THE WALKERTON HEALTH STUDY
2002-2008

Final Report
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and Long-Term Care

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Walkerton Health Study

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EXECUTIVE SUMMARY

BACKGROUND
In May of 2000 many of the current WEL (Walkerton E. coli Long-Term) Investigators were busy treating children and adults severely ill as a result of the contamination of the municipal water supply of a small Ontario rural community called Walkerton. The explosive onset and magnitude of involvement (almost 50% of the community) focused acute medical care predominantly on severely afflicted children and adults. Previous biological and observational studies had suggested that survivors of E. coli O157:H7 and campylobacter gastroenteritis may have poor long term health outcomes, regardless of whether they initially experienced overt severe clinical symptoms culminating in haemolytic uremic syndrome (HUS). This concern about a significant unrecognized long-term burden of illness secondary to the bacterial water contamination stimulated a small group of physicians (original WEL Investigators) to develop a simple screening program to identify silent complications of the water contamination. They then arranged a meeting with Walkerton area physicians. The meeting escalated from an informal exchange of screening advice to a formal presentation, attended by more than 120 municipal leaders, concerned citizens, physicians and allied health workers. The WEL Investigators were strongly encouraged by these representatives to go back to the drafting boards for a new proposal with a more complete long-term screening program, embracing direct health care interventions and epidemiologic research. The advice led to a formal submission to the Ontario Ministry of Health requesting support for a seven-year prospective longitudinal study to characterize and manage the long-term medical complications from the water contamination in Walkerton Ontario in May 2000. The Ministry of Health and Long-Term Care, after reviewing a detailed proposal, agreed to fund what is now the Walkerton Health Study. The proposal incorporated a union of clinical practice and research to:

a) characterize the long-term burden of illness attributable to the water contamination by a serial, active screening process,
b) to co-ordinate health services by identification and referral of individuals at risk for complications for more complete investigation and treatment in order to reduce and prevent long term medical complications.

METHODS
The study was a retrospective population-based cohort study with prospective follow-up. Beginning in 2002 we invited all residents of Walkerton and the surrounding areas, regardless of whether or not they drank the water, to participate in the long term follow-up by attending an annual clinic. The screening clinic operated from March to August of every year. Off-site clinics were offered at the Nursing Home, Retirement Home and local high schools. Specialty clinics operated from May to August of every year, allowing participants immediate access to care provided by nephrologists, paediatricians, gastroenterologists, endocrinologists, and rheumatologists.

RESULTS
Sample Description
Between March 2002 and August 2008 4,561 residents of Walkerton and the surrounding area participated in the study. The age and sex distribution of the
participants was characteristic of the population of Walkerton at the time of the outbreak. Most participants (70%) were from the immediate Walkerton area defined by the postal code of N0G 2V0. Although the majority (98%) reported drinking Walkerton tap water at the time of the outbreak, only 65% experienced any illness as a result. The symptoms ranged from mild stomach upset (5%) to more severe gastroenteritis with bloody diarrhea. Participants attended an average of 5 follow-up assessments with an average of 6 years between their first and last assessment.

**Self-Reported Health Outcomes**

Beginning in 2004, participants were asked to rate their overall health status in general and compared to the previous year. Of 3,763 participants who had an opportunity to respond to this question, 85% reported being in good to excellent health at their last assessment and 83% reported their health being stable or better than last year. Chronic gastrointestinal complaints were common, with 28% of participants complaining of regular problems with abdominal pain or discomfort, constipation, or diarrhea on average 4 or more days a month at their last assessment. The percent of participants with gastrointestinal complaints decreased from 47% in the first year of screening to 27% in year 7. In response to concerns about irritable bowel syndrome, a booklet, authored by Dr. John Howard, was distributed to over 1,200 participants, and was made available in doctors’ offices and the public library. In addition, over 1,000 participants, as well as their family members, were invited to attend group information sessions designed to help individuals cope with the symptoms of irritable bowel syndrome. These sessions were also advertised locally and open to the public free of charge. Those with more serious complaints were seen individually by a gastroenterologist. The incidence of other self-reported health outcomes was within expected limits. The association of acute gastroenteritis with subsequent hypertension, diabetes, and/or arthritis was examined in more detail as part of specific research protocols.

**Impact Of Surveillance On Blood Pressure Control In The Walkerton Health Study**

A trend towards improved detection and treatment of hypertension was observed over the course of the WHS. In the first year of screening, the proportion of hypertensive participants with controlled blood pressure was only 9%. After four years of screening, the control rate stabilized to approximately 50%. The prevalence of hypertension among all adult participants increased from 27% in 2002 to 42% in 2008, largely the result of surveillance. During this time, the proportion of participants who achieved successful control of their blood pressure increased from 3% to 22%.

**Clinical Care**

At the completion of the study in August, 2008, 3,219 referrals had been made for 2,244 participants to specialist assessment or follow-up laboratory investigation. Over the course of the study, 1190 referrals were made for possible kidney disease (based on elevated blood pressure, serum creatinine or proteinuria) among 464 adult patients; 437 were seen by a nephrologist at least once. Of 252 children identified with possible kidney disease, 97% were seen by a nephrologist or are awaiting an appointment. Gastroenterologist consults were offered to 538 participants, and 523 were seen in clinic. Dysglycemia was identified in 783 participants and 610 agreed to further testing. Specialty clinics were established to provide follow-up and counseling to newly identified diabetics. Participants referred for possible reactive arthritis were invited to an assessment by a rheumatologist.
LONG-TERM HEALTH SEQUELAE FOLLOWING EXPOSURE TO WATER CONTAMINATED WITH E. coli O157:H7 AND CAMPYLOBACTER

Research suggests that survivors of severe E. coli O157:H7 infection and Campylobacter gastroenteritis have poorer long-term health regardless of whether they initially experienced overt Haemolytic uremic syndrome. The WHS provided a unique and rare opportunity to characterize new and existing epidemiological associations between acute gastroenteritis and chronic diseases.

Diseases studied included renal disease (hypertension, albuminuria, and glomerular filtration rate), diabetes, irritable bowel syndrome (IBS), and reactive arthritis. Long-term renal sequelae were evaluated separately for children and adults.

A summary of the long-term health sequelae among adults is presented in Figure 1. Within 2 years of the outbreak, a more than three-fold increase in the risk of developing IBS was observed among Walkerton residents who experienced bacterial gastroenteritis during the outbreak. Within 4 years of the outbreak, a 33% increase in the risk of developing hypertension and a 38% increase in the risk of developing reactive arthritis was seen among those with symptoms of severe gastroenteritis as compared to those who were not ill at the time of the outbreak. A similar graded association was seen for reduced kidney function. No associations were observed between gastroenteritis and the subsequent risk of albuminuria or dysglycemia (diabetes mellitus, impaired glucose tolerance or impaired fasting glucose). Among women who became pregnant after the outbreak, higher mean arterial pressure and pregnancy-related hypertension were observed among women who reported symptoms of gastroenteritis compared to those who were asymptomatic; however, the observed differences were not statistically significant, possibly due to the small sample size.

No renal sequelae were observed among children within 4 years of experiencing gastroenteritis without Haemolytic uremic syndrome (HUS) during the outbreak. Despite the absence of evidence of renal damage in this group of children, most progressive renal disease involves a protracted time course; therefore a longer follow-up of this is planned to clarify the risk of nephropathy after childhood E. coli O157 bacterial gastroenteritis.

Childhood survivors of HUS were more likely to show microalbuminuria (Figure 2) and lower glomerular filtration rate (GFR) than healthy controls; however, the prognosis of these cases was better than reported in previous research. None of the HUS survivors in the WHS cohort had overt proteinuria or GFR less than 80 ml/min, and their blood pressure was no higher than expected for community norms.
Figure 1. Age and sex standardized rates of long-term health sequelae following exposure to water contaminated with *E. coli* O157:H7 and Campylobacter.

*Pregnancy-related hypertension. **Irritable bowel syndrome.

Figure 2. Rate of microalbuminuria among childhood survivors of haemolytic uremic syndrome (HUS).
**DISSEMINATION OF RESULTS**

An important goal of the Walkerton Health Study was to disseminate research findings to a wide audience that included both the Walkerton community and the research community. Dissemination of results to the Walkerton community was primarily accomplished through newspaper articles and Town Hall meetings, which were held annually in Walkerton. During Town Hall meetings, WEL investigators presented results from the previous year, highlighted any new initiatives for the upcoming year and answered questions from the public. Participants also received an annual summary report, and highlights of the previous year’s findings were reported in the Walkerton Herald Times.

Dissemination of results to the research community occurred primarily through publications in peer reviewed scientific journals and presentations at conferences. In addition, highlights from the study were shared with the medical community at a special symposium in 2008 that focused on thrombotic thrombocytopenic purpura / haemolytic uremic syndrome (HUS/TTP). The purpose of the HUS/TTP symposium was to present findings on the long-term outcomes following exposure to *E. coli* O157:H7. A half-day session was reserved for the presentation of results from the Walkerton Health Study.
BACKGROUND:
The most serious case of water contamination in recent Canadian history occurred in May of 2000, when the municipal water of Walkerton, Ontario was contaminated with *E. coli* O157:H7, campylobacter species and salmonella. Heavy rainfall contributed to the transport of livestock fecal contaminants from a nearby farm into a shallow municipal well. Inadequate chlorination resulted in the bacterial contamination of the Walkerton drinking water system and the inevitable exposure of thousands of individuals from Walkerton and the surrounding areas by means of primary or secondary contact. The result was an estimated excess of 2,300 cases of gastrointestinal illness, more than 750 emergency room visits, 65 hospital admissions, 27 recognized cases of haemolytic uremic syndrome (HUS), and seven deaths. During the catastrophe, initial medical care focused on the acute management of infected individuals. Due to the intense load on the health care system, children were encouraged to seek medical care; whereas, adults were not. However, previous biological and observational studies suggest that survivors of campylobacter gastroenteritis and severe *E. coli* O157:H7 infection may have poorer long-term heath, regardless of whether they initially experienced overt haemolytic uremic syndrome. The Walkerton Health Study (WHS) was funded by the Ontario Ministry of Health and Long-Term Care to direct attention towards the potential, significant, unrecognized, long term burden of illness from complications caused by the initial infection. The screening program was established not only to monitor asymptomatic, silent disease, but also to provide access to care for patients who were symptomatic and had complications related to *E. coli* O157:H7 or campylobacter species or a combination of both. In this way the WHS incorporated an effective union of clinical practice and research to meet both the needs of the community and provide a unique opportunity to characterize the association between acute bacterial gastroenteritis and chronic diseases, including arthritis, hypertension, renal disease, diabetes, post-infectious irritable bowel syndrome, and inflammatory bowel disease.

OPERATIONS
The Walkerton Health Study was a collaborative effort of an experienced team of researchers and clinicians who were involved in the initial response and care of the community at the time of the outbreak in 2000. The WEL Investigators, consisting of Dr. W. Clark, Dr. A. Garg, Dr. Howard, Dr. Matsell, Dr. L. Moist, Dr. M. Salvadori and Dr. R. Suri in collaboration with Dr. S. Collins and Dr. J. Marshall brought with them expertise in Nephrology, Paediatrics, and Gastroenterology. Additional expertise was provided by research consultants in Nephrology (Dr. J. Garland), Epidemiology (Dr. J. Macnab & Dr. J. Sontrop), Endocrinology (Dr. J. Mahon), Geography (Dr. Joy Parr), Rheumatology (Dr. J. Pope), and Neurology, (Dr. J. Ray). Support staff over the years included Project Administrators (Ms. Ruby Gordon, Ms. Jennifer Dunn & currently, Ms. Shawn Leinweber-Miller), a Systematic Review Analyst (Dr. P. Rosas-Arellano), and research assistants (Ms. Marroon Thabane, Dr. Gina Garofeanu and Ms. Salina Chen).

WALKERTON SCREENING CLINIC
The Walkerton Health Study Clinic was located in the South Bruce Grey Health Centre in Walkerton, Ontario and was managed by an on site Nurse Coordinator (Mrs. Arlene Richards). The clinic employed additional Clinical Care Assistants (most recently - Mrs. Lisa Finlay and Mr. Peter Richards) and clerical personnel (most recently - Mrs. Sheryl Campbell and Mrs. Kathleen Keeshan). The Nurse Coordinator and Clinical Care Assistants performed height, weight and blood pressure measurements as well as
conducting an annual health interview. Clerical personnel were involved in appointment scheduling, patient follow-up, data entry, and quality control procedures. Specialty clinics, staffed by a nephrologist, paediatrician, gastroenterologist, endocrinologist, rheumatologist, and/or neurologist were operated every summer from May to August for patients in need of further assessment or care.

**OPERATIONS AND RESEARCH COMMITTEE**

The Operations Committee and the Research Committees chaired by Dr. W.F. Clark served to oversee the conduct of all aspects of the study. The operations committee met monthly and was open to WEL investigators, clinic staff, and representatives from the Ministry of Health. The research committee provided a forum to guide the development of a number of relevant and collaborative research foci, in the context of the Walkerton E. coli outbreak, yet distinct from the clinical responsibilities of the group. Evidence for all research was supported by preliminary reviews, conducted by our systematic review analyst, Dr. P. Rosas-Arellano and more latterly by Ms. Salina Chen and Dr. Jessica Sontrop.

**METHODS**

**STUDY DESIGN AND COHORT DEFINITION**

The Walkerton Health Study was a retrospective population-based cohort study with prospective follow-up. Beginning in 2002 we invited all residents of Walkerton and the surrounding areas, regardless of whether or not they drank the water, to participate in the long-term follow-up by attending an annual clinic. The majority of participants joined the study in 2002; however, new participants were allowed to enter the study each year to ensure that no one missed the opportunity for screening and/or clinical care. On an annual basis, an extensive advertising campaign was mounted in the local newspapers, radio, and Cable TV. Posters were displayed in hospitals, physician offices, pharmacies, the library and other strategic locations around town additionally flyers were inserted into all of the town’s post office boxes. Interviews were conducted with both the local and national media. Yearly, we presented the findings to the people of Walkerton at a Town Hall meeting and a summary letter was sent to each participant. In addition, in 2003, a telephone campaign was conducted to encourage participation among residents of the NOG 2V0 postal code by contacting 1,147 non-participating households. The screening clinic operated from March to August of every year and provided evening and Saturday appointments in addition to regular workday hours. Off-site clinics were offered at the Nursing Home, Retirement Home and local high schools. The reception staff personally contacted all participating households, so that direct contact could be made to book appointments. Reminder calls were made the day before all clinics and no-shows were diligently followed-up. Individuals who moved away from the area were able to complete the screening survey by telephone and have their laboratory testing and other measurements completed through their family physician. The WHS enrolled participants from as far away as Newfoundland, Manitoba, Saskatchewan, North West Territories and the United States. A modest honourarium was offered to all participants who attended the screening clinic to offset their costs for lost time.

**DATA COLLECTION**

To assist in the identification of pre-existing disease and to collect evidence of level of exposure, consent was obtained from 98% of participants for an audit of laboratory data
and medical charts. Participant information was linked to information collected at the time of the outbreak by means of name, date of birth, telephone and/or address. Participant information was linked to laboratory data collected through the Triple G system servicing the Walkerton area from 1990-2002 by means of the hospital identification number.

All data was collected using computer assisted personal interviews (CAPI). Upon entry to the study all participants completed a series of baseline questions that documented their demographic information, exposure and illness at the time of the outbreak, previous medical history, family history, and risk factors. In subsequent years participants were asked to report on their general overall health, gastrointestinal complaints, and any health conditions diagnosed by a health professional; including diabetes, hypertension, cardiovascular disease, inflammatory bowel disease, cancer, arthritis, and gallstones. The development of questions on the health survey was guided by the US Third National Health and Nutrition Survey and Statistics Canada’s National Population Health Survey. All participants were requested to complete a random urinalysis, serum creatinine, random glucose, and 24 hour urine collection upon entry to the study. A serum creatinine and random urinalysis was ordered annually. Additional testing varied by study year, so as not to place too high a burden upon the participants, and included fasting serum glucose, oral glucose tolerance testing (when indicated), and repeat 24 hour urine collection. In the final year a more definitive test of renal function, Cystatin C, was added to the laboratory protocol. This measure will be used to obtain a more accurate assessment of the estimated glomerular filtration rate (GFR).

Figure 3. Study design and data collection in the Walkerton Health Study
WEB-BASED DATA CAPTURE AND PATIENT MANAGEMENT SYSTEM

PrivIT Healthcare, previously known as Medix Technologies, supported the development and ongoing maintenance of our web-based data capture and electronic medical record system. The production database was housed on a server located in the Walkerton Hospital. Only clinic staff had access to this server. An export server, test server and backup server were housed in a secure data centre located in the Stiller Centre, at the University of Western Ontario (UWO) Research Park. Working closely with the Privacy/Ethics Review Boards recommendations, PrivIT Healthcare supports scientists and researchers to store, manage and preserve their data to ensure their enhancement and their continuing long-term use. Password protection and data encryption are used to ensure the privacy of the electronic patient medical record. In 2003 an interface with the Triple G laboratory system was developed to batch import lab results directly from Triple G into our database. In 2007, a new real-time interface with the CERNER system at the South Bruce Grey Health Centre was implemented to allow for the direct transfer of laboratory data. Laboratory data collected outside of the CERNER system were entered by hand into the database by means of the manual laboratory data interface. The system included automated queries that facilitated clinic operations by automatic monitoring of clinical care pathways. Medical records were electronically tracked and clinic staff was alerted of any missing laboratory or form data. Data validation procedures, implemented at the time of data entry, minimized the time required for data cleaning prior to analysis and ensured the highest standards of quality for clinic operations. The system facilitated research operations by allowing for the easy generation of flat tables appropriate for data analysis. Personal identifiers are removed prior to exporting data for analytical purposes. At the completion of the study we will be able to generate an electronic Health Report that will be shared with both the participants and the community physicians. By March 2009, all hard copies of clinical records will have been scanned and stored as electronic documents; paper records will be destroyed. The web site will be disassembled with all data stored in electronic anonymized flat tables. For patients who have consented to long-term data linkage, numeric identifiers will be stored in a separate linkage file. All data will be stored on a secure server at the Lawson Health Research Institute. All data will be destroyed after the period of consent has expired.

RESULTS

SAMPLE DESCRIPTION

At the conclusion of the study in August 2008, 4,561 participants had registered in the Walkerton Health Study. Figure 4 shows study accrual over the past seven years. Annual attendance figures ranged from a high of 3,959 in year 1 to a low of 2,432 in year 6. New participants were welcome to enter the study every year; 602 new participants joined the study after the first year. Each year, about 7% of participants were either lost to follow-up, died, or withdrew from the study. In total, 21% withdrew before completing the year 7 survey, 23% were lost to follow up, and 3% died. On average, participants attended 70% of all follow-up assessments.
Figure 4. Study flow chart.

<table>
<thead>
<tr>
<th>STUDY YEAR</th>
<th>REGISTER</th>
<th>SCREEN</th>
<th>TERMINATE</th>
</tr>
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<tbody>
<tr>
<td>2002</td>
<td>3959</td>
<td>3959</td>
<td>519</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98 Lost to follow up 388 Withdrawn 33 Deaths</td>
</tr>
<tr>
<td>2003</td>
<td>356</td>
<td>3373</td>
<td>277</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66 Lost to follow up 192 Withdrawn 19 Deaths</td>
</tr>
<tr>
<td>2004</td>
<td>182</td>
<td>3462</td>
<td>331</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>139 Loss to follow up 163 Withdrawn 29 Deaths</td>
</tr>
<tr>
<td>2005</td>
<td>22</td>
<td>3161</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>154 Lost to follow up 187 Withdrawn 19 Deaths</td>
</tr>
<tr>
<td>2006</td>
<td>18</td>
<td>2739</td>
<td>349</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>259 Lost to follow up 70 Withdrawn 20 Deaths</td>
</tr>
<tr>
<td>2007</td>
<td>13</td>
<td>2432</td>
<td>274</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>232 Lost to follow up 32 Withdrawn 10 Deaths</td>
</tr>
</tbody>
</table>
Figure 5 and Figure 6 summarize the number of follow-up visits (out of a maximum of 7) and the number of years of follow-up between the first and last assessment, respectively. Overall, 1,568 participants completed all 7 follow-up assessments, 612 attended 6 assessments, 524 attended 5 follow-up assessments, 406 participants attended 4 assessments, 404 attended 3 assessments, 428 attended 2 assessments and 619 attended only 1 assessment. The years of follow-up between the first and last assessment ranged from 1 to 7 years with a median of 6 years of follow up.

Figure 5. Total number of follow-up assessments.

Figure 6. Years followed from study entry to study exit.

Figure 7 shows the sample age distribution relative to the age distribution from population estimates for the town of Walkerton and Brockton Township from the 1996 and 2001 census. Participation varied with age and sex; with lower participation rates in the 20-24 and over 75 age categories, and with females being more likely to participate than males (Figure 8). Overall, the study age and sex distribution is representative of the population of Walkerton at the time of the outbreak.
Figure 7. Age distribution of study participants relative to the age distribution of the town of Walkerton and Brockton Township.


Figure 8. Age distribution of WHS participants at time of outbreak: Males versus Females.
Most (70%) participants were from the immediate Walkerton area, as defined by the postal code of N0G 2V0. Although the majority (98%) of participants reported drinking Walkerton tap water at the time of the outbreak, only 65% experienced any illness as a result. The symptoms ranged from mild stomach upset (5%) to more severe gastroenteritis with bloody diarrhea (see Figure 9).

Figure 9. Self-reported illness at the time of the outbreak in May 2000.

**SELF REPORTED HEALTH OUTCOMES**

Beginning in 2004, participants were asked to rate their overall health status in general and compared to the previous year. Of the 3,763 participants who responded to this question, 85.3% reported being in good to excellent health at their last assessment and 82.5% reported their health being stable or better than last year (Figure 10 and Figure 11). Among the 552 participants who reported their health as fair to poor, 44% reported that their health had remained stable or improved compared to last year; whereas, 57% reported that their health had continued to decline. Chronic gastrointestinal complaints continue to be a concern with 28% of participants complaining of regular problems with abdominal pain or discomfort, constipation, or diarrhea on average 4 or more days a month at their last assessment. This concern is slowly improving resulting in a decline in complaints from 47% in the first year of screening to 27% in year 7. In response to the on-going concerns about irritable bowel syndrome, a booklet, authored by Dr. John Howard especially for the citizens of Walkerton was distributed to over 1,200
participants, as well as being made available in doctors’ offices and the public library. Every year group information sessions were held to help individuals better cope with the symptoms of irritable bowel syndrome. Over 1,000 participants, as well as their family members, were invited to attend. In addition, the sessions were advertised locally and open to the public free of charge. Individuals with more serious complaints were seen one on one by a gastroenterologist.

The incidence of self-reported diagnoses is presented in Figure 12. Yearly incidence is presented after the outbreak. Although self-reported data cannot be considered definitive, it does provide us with a quick snapshot of the health profile of the community. The incidence of most health outcomes is well within expected limits. Hypertension, diabetes, and arthritis may be slightly higher than expected and as such were investigated as part of specific research protocols.

Figure 10. Self-reported health status at last assessment
Figure 11. Health compared to last year at last assessment.
Figure 12. Self-reported health outcomes.
IMPACT OF SURVEILLANCE ON BLOOD PRESSURE CONTROL IN THE WHS

Hypertension is the most common treatable risk factor for cardiovascular disease. Treating hypertension results in a substantial decrease in cardiovascular morbidity and mortality. Although treating and controlling hypertension is relatively straightforward and achievable, the silent nature of the condition means that many escape detection in the absence of active surveillance or regular medical check-ups. This may be particularly true in rural communities if access to health care professionals is limited. Unlike most medical conditions, community surveillance has been the most common approach to increase awareness, treatment and control of high blood pressure.

While treatment for hypertension has improved dramatically since the 1960’s, the majority of hypertension cases live with undetected or poorly controlled hypertension. The prevalence of hypertension in Canada is estimated to be between 21%-34%.

A trend towards improved detection and treatment of hypertension was observed over the course of the WHS. The prevalence of hypertension among adult participants increased from 27% in 2002 to 42% in 2008, largely the result of improved identification of previously unidentified hypertension by means of serial surveillance (Figure 13). During this time, the proportion of participants who achieved successful control of their blood pressure to normotensive levels increased from 3% to 22%. In contrast, the proportion with uncontrolled hypertension decreased from 25% to 20%.

Figure 13. Prevalence and control of hypertension among WHS participants (Adults, 18+).

Among participants with hypertension, the proportion receiving treatment increased substantially, from 18% in 2002 to 77% in 2008. In the first year of screening, the proportion of hypertensive participants with controlled blood pressure was only 9% (Figure 14). After four years of screening, the control rate stabilized to approximately 50%. Following the opposite trend, the rate of uncontrolled hypertension among hypertensive participants decreased from 91% in 2002 to 48% in 2008. These results
demonstrate a clear benefit of community-screening programs on awareness, treatment and control of hypertension.

Figure 14. Rate of hypertension control among hypertensive participants.

![Rate of hypertension control among hypertensive participants.](image)

**FLUID INTAKE AND WATER CONSUMPTION**

Five years after the outbreak, participants were asked about their beliefs and behaviours with respect to water consumption. The majority of WHS participants indicated they consumed an average of 5-8 glasses of fluid per day (61%); however 23% reported drinking 9-12 glasses/day and 6% reported drinking more than 12 glasses per day, despite being aware of the recommended daily intake of 6-8 glasses per day. Nearly all (99%) participants believed that water was a key ingredient in a healthy diet and believed that most people did not drink enough water. Eighty percent (80%) of participants indicated they made a 'conscious effort to drink water every day' and 30% believed that 'you cannot drink too much water'. Additional beliefs about water consumption and bottled water are summarized in Figure 15.
Figure 15. Participant beliefs about water consumption and bottled water.

- Believe bottled water is healthier than tap water
- Take bottled water when going out
- Prefer bottled water to tap water
- Believe drinking water helps with weight loss
- Make a conscious effort to drink water everyday

CLINICAL CARE
At the completion of the study in August 2008, 2,244 of the participants had been offered multiple referrals to specialty clinics or follow-up laboratory investigation. The number of referrals per patient ranged from 1 to 11. A total of 1,947 specialty assessments were completed over the seven years as well as 801 special investigations for oral glucose tolerance and high volume proteinuria. A summary of the specialty visits and special investigations is presented in Figure 16.
KIDNEY DISEASE - ADULT
Participants who were 18 years of age or older and were identified, based on either physical exam or laboratory results, as having proteinuria, elevated serum creatinine, or elevated blood pressure were offered a referral to an adult nephrologist. Over the course of the study, 464 participants were offered anywhere from 1 to 6 assessments with an adult nephrologist. A total of 654 consults were completed for 437 patients. The majority of these patients (71%) required only 1 assessment; however, 126 were seen up to 6 times in repeated assessments.

KIDNEY DISEASE - PAEDIATRIC
There were 252 children who were identified by an internal algorithm, which screened for elevated blood pressure, abnormal kidney function, or a past history of developing haemolytic uremic syndrome during the contaminated water outbreak. All children were offered appointments with a pediatric nephrologist. A total of 430 consults were completed for 243 children; 7 families declined the appointments or were unavailable. Most children (68%) were seen at least once and children who had experienced HUS at the time of the outbreak were offered appointments annually.
GASTROINTESTINAL DISEASE
In addition to yearly information sessions on irritable bowel syndrome, specialty clinics were offered in gastroenterology for patients with more serious gastrointestinal complaints. Five hundred and thirty-eight (538) patients were offered one or 2 individual consults with a gastroenterologist. A total of 562 consults were completed for 523 patients.

DIABETES
Beginning in the second year of the study, patients with HUS at the time of the outbreak and all participants over the age of 10 years who were not aware of being previously diagnosed with diabetes were asked to withhold from eating or drinking for 12 hours prior to their appointment. At that time a fasting serum glucose test was performed. Seven hundred and eighty-three (783) patients identified as dysglycemic based on fasting glucose levels between 5.3 and 6.9, potentially indicative of the presence of diabetes, were recalled for glucose tolerance testing and 610 completed the test. All newly identified diabetics were referred back to the care of their family doctor and the family doctor was provided with a copy of current practice guidelines for the management of diabetes. Repeat oral glucose tolerance testing was offered to 135 patients and 102 completed the test. Specialty clinics were set up to provide follow-up and counseling to any patient identified as being diabetic on the basis of their oral glucose tolerance testing. One hundred and nine patients (109) identified by the screening procedures were offered one or more follow-up consults with an endocrinologist. Seventy-eight (78) patients attended, with 6 returning for a repeat consult. Testing identified 45 new diabetics in that they have no previous history of diabetes based on either self-report or an audit of medical and laboratory records. Fifty-one (51) participants were flagged as being in the “pre-diabetic” range and were monitored closely in subsequent years.

RHEUMATOLOGY
In the first year of the study, 125 participants who indicated they had red, hot, swollen joint(s) were assessed by a rheumatologist. The vast majority of patients had either osteoarthritis or lower back syndromes and a minority was diagnosed with inflammatory arthritis. Those with reactive arthritis were treated and followed-up as deemed necessary by the rheumatologist. In subsequent years a more sensitive series of screening questions were added to the health survey. Patients were invited to be seen if they screened positive on the inflammatory arthritis questions. One hundred and fifty-nine (159) participants with possible inflammatory arthritis were seen by Dr. Pope in consultation, 59 declined the appointment. All participants were given advice on what to do with their mechanical or musculoskeletal complaints.

COUNSELING
In the first year of the study, there were 231 self-referrals for stress related to the water contamination of May 2000. Of these, 160 when re-contacted were not interested in attending counseling sessions. The most common diagnosis was anxiety or depression. Of those, the majority have improved or their symptoms are unchanged and only in one situation have symptoms noted to worsen.
Investigation of High Volume Proteinuria

In Year 1 and Year 2 of the study, 108 subjects were noted to have high urine volumes ranging from 3 to more than 9 L/day with a mean of 3.7 L/day; and elevated urine protein in excess of 0.2 g/day with a mean of 0.4 g/day. They presented within the normal range for 24-hour urine creatinine, had a normal albumin:creatinine ratio, and had no history of diabetes. This unusual picture of polyuria and proteinuria was originally thought to be suggestive of possible nephrogenic diabetes insipidus brought on by tubular damage in the kidneys. Therefore, in 2004, all 108 were invited to participate in a more detailed investigation. Seventy-one (71) consented and after being requested to limit their water intake to less than 2 L/day for 1 week. Forty-three (43) had normal urine osmolality after eight hours requested water deprivation (450-1069mOsm/kg) and 28 had abnormal urine osmolality (59-450mOsm/kg). Patients with abnormal urine osmolality results were booked for a special clinic for an observed 8-hour water deprivation test. All of the 22 patients who attended were able to concentrate within 8 hours. Repeat 24 hr urine specimens were ordered for 87 suspect HVP subjects in years 2005-7. Our investigation suggests that this unusual case group is not directly related to the water contamination, but is spilling protein into their urine due to hyper-filtration brought on by excessive fluid intake. We suspect this problem is not unique to Walkerton and may have import for future cases of accelerated loss of kidney function.

Research Initiatives from the Walkerton Health Study

The initial focus of the Walkerton Health Study (WHS) was on the acute management of infected persons; however, the follow-up of long-term health outcomes is of equal importance. Research suggests that survivors of severe E. coli O157:H7 infection and campylobacter gastroenteritis have poorer long-term health regardless of whether they initially experienced overt haemolytic uremic syndrome. The WHS provides a unique and rare opportunity to characterize new and existing epidemiological associations between acute gastroenteritis and chronic diseases. In the context of the Walkerton E. coli outbreak, and distinct from the clinical responsibilities of the group, a number of relevant and collaborative research foci have developed. Summaries of these research projects are presented below.

The Risk of Long-Term Renal Disease after Diarrhea-Associated Haemolytic Uremic Syndrome

Long-Term Renal Prognosis Of Diarrhea-Associated Haemolytic Uremic Syndrome: A Systematic Review, Meta-Analysis, And Meta-Regression

Background and Objectives: The long-term renal prognosis of patients with diarrhea-associated haemolytic uremic syndrome (HUS) remains controversial. The purpose of this study was to quantify the long-term renal prognosis of patients with diarrhea-associated HUS and to identify reasons for different estimates provided in the literature.

Methods: Data Sources: We searched MEDLINE and Experta Medica (EMBASE) bibliographic databases and conference proceedings, and we contacted experts until February 2003. We also searched the Institute for Scientific Information index and
reference lists of all studies that fulfilled our eligibility criteria. The search strategy included the terms haemolytic-uremic syndrome, purpura, thrombotic thrombocytopenic, Escherichia coli O157, longitudinal studies, kidney diseases, hypertension, and proteinuria. Study Selection: Any study that followed up 10 or more patients with primary diarrhea-associated HUS for at least 1 year for renal sequelae. Data Abstraction: Two authors independently abstracted data on study and patient characteristics, renal measures, outcomes, and prognostic features. Disagreements were resolved by a third author or by consensus.

Results of Data Synthesis: Forty-nine studies of 3,476 patients with a mean follow-up of 4.4 years (range, 1-22 years at last follow-up) from 18 countries, 1950 to 2001, were summarized. At the time of recruitment, patients were aged 1 month to 18 years. In the different studies, death or permanent end-stage renal disease (ESRD) ranged from 0% to 30%, with a pooled incidence of 12% (95% confidence interval [CI]: 10% - 15%). A glomerular filtration rate lower than 80 mL/min per 1.73 m², hypertension, or proteinuria was extremely variable and ranged from 0% to 64%, with a pooled incidence of 25% (95% CI: 20% - 30%). A higher severity of acute illness was strongly associated with worse long-term prognosis. Studies with a higher proportion of patients with central nervous system symptoms (coma, seizures, or stroke) had a higher proportion of patients who died or developed permanent ESRD at follow-up (explaining 44% of the between-study variability, p = 0.01). Studies with a greater proportion of patients lost to follow-up also described a worse prognosis (p = 0.001) because these patients were typically healthier than those followed up. One or more years after diarrhea-associated HUS, patients with a predicted creatinine clearance higher than 80 mL/min per 1.73 m², no overt proteinuria, and no hypertension appeared to have an excellent prognosis.

Conclusions: Death or ESRD occurs in about 12% of patients with diarrhea-associated HUS, and 25% of survivors demonstrate long-term renal sequelae. Patients lost to follow-up contribute to worse estimates in some studies. The severity of acute illness, particularly central nervous system symptoms and the need for initial dialysis, is strongly associated with a worse long-term prognosis.

Reference:


Background and Objectives: In Canada, the majority of cases of childhood haemolytic uremic syndrome (HUS) are associated with a diarrheal illness (D+) due to verotoxin-producing E. coli (VTEC). While the ingestion of undercooked beef is an important cause, we report on the largest outbreak of E. coli illness due to a contaminated municipal water supply. We describe the clinical features and short-term outcomes of 22 children who simultaneously developed D+HUS.

Methods: During the outbreak children who presented to their family doctor's office, or to the local emergency room, with diarrhea had stool samples screened for bacterial
pathogens including *E. coli* O157:H7. In addition a complete blood count, urea, creatinine, electrolyte panel, and urinalysis were performed. Children with haemolytic uremic syndrome (HUS) were identified by the development of anemia with microscopic evidence of hemolysis on blood smear, thrombocytopenia with a platelet count ≤ 150 x 10⁹/L, and by evidence of kidney injury with a rise in serum creatinine, and/or by the development of hematuria or proteinuria. Urine albumin to creatinine ratios were calculated on a random urine specimen.

**Results:** A total of 24 children (<16 yr) with HUS were identified, and were treated at three medical sites. We report on 22 of the 24 children. The mean age at presentation was 4.8 ± 3.3 years. However, thirteen patients (56%) were less than 4 years, 7 (31%) between 4-8 years and 2 (9%) older than 10 years of age.

Eight of the 22 children admitted with HUS required dialysis. All had significantly higher serum urea and creatinine levels at admission than those who did not require dialysis. The mean length of time on dialysis was 11.4 ± 5.7 days with a range of 2 to 19 days. During hospitalization 11 children required packed red blood cell transfusions (PRBC), while 7 children required platelet transfusions. Children requiring dialysis were more likely to receive a platelet transfusion than children who did not require dialysis (p<0.05). One child died shortly after admission to hospital. All surviving children recovered renal function and were discharged from hospital off dialysis.

Patients evaluated at one-year follow up had hemoglobin, white cell and platelet counts within normal ranges. The mean GFR (± SD) for all patients was 98.4 ± 11.6 ml/min/1.73 m², 99.8 ± 13.9 for patients who required dialysis, 97.6 ± 10.8 for patients who did not require dialysis.

**Interpretation and Discussion:** Of 564 children with diarrheal illness among a total of 1,440 residents of Walkerton who were younger than 19 years old, only 24 children, or approximately 4%, went on to develop the complete picture of HUS. This estimate of 4% is lower than previous published estimates from retrospective data. At one year follow up, there were no overt clinical signs of altered kidney function in any of the children; however, 2 had mildly decreased GFRs and 6 had proteinuria.

**Conclusion:** Only a small proportion of children who were exposed to *E. coli* O157:H7 contaminated water went on to develop clinically apparent disease. It is unclear whether the one year renal outcomes reflect irreversible and progressive kidney injury; however, the prospective evaluation of this cohort of children who developed HUS will enable more accurate estimates of the likelihood of long-term renal consequences resulting from *E. coli* O157:H7 exposure and the development of HUS.

**Reference:**

**Renal Sequelae After Childhood Escherichia Coli O157 Haemolytic Uremic Syndrome**

**Background and Objectives:** Nearly all childhood cases of haemolytic uremic syndrome (HUS) are caused by Shiga toxin-producing *Escherichia coli* O157:H7 and this
syndrome is an important cause of renal failure worldwide. The long-term prognosis of patients with HUS is controversial. In some studies, minimal sequelae are observed, whereas others describe survivors with hypertension, proteinuria, or decreased glomerular filtration rate (GFR); in some studies, large proportions of children showed such sequelae. To our knowledge, no previous study has used an asymptomatic healthy control group to quantify the incremental risk of renal sequelae in those who recover from HUS.

Knowledge of the long-term renal prognosis of patients with diarrhea-associated haemolytic uremic syndrome is important for patient counseling and follow-up. The purpose of this study was to compare the risk of renal sequelae at 3 and 5 years following the initial infection between pediatric survivors of HUS and healthy controls in the Walkerton cohort. In addition, trends in these sequelae were examined over time.

Methods: Paediatric survivors of HUS were compared to children who were healthy at the time of the outbreak. Outcomes included proteinuria, blood pressure, glomerular filtration rate, and biochemical measures.

Results (three years after the outbreak): Compared to healthy controls, children who recovered from HUS demonstrated more microalbuminuria [32% vs. 5% (Figure 17); relative risk 4.8 (95% CI: 1.1 - 22.0)], a nonsignificant trend toward lower GFR (124 vs. 134 mL/min per 1.73 m²), and no difference in blood pressure.

Results (five years after the outbreak): Compared to healthy controls, children who recovered from HUS demonstrated more microalbuminuria (3% versus 20% (Figure 17); relative risk, 6.0; 95% CI: 1.1 - 32.8). There were no differences between groups in blood pressure or GFR (estimated with serum creatinine). GFR estimated by cystatin C level was lower in HUS survivors compared with controls (100 versus 110 mL/min/1.73 m²; p = 0.02), but no child had a GFR less than 80 mL/min/1.73 m². Other results, including fasting glucose, albumin, and C-reactive protein levels, did not differ between groups.

Interpretation and Discussion: Although HUS survivors were more likely to show microalbuminuria and lower GFR than healthy controls, the prognosis of these cases was better than reported in other studies. None of the HUS survivors in the WHS cohort had overt proteinuria or GFR less than 80 mL/min, and their blood pressure was no higher than expected for community norms.

Although these 5-year results are encouraging, the clinical relevance and prognostic importance of microalbuminuria and small GFR decreases are uncertain and require further consideration and follow-up.

Conclusion: No major long-term renal sequelae were observed in child HUS survivors in the WHS cohort. The prognosis of these children was better than in other literature reports. Ongoing follow-up will clarify the clinical relevance of microalbuminuria and mild decreases in GFR 5 years after HUS recovery.
Figure 17. Rate of microalbuminuria among childhood survivors of haemolytic uremic syndrome (HUS).

References:


Future Research Projects Related To Long-Term Renal Disease After Diarrhea-Associated Haemolytic Uremic Syndrome


The Risk of Long-Term Renal Disease after Acute Gastroenteritis

Risk Of Hypertension And Reduced Kidney Function After Acute Gastroenteritis From Bacteria-Contaminated Drinking Water

Background and Objectives: Escherichia coli O157:H7 and Campylobacter jejuni infections may have long-term consequences beyond the period of acute illness.
Receptors for the E. coli O157:H7 Shiga toxin, are found in the kidney, and exposure to this pathogen may result in substantial loss of nephrons and subsequent hyperfiltration, which can lead to long-term systemic hypertension and reduced kidney function.

The aim of this prospective cohort study of the Walkerton population was to quantify the long-term risk of developing significant renal disease (hypertension, proteinuria, or a decrease in glomerular filtration rate) after exposure to contaminated water. This project was funded by a grant from the Kidney Foundation for $100,000 for the period of 2002 to 2004.

**Methods:** A total of 1,958 adults with no known history of hypertension or kidney disease before the outbreak participated in this long-term follow-up study. Of the participants, 675 had been asymptomatic during the outbreak, 909 had had moderate symptoms of acute self-limited gastroenteritis, and 374 had had severe symptoms that necessitated medical attention. The outcomes of interest were a diagnosis of hypertension or the presence of reduced kidney function and albuminuria during the follow-up period.

**Results:** After a mean follow-up of 3.7 years after the outbreak, hypertension was diagnosed in 492 for an age- and sex-standardized rate of 31.1%. Hypertension was detected in 27.0% of participants who had been asymptomatic during the outbreak and in 32.3% and 35.9% of those who had had moderate and severe symptoms of acute gastroenteritis respectively (trend p = 0.009) (Figure 18). Compared with the asymptomatic participants, those with moderate and severe symptoms of gastroenteritis had an adjusted relative risk of hypertension of 1.15 (95% CI: 0.97 - 1.35) and 1.28 (CI: 1.04 -1.56) respectively. A similar graded association was seen for reduced kidney function, defined as the presence of an estimated glomerular filtration rate below 60 mL/min per 1.73 m² (trend p = 0.03). No association was observed between gastroenteritis and the subsequent risk of albuminuria.

**Interpretation and Discussion:** Within 4 years of the outbreak, a 33% relative increase and a 9% absolute increase in newly diagnosed hypertension was observed among WHS participants who experienced severe gastroenteritis during the outbreak. Increased rates of hypertension were accompanied by evidence of reduced kidney function. The findings from this study are in line with other reports in which long-term renal sequelae were observed among individuals after recovery from haemolytic uremic syndrome, the most toxic form of acute E. coli O157:H7 infection. In this study, it is hypothesized that the long-term renal complications after E. coli gastroenteritis may be the result of subclinical or unrecognized haemolytic uremic syndrome.

**Conclusion:** Acute bacterial gastroenteritis necessitating medical attention was associated with an increased risk of hypertension and reduced kidney function within 4 years of infection. This study’s findings suggest that transient bacterial contamination has implications well beyond the period of acute self-limited illness.
Reference:

Renal Sequelae After Childhood *Escherichia Coli* O157 Gastroenteritis

**Background and Objectives:** A quarter of children who survive diarrhea-associated haemolytic uremic syndrome develop long-term renal sequelae; however, the prognosis of acute, self-limited *Escherichia coli* O157:H7 gastroenteritis has not been previously studied. The purpose of this study was to examine whether the risk of long-term renal sequelae was increased in children four years after the Walkerton contaminated water outbreak.

**Methods:** High blood pressure was defined as systolic or diastolic pressure >95th percentile expected for age, sex, and height. Reduced kidney function was assessed using measures of estimated glomerular filtration rate, random urine albumin to creatinine ratios, and microalbuminuria.

**Results:** Of the 951 participants, 313 were asymptomatic during the outbreak, 305 had moderate symptoms of acute gastroenteritis, and 333 had severe symptoms that necessitated medical attention. An additional 23 children who developed haemolytic uremic syndrome during the outbreak were excluded from this analysis. There were no
differences in mean systolic blood pressure between those who had no, moderate, or severe symptoms of acute gastroenteritis during the outbreak (109, 110, and 107 mm Hg). Similarly, there were no group differences in diastolic blood pressure, estimated glomerular filtration rate, or random urine albumin to creatinine ratio (p ranged from 0.14 to 0.52), or in the adjusted relative risk of high blood pressure, a glomerular filtration rate <80 ml/min per 1.73 m², or microalbuminuria (p ranged from 0.23 to 0.89).

**Interpretation and Discussion:** Children who presented for medical attention for gastroenteritis during the Walkerton *E. coli* O157:H7 outbreak, had no evidence of renal sequelae 4 years later.

Given that the control group in this study may have ingested contaminated municipal water during the outbreak, it is theoretically possible that asymptomatic *E. coli* O157:H7 exposure resulted in silent renal disease. While this could account for the absence of differences in renal sequelae between asymptomatic and symptomatic children, it is unlikely given that the renal parameters measured in the asymptomatic children were similar or lower than those of healthy children based on population reference standards. Despite the absence of evidence of renal damage in this group of children, most progressive renal disease involves a protracted time course, and a longer follow-up of this cohort would help to clarify the risk of nephropathy after childhood *E. coli* O157 bacterial gastroenteritis.

**Conclusion:** An absence of renal sequelae were observed among children who experienced gastroenteritis during the Walkerton *E. coli* O157:H7 outbreak 4 years previously. With no existing data to support screening after self-limited *E. coli* O157:H7 gastroenteritis, we recommend that only those children who develop recognized features of haemolytic uremic syndrome be followed for long-term renal health.

**Reference:**

**Future Research Projects On The Risk Of Long-Term Renal Disease After Acute Gastroenteritis**

Long-term outcomes from the Walkerton water contamination outbreak: Risk of hypertension and reduced kidney function. Investigators: Clark WF, Macnab JJ, Moist, Salvadori M, Sontrop JM, Suri RS, Garg AX.

Risk of cardiovascular disease after acute gastroenteritis from bacteria-contaminated drinking water. Investigators: Garg AX, Moist L, Clark WF.

Effect of acute gastroenteritis on renal function among individuals with pre-existing renal impairment. Investigators: Sontrop JM, Garg AX, Macnab JJ, Moist L, Salvadori M, Suri RS, Clark WF.
The Risk of Diabetes Mellitus After Exposure to E. coli O157:H7

Diabetes During Diarrhea-Associated Haemolytic Uremic Syndrome: A Systematic Review And Meta-Analysis

Background and Objectives: To quantify the incidence of diabetes during the acute phase of diarrhea-associated haemolytic uremic syndrome (D + HUS) and to identify features associated with its development.

Methods: A systematic review and meta-analysis of articles assessing diabetes during D + HUS was conducted. Relevant citations were identified from Medline, Embase, and Institute for Scientific Information Citation Index databases. Bibliographies of relevant articles were hand searched. All articles were independently reviewed for inclusion and data abstraction by two authors.

Results: Twenty-one studies from six countries were included. Only 2 studies reported a standard definition of diabetes; 14 defined diabetes as hyperglycemia requiring insulin. The incidence of diabetes during the acute phase of D + HUS could be quantified in a subset of 1,139 children from 13 studies (1966-1998, age 0.2-16 years) and ranged from 0 to 15%, with a pooled incidence of 3.2% (95% CI: 1.3 - 5.1, random-effects model, significant heterogeneity among studies, p = 0.007). Children who developed diabetes were more likely to have severe disease (e.g., presence of coma or seizures, need for dialysis) and had higher mortality than those without diabetes. Twenty-three percent of those who developed diabetes acutely died, and 38% of survivors required long-term insulin (median follow-up 12 months). Recurrence of diabetes was possible up to 60 months after initial recovery.

Conclusions: Children with D + HUS should be observed for diabetes during their acute illness. Consideration should be given to long-term screening of D + HUS survivors for diabetes.


The Risk Of Diabetes Mellitus After Exposure To E. coli O157:H7

Background and Objectives: Diarrhea-associated HUS may be complicated by acute insulin deficiency. At least 1/3 of survivors may be left with permanent diabetes mellitus (DM), with relapse possible several years after initial resolution. While HUS is the most severe form of infection with E. coli O157:H7, most diseases operate through a gradient of symptoms and sequelae. Groups of people with E. coli O157:H7 gastroenteritis likely include persons with sub-clinical or undetected HUS who may sustain incomplete islet cell injury during the acute infection. Loss of beta cell mass in these individuals could limit rises in insulin production in response to any future potential reductions in insulin sensitivity, putting them at increased risk of developing overt type 2 diabetes and glucose intolerance.
To test this hypothesis, we prospectively followed 3,259 individuals aged 7 and older, without previous evidence of diabetes, who ingested contaminated water in May 2000. We sought to determine if, compared to asymptomatic individuals, persons with symptomatic gastroenteritis during the outbreak had an increased long-term risk of developing dysglycemia, defined as the composite of DM, impaired glucose tolerance, or impaired fasting glucose. This project was funded by a grant from the Canadian Diabetes Association for $65,000 for the period of 2003 to 2005.

**Methods:** Year 1 to Year 3 participants, who were aged 7 and older on April 15th, 2000, had no history of chronic diarrhea, irritable bowel syndrome, inflammatory bowel disease, celiac disease or dysglycemia before April 15th, 2000, had no confirmed HUS at the time of outbreak, were included in this study. In 2002, all participants without known DM underwent a random plasma glucose test. In 2003 and 2005, all participants were asked to complete an 8-hour fasting plasma glucose, excluding those with known diabetes, those who were pregnant, and those less than age 10. Eligible participants who had fasting plasma glucose of 5.3 to 6.9 mmol/L without previous evidence of DM were asked to undergo an oral glucose tolerance test. In 2005 the lower threshold limit was increased to 5.5 mmol/L due to budgetary and logistical constraints. Participants were classified based on their symptoms during the outbreak into 1 of 3 groups: 1) asymptomatic; 2) possible gastroenteritis; and 3) confirmed gastroenteritis.

**Results:** Three thousand two hundred and fifty nine (3,259) eligible participants were included in the dysglycemia study. One thousand one hundred and thirty nine (1,139) had no symptoms at the time of outbreak, 1,492 had possible gastroenteritis and 628 had confirmed gastroenteritis.

There were no observed differences in the age- and sex-standardized rates of newly diagnosed dysglycemia between groups. There were no differences between groups in the age- and sex-standardized rates of DM, IFG, or IGT. There was no difference in the age- and sex-adjusted mean fasting glucose between groups.

**Conclusion:** There is no evidence that individuals infected with *E. coli* O157:H7 who develop symptomatic gastroenteritis without HUS are at increased long-term risk of abnormal glucose homeostasis. However, individuals presenting with diarrhea-associated HUS should have aggressive surveillance and treatment of hyperglycemia, and consideration should be given to long-term screening of survivors for DM with oral glucose tolerance tests.

**References:**

THE EFFECTS OF WATER CONTAMINATION ON PREGNANCY

The Risk Of Pregnancy-Related Hypertension After Exposure To Contaminated Water

Background and Objectives: Exposure to E. coli O157:H7 may result in sub-clinical kidney injury manifesting as hypertension during pregnancy. Hypertensive disorders during pregnancy complicate between 6% and 22% of pregnancies and are associated with 15% of maternal deaths.

This study of WHS participants was designed to evaluate the risk of pregnancy-related hypertension (PRH) among previously healthy females who conceived within five years of the outbreak. The incidence of PRH, chronic and gestational hypertension was compared between those who reported moderate to severe symptoms of gastroenteritis at the time of the outbreak to those who were asymptomatic. Differences in mean arterial pressure (MAP) were also evaluated.

Funding for this initiative was received from the Lawson Health Research Institute, London, Ontario.

Methods: Ontario Ministry of Health Antenatal forms were used to determine outcomes and risk factors. PRH was defined as any systolic or diastolic blood pressure (BP) >140 mmHg and >90 mmHg, respectively. Chronic and gestational hypertension were defined, respectively, as elevated BP observed prior to or >20 weeks gestation. Risk of PRH was evaluated using a modified Poisson regression model that controlled for known risk factors.

Results: A total of 2,553 women participated in the WHS between 2002-6, and 148 were pregnant between Jan 2001 and May 2006. After exclusions for miscarriage-abortion, pre-existing medical conditions, and incomplete data, 135 pregnancies were included, of which 48 (36%) were asymptomatic and 87 (64%) were symptomatic at the time of the outbreak. PRH was detected in 20.7% pregnancies, of which 6.7% were chronic hypertension and 14.1% gestational hypertension. Although non-significant, a consistent trend toward higher rates of PRH and mean arterial pressure, particularly prior to 20 weeks gestation, was observed among women who reported symptomatic gastroenteritis compared to asymptomatic women (Figure 19).

Interpretation and Discussion: In this study, higher MAP, PRH, chronic and gestational hypertension were observed among women who reported symptoms of gastroenteritis compared to those who were asymptomatic; however, no differences were statistically significant, possibly due to small sample size. Given the small number of pregnancies in the WHS cohort, several more years of data collection would be necessary to ensure a sufficiently large sample; however, any conclusions reached from such an analysis would be limited by the longer time span between exposure and outcome.
Figure 19. Mean arterial pressure during pregnancy 5 years after an outbreak of acute gastroenteritis from bacteria-contaminated drinking water (n=135).

Conclusions: This study's findings suggest that any effect of acute gastroenteritis on blood pressure occurs prior to or early in pregnancy (<20 weeks gestation). Blood pressure should be monitored closely in pregnant women after exposure to contaminated water.

Reference:

THE RISK OF REACTIVE ARTHRITIS AFTER ACUTE GASTROENTERITIS

**Campylobacter Reactive Arthritis: A Systematic Review**

**Background and Objectives:** To review the literature on the epidemiology of Campylobacter-associated reactive arthritis (ReA).

**Results:** The literature available to date suggests that the incidence of Campylobacter ReA may occur in 1 to 5% of those infected. The annual incidence of ReA after Campylobacter or Shigella may be 4.3 and 1.3, respectively, per 100,000. The duration of acute ReA varies considerably among reports, and the incidence and impact of chronic ReA from Campylobacter infection is virtually unknown.

**Conclusions:** Campylobacter-associated ReA incidence and prevalence varies widely among reviews due to case ascertainment differences, exposure differences, lack of diagnostic criteria for ReA, and perhaps genetics and ages of exposed individuals. At the population level it may not be associated with HLA-B27, and inflammatory back involvement is uncommon. Follow-up for long-term sequelae is largely unknown. Five percent of Campylobacter ReA may be chronic or relapsing (with respect to musculoