293-342), vigilance for deficiencies or imbalances and swift correction with the tolerated medication and dosage is important.

  - As noted in the Canadian Community Health Survey 2005 (**Table 4**), there is a strong overlap of MCS and gastrointestinal disorders. Gut inflammation could be related to direct effects on the gut mucosa from ingestion of toxic substances, or altered immune resistance to pathological organisms. "Probiotic therapies have attempted to modify disease expression by favourably altering bacterial composition, immune status and inflammation" (Tamboli CP, Neut C., Desreumaux P, Colombel JF. Dysbiosis in irritable bowel disorder, Gut, January 2004; 53(1):1-4; Rao AV, Bested AC, Beaulne TM, Katzman MA, Iorio C, Berardi JM, Logan AC. A randomized, double-blind, placebo-

controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome, Gut Pathogens 2009, 1:6, Biomed Central). The Dallas Environmental Health Center has long found that intravenous nutrient repletion has been useful in bypassing inflamed GI tracts with impaired nutrient absorption (Rea W.J. Chemical sensitivity, Volume 4, Lewis Publishers, 1997:2438, 2594, 2653-66).

- ***Decreasing Body Burden***
  - If avoidance of symptom triggers and toxics reduction, along with described enhancement of metabolism and elimination of chemicals are insufficient to provide relief, and there are retained substances that may be prolonging a patient's illness, it is important to assess what could be done to decrease that body burden- e.g. by removing mercury amalgam fillings (Health Canada. The safety of dental amalgam fillings, 1996; http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/pubs/dent_amalgam-eng.php#a11; Haley B. A study on the release of mercury from dental amalgams…, May, 2007, http://iaomt.org/articles/category_view.asp?intReleaseID=278&month=7&year=2007&catid=36), following a careful protocol (International Academy of Oral Medicine and Toxicology. Safe removal of amalgam fillings, http://www.iaomt.org/articles/files/files288/Safe%20Removal%20of%20Amalgam%20Fillings.pdf).

  - Some medical specialists are trained in the appropriate application of a careful protocol for chelation of retained heavy metals (Genuis SJ. Elimination of persistent toxicants from the human body, Hum Exp Toxicol OnlineFirst, April 16, 2010, doi:10.1177/0960327110368417).

  - Increased excretion of some persistent compounds via sweat has been reported using a combination of exercise and sauna while maintaining optimal metabolism and elimination (Rea WJ, Pan Y, Johnson AR, Ross GH, Suyama H, Fenyves EJ. Reduction of chemical sensitivity by means of heat depuration, physical therapy and nutritional supplementation in a controlled environment, Journal of Nutritional and Environmental Medicine, 1996; 7:141-8; Dahlgren J, Cecchini M, Takhar H, Paepke O. Persistent organic pollutants in 9/11 world trade center rescue workers: reduction following detoxification, Chemosphere, 2007; 69:1320-5; Genuis SJ. Elimination of persistent toxicants from the human body, Hum Exp Toxicol OnlineFirst, April 16, 2010, doi: 10.1177/0960327110368417).

  - Very recently, clearance of persistent, bioaccumulated perfluorinated compounds via stool has been reported using a bile acid sequestrant cholestyramine, and, although further trials are needed, thus far the method appears to be safe and effective (Genuis SJ, Birkholz D, Ralitsch M, Thibault N. Human detoxification of perfluorinated compounds, Public Health 2010;124:367-75; Genuis SJ. Human detoxification of perfluorinated compounds, Syllabus, 45th Annual Scientific Assembly, American Academy of Environmental Medicine, 21 October, 2010, La Jolla, CA).

- ***Symptomatic Treatment and Desensitization***
  - As noted previously, there is a strong overlap of allergies with ES-MCS. Symptomatic treatment with antihistamines, decongestants or analgesics may be tried, usually starting at one quarter to one half the usual dose to assess tolerance. However, medications are often poorly tolerated, and standard dose desensitization with escalation may exacerbate allergy symptoms. Individually formulated desensitization with only needed antigens included in the formula, at the level of sensitivity to that antigen for that patient, with gentle or no

escalation, has repeatedly been reported to be helpful for those with ES-MCS at American Council of Continuing Medical Education-accredited conferences of the American Academy of Environmental Medicine (www.aaemonline.org).

- ***Oxygen***
  - Baseline and post-chemical challenge brain perfusion decreases have been noted in MCS patients vs controls on single photon emission computed tomography (SPECT) brain scans (Orriols R, Costa R, Cuberas G, Jacas C, Castell J, Sunyer J. Brain dysfunction in multiple chemical sensitivity, Journal of the Neurological Sciences, 2009; 287:72-8). This may be why oxygen helps to relieve acute reactions (Rea WJ. Chemical sensitivity, Volume 4, CRC Lewis Publishers, 1997:2554-63). Empirically, Rea has also noted that severely ill chemically sensitive patients sometimes respond well to daily oxygen inhaled for two hours over an average of eighteen days. A hypothesized mechanism is that oxygen supplementation enables a microcirculation switch to allow better blood flow, more extraction of oxygen to the tissues and normalization of pH. (von Ardenne M. Oxygen multistep therapy: Physiological and Technical Foundations. Trans. Kirby P, Kruger W. New York: Georg Thieme Verlag Stuttgart, 1990: 1-73).

- ***Randomized Controlled Trials of Therapies***
  - While randomized controlled trials (RCTs) are extremely useful for deciding on the efficacy of a specific treatment such as a medication in comparison with other treatments or placebo, treatments such as desensitization for those with ES-MCS and severe allergies are individualized with respect to antigens, doses and timing, and so are not amenable to group RCTs. Two systematic reviews by the Succinct and Timely Evaluated Evidence Reviews (STEER) group in 2001 and 2003 noted this limitation. STEER was mounted to assist funding decisions in the National Health Service in the United Kingdom.

  - In group RCTs, there must be strict subject inclusion and exclusion criteria to reduce the 'noise' of other variables in assessing treatment outcomes. The population of potential ES-MCS subjects is extremely heterogeneous, and so, even if sufficient subjects could be found to meet eligibility criteria, the results would be unlikely to be generalizable to individual patients presenting to their physicians. Outcomes may be heterogeneous and difficult or impossible to quantify.

  - We are familiar with the method of critically appraising scientific papers called Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method (Guyatt GH et al, GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, BMJ 2008; 336: 924-926) as two of us, along with other members of the Environmental Health Committee of the Ontario College of Family Physicians, met with Dr. Gordon Guyatt last year about the possibilities of implementing the method in literature reviews in environmental health. As already discussed, environmental health is an extremely complex area to study.

  - Single subject (N-of-1) longitudinal treatment trials with extreme limitation of extraneous exposures in an environmental control unit have been suggested (Spencer TR, Schur PM. The challenge of multiple chemical sensitivity, Journal of Environmental health, June 2008; 70(10):24-7), and were successful in relieving symptoms, but with the disadvantage of extreme cost (Ross GH. History and clinical presentation of the chemically sensitive patient. Toxicol. Ind. Health. 1992; 8, 21-28).

- In theory, N-of-1 randomized controlled, double blind crossover trials of therapies, although cumbersome, might provide a level of evidence similar to group RCTs and have been tried with a university-based referral service doing N-of-1 trials at the requests of community and academic physicians (Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The n-of-1 randomized controlled trial: clinical usefulness, our three-year experience, Annals of Internal Medicine, February 15, 1990; 112(4):293-99). However, their utility was questioned (Tsapas A, Matthews DR. Using N-of-1 trials in evidence-based clinical practice, JAMA, March 11, 2009; 301(10), and Montori and Guyatt replied that the method worked best in individuals with a stable condition seeking symptom relief, and that the effect of the intervention should be short-lived (Montori VM, Guyatt GH. Reply, JAMA, March 11, 2009; 301(10). Unfortunately, this method may not be applicable to individuals with ES-MCS, given that their condition is chronic and very unstable depending on their daily exposures, and improvement would need to be evaluated over a longer period.

- ***Self-management Strategies***
  - In addition to reduction of exposure to triggering or toxic agents, individuals with MCS, as with other chronic illnesses, try many therapies to relieve symptoms and to improve quality of life. In the Gibson et al survey, a very wide range of therapies had been tried by a variable number of subjects for variable lengths of time. The therapies tried were perhaps attempts to address various determinants of health, for example nutritional/dietary interventions, physical therapies, medical interventions (e.g. oxygen therapy), psychosocial support therapies, and contemplative therapies. For example, our team has found, as did Gibson et al, that prayer, meditation and other contemplative methods, chosen according to each patient's needs and preferences, are frequently somewhat helpful, often in combination with other therapies listed. They are hypothesized to both dampen the overstimulation of the sympathetic nervous system related to the body's repeated recognition and response to symptom-initiating exposures in MCS, and to assist with coping (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1498-1504).

  - In attempting to enhance the doctor-patient relationship and to encourage self management, we at the Environmental Health Clinic (EHC) in Ontario have sometimes used a slightly whimsical metaphor, asking patients what they think might be needed in their particular situation to "plant a health garden", so that we could enjoy watching their health slowly grow. Tongue in cheek, we have noted that weeding, seeding and feeding is usually needed to grow a garden, and have asked what unnecessary aggravators they might 'weed' out of their lives, ask them to work with us on the individual components of planting SEEDS of health, and then 'feed' whatever helps. SEEDS is an acronym for Sleep, Exercise (and pacing), Environment, Diet (nutrition), and Support, and provides a framework for self-management that patients seem to find easy to follow. The application of this framework is described in a requested article based on a presentation to physicians at "Saturday at the University" at the University of Toronto (Marshall LM, Bested AC, Bray RI. Tools to treat Multiple Chemical Sensitivities, Chronic Fatigue Syndrome and Fibromyalgia, Canadian Journal of CME, University of Toronto Edition, January, 2004: 56-65).

  - An EHC physician is the primary author of a book with many self-management ideas (Bested AC, Logan AC, Howe R. Hope and help for chronic fatigue syndrome and fibromyalgia, 2nd Edition, 2008, Cumberland House, Nashville, Tennessee).

- The EHC nurse provides a set of printed resources as well as individualized verbal and written information and web links as appropriate to each patient, and is available to answer questions by telephone. Under her tutelage, University of Toronto nursing students research the literature and develop easily understood posters and pamphlets.

- Das-Munshi et al suggested that "A multifactorial model incorporating behavioural, physiological and sociological approaches may be useful", but focused on psychological, behavioural and conditioning factors and only suggested treatment in these areas, sometimes in combination with antidepressants (Das-Munshi J, Rubin GJ, Wessely S. Multiple chemical sensitivities: review, Current Opinion in Otolaryngology & Head and Neck Surgery, 2007; 15:277). The evidence of effectiveness cited by the authors, two psychologists and a psychiatrist, seemed to be largely based on single case reports or small case series. The authors also did not mention that antidepressants were found more likely to harm than help in the Gibson et al survey (Gibson PR, Elms AN-M, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, Environmental Health Perspectives, September 2003; 111(12):1502).

- The experience of the EHC team and other clinicians in Ontario and the U.S. has been in agreement with Gibson et al's finding that individuals with MCS often tolerate medications poorly. If prescribed, they commonly require much lower doses than usual, possibly because their capacity to metabolize drugs is compromised. Thus pharmaceuticals in MCS not only may not suppress symptoms, but also may exacerbate them. If symptoms are relieved, the underlying etiology may be obscured. Also, following avoidance of triggering agents, the symptoms in various body systems, including the central nervous system (e.g. emotional and cognitive symptoms), may improve significantly without need for medication.

- In response to a clinic needs assessment, EHC offered group classes to inform EHC patients about indoor air quality, nutrition, exercise and pacing, and the adverse impact of negative thinking on progress.

- In addition, from 1999-2005 (until resources ran out), a psychologist and an EHC physician ran an annual 10-week group psycho-educational program for EHC patients for 2 hours weekly, along with a 1 year follow-up group session for consolidation and evaluation, and a parallel individual counselling program. The program was conducted in a fragrance free environment, stretching and moving around as needed were encouraged, and a "smorgasbord" of strategies was used to meet needs while recognizing fluctuating neurocognitive deficits. The strategies included use of film clips to bridge sensation, affect and cognition, meditative inductions for grounding, relaxation, and symptom relief, education about the General Adaptation Syndrome (Selye H. The Stress of life, New York: McGraw-Hill, 1956), dealing with stressful situations, creating boundaries, and strengthening the ego, as well as locating new life purpose. Qualitative evaluations one year after completion of each group program repeatedly revealed surprisingly strong and unique uptakes and applications of various features of the program.

- Telemedicine, recently being piloted in the EHC, offers a tantalizing opportunity to serve more Ontarians with complex, chronic conditions with individual clinical consultations

and group programs close to home, as well as with educational programs for patients and health professionals.

Primary Prevention:

Dr. Herbert Needleman, Professor of Psychiatry and Pediatrics at the University of Pittsburgh suggested "We are conducting a vast toxicological experiment in which our children and our children's children are the experimental subjects" (Quoted by Dr. Philip Landrigan, Mount Sinai School of Medicine, keynote address to Children's Environmental Health II: A Global Forum for Action, Washington, DC, September, 2001, CPCHE Primer, August 2005:5). Protective policies have been successfully implemented in the face of some remaining scientific uncertainties in the case of tobacco smoke and pesticides. Reduction of exhaust fumes from vehicle idling, decreased exposure to smoke in public places, and the banning of the use of pesticides for cosmetic purposes have reduced exposure to these harmful substances for the entire population, and have been particularly helpful for the chemically sensitive.

- ***Health Promotion and Partnerships***
  - Although we at the Environmental Health Clinic work at the individual clinical level through comprehensive assessments and development of individualized treatment plans, we also work, often as volunteers, towards preventing or minimizing environment-associated illnesses at the population level through collaboration with universities, associations, and coalitions of like-minded, multi-sector organizations in research, education and promotion of policy changes. There has been growing public awareness of the impacts of various environmental exposures on health, aided in part by increased media attention and the explosion of information available on the internet. Since internet information is not always trustworthy, more and more patients are asking their most trusted health advisors, their physicians and other healthcare professionals, what actions they should be taking to protect themselves and their families (Hesse BW, Nelson DE, Kreps GL, Croyle RT, Arora NK, Rimer BK, Viswanath K. Trust and sources of health information, Archives of Internal Medicine, December 12/26 2005; 165:2618-24). This may be particularly so if patients have noticed associations between their symptoms and exposures to environmental substances or locations, or if their symptoms are ongoing and unexplained.

  - We think the physicians of tomorrow will need to be very conversant with the latest credible environmental health information. We teach/train a small number of medical and environmental studies students, nurses, residents and graduate physicians in collaboration with the Departments of Family and Community Medicine and Continuing Education and Professional Development at the University of Toronto. As long as clinic resources would permit, we also maintained a series of six annual accredited rounds and a one-year academic Environmental Health Fellowship Program. We also lecture to medical students at the University of Ottawa, University of Western Ontario, Northern Ontario School of Medicine, and to Master of Public Health students at Lakehead University.

  - The Environmental Health Clinic Staff Physicians, Nurse Educator, and Community Outreach Coordinator have served on international, national, provincial and local committees and panels to try to influence precautionary, protective policy development-for example, on an international Expert Medical Consensus Panel on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome selected by Health Canada; on Health Canada Committees and in Workshops on Children's Environmental Health and Impacts of the Environment on Older Adults; on the Canada Mortgage and Housing

Corporation's Task Force on Material Emissions; on the Ontario Ministry of the Environment's Toxics Reduction Scientific Expert Panel; on the Ontario Accessible Built Environment Standards Development Committee; and on the Occupational and Environmental Working Group of the Toronto Cancer Prevention Coalition.

- We have also participated in many reviews of scientific studies, synthesis of the evidence, and translation into papers, reports, primers, brochures, websites, case studies, teaching modules, and presentations for a variety of target groups locally, provincially, nationally, and internationally, in partnership with many different organizations.

- Some of our productive partnerships in environmental health promotion are listed in **Table 6** with websites for more information, and brief descriptions of projects we have, or are collaborating on with the listed organizations.

Table 6:

Examples of Environmental Health Promotion via Partnerships

Staff Physicians, Nurse Educator, and Community Outreach Coordinator of the provincial Environmental Health Clinic, Ontario, at Women's College Hospital

Canadian Coalition for Green Health Care (www.greenhealthcare.ca)- on an Ontario Trillium Foundation (OTF)-funded project on toxics reduction in health care facilities, fragrance free program/policy development, local food use in hospitals, + active problem solving via listserv.
Canadian Environmental Law Association (www.cela.ca) and the **Environmental Health Institute of Canada** (www.ehicanada.ca)- on an Ontario Law Foundation-funded project "Making the Links" between pollution, chronic health effects and poverty in six Ontario communities, selected for high prevalence of these and interest in addressing them.
Canadians for a Safe Learning Environment (www.casle.ca)- on "Guidelines to Accommodate Students and Staff with Environmental Sensitivities"
Canadian Institute of Child Health (www.cich.ca)- on Physician Master Training Program to train physicians to adapt World Health Organization modules on Children's Health and the Environment to their communities and to present them in day-long workshops. Five workshops were presented across Ontario in 2009, funded by the Ontario Ministry of the Environment.
Canadian Institutes of Health Research-funded "Toxic metals in Canadians and their environments- Exposures, health effects and physical and public health management standards: A scoping review"- Co-principal investigators Drs. Margaret Sears and Riina Bray; acknowledged consultants Drs. John Molot and Lynn Marshall.
Canadian Partnership for Children's Health and the Environment (CPCHE) www.healthyenvironmentforkids.ca- 12 health, public health, environmental, and child care partner organizations that have worked together on multiple projects since 2001- e.g. collection of training materials and resources, fact sheets and flyers posted on website in English and French including Child Health and Environment: A Primer, and the CPCHE brochure Playing it Safe: Childproofing for Environmental Health, 2005; Playing It Safe: Service Providers Strategies to Reduce Environmental Risks to Preconception, Prenatal and Child Health, 2006; National Policy Consultation in 2007; First Steps in Lifelong Health: A Vision and Strategy for Children's Environmental Health in Canada, 2008; a multi-year "Engage, Enable and Empower (E3)" project, funded by the Public Health Agency of Canada (PHAC) to create local community champions, completed in 2009; Advancing Environmental Health in Child Care Settings: A Checklist for Child Care Practitioners and Public Health

Inspectors, funded by the Ontario Trillium Foundation and Health Canada, 2010. **CPCHE and Ontario Chronic Disease Prevention Alliance** (www.ocdpa.on.ca)- together on an Ontario Trillium Foundation (OTF)-funded project studying early life exposures and the risk of chronic disease- held day-long evidence/policy workshop on bisphenol A in May, 2010.
Canadian Transportation Agency-on a commissioned report "Air travel and chemical sensitivities", co-authors Drs. John Molot, Lynn Marshall and Margaret Sears.
Centre for Equality Rights in Accommodation (www.equalityrights.org/cera)- on an OTF-funded "Creating Healthy Housing" project to address the needs of the chemically sensitive.
Community Care Access Centres Ontario- on interactive presentations and resources to improve accessible home care for those with MCS.
Environmental Health Association of Nova Scotia (www.environmentalhealth.ca)- e-mail contact and use of guide to less toxic cleaning, laundry, and personal care products, www.lesstoxicguide.ca.
Environmental Health Association of Ontario (www.ehaontario.ca) provides representative consumer advisors to the Ontario Environmental Health Clinic on an ongoing basis.
Environmental Health Association of Quebec (www.aseq-ehaq.ca)- on simultaneously translated workshops on Children's Health and the Environment and Complex Chronic Conditions ME/CFS, FM and MCS at Annual Scientific Assembly, November 2009, which had an Environmental Health theme.
Environmental Health Institute of Canada (www.ehicanada.ca)- on the "Making the Links" project with the Canadian Environmental Law Association, the Ontario Trillium Foundation grant on toxics reduction in health care with the Canadian Coalition for Green Health Care, and on the Environmental Health Day to be held in November, 2010.
Healthy Indoors Partnership (www.healthyindoorspartnership.ca)- on development of multi-stakeholder consensus brochures on "Products and Services with Low Chemical Emissions".
Myalgic Encephalomyelitis Association of Ontario (MEAO) www.meao.ca- provides ongoing consumer advisory service to the Ontario Environmental Health Clinic; worked with **National ME/FM Action Network** www.mefmaction.net, and **Environmental Health Association Ontario (EHAO)** www.ehaontario.ca - on International ME/FM/MCS Day, May 12, 2010.
National ME/FM Action Network www.mefmaction.net- on extracting needed data from the public use microdata files of the Canadian Community Health Survey, Statistics Canada.
Nurses' Environmental Reference Group, now part of the **Canadian Nurses' Association**- a teleconference and listserv started by the Environmental Health Clinic nurse after publication of an article in Canadian Nurse (Fraser G. Environmental Health and Nursing, Canadian Nurse, 16 January, 2004). http://www.cna-aiic.ca/CNA/issues/environment/default_e.aspx
Ontario College of Family Physicians www.ocfp.on.ca →**Environmental Health Committee**- on many projects e.g. on Children's Environmental Health, Complex Chronic Conditions, Heavy Metals, Outdoor and Indoor Air quality, Uranium Mining, Urban Sprawl etc. Affiliated with Environmental Health Committees of the **College of Family Physicians of Canada** and the **World Organization of Family Doctors, WONCA**.
Toronto Cancer Prevention Coalition www.toronto.ca/health/resources/tcpc - on a GTA Cancer Prevention and Screening Network-funded pilot project to increase awareness of environmental links to breast cancer, and spearheaded the establishment of an Environmental Disclosure and Reporting Bylaw in Toronto: the first "community right to know" bylaw in Canada.
Toronto Public Health and South Riverdale Community Health Centre- on updated resource

for prenatal educators, Hidden Exposures: Informing pregnant women and families about harmful environmental exposures http://www.toronto.ca/health/hphe/pdf/hidden_exposures.pdf .
University of Toronto Medical students' 'Determinants of Community Health 2'- on course projects annually- e.g. in 2009-2010 a student interviewed patients and hospital staff for ideas on updating "Environmental Health in Hospitals: Environment-sensitive Care" guidelines, that are posted as a patient/physician resource on www.mcscanadian.org/hospital.html.
U.S. Environmental Protection Agency-funded study of heat depuration/nutrition treatment in chronically ill, chemically sensitive 9/11 rescue workers is underway- co-investigator Dr. Kathleen Kerr, Environmental Health Clinic physician.
Women's College Hospital Green Team- energy conservation, recycling, and toxics reduction, e.g. mercury in medical devices, safer cleaning products, fragrance free program/policy.
Women's Health Matters www.womenshealthmatters.ca **-Environmental Health Centre-** information and answers to questions from the public.

APPENDIX C

SEEDS of Health

Complex Chronic Conditions Contributors- Gene-Environment Interactions

Genetic Susceptibilities- Family history- a warning about potential hazards
Environmental Factors- Minimize hazard- maximize function

The Weed, SEEDS, and Feed Approach:

Weed out as many stressors as possible.

Plant SEEDS of Health: S leep
E xercise
E nvironment
D iet/Drugs
S upport

Feed whatever works!

SEEDS of Health Examples

S leep- Onset, awakenings, restless legs, apnoea, pain or other symptoms

Sleep hygiene, symptom relief, self hypnosis, melatonin, hypnotics if necessary

E xercise- Balance between conditioning and over-exertion

Recognition of physiological limitations, pacing activities with rest, building

E nvironment- External- Air quality- outdoors, indoors
Food- pesticides, additives, colourants, allergies, intolerances
Water- chemical contaminants, microbes
Contactants and consumer products- hazardous chemicals, endocrine disruptors

Minimize (avoid) unnecessary exposures that put extra load on body's defence mechanisms

Internal- Imbalances in operation of any/many body systems from environmental overload (influenced by genetic susceptibilities)→ reduced defences against infections, injuries, chemicals, electromagnetic radiation, stressful events → chronic inflammation, oxidative stress within cells→ more malfunctioning

Correct imbalances, along with reducing environmental load

D iet and Drugs- Macro and micronutrients intake, absorption, utilization
Medications- effects and side effects

Ensure adequate nutrition to compensate for increased metabolic need

S upport- External- Family, friends, health care system respect, health care providers, religious communities, financial, safe housing, social services, activities of daily living

Family/friend/caregiver individual or group educational and support meetings
Health provider case conferences
Advocacy for financial, housing and social service support

Internal- Self support- resilience-sustaining thoughts, activities

Encouragement through individual health professional or religious support and/or groups

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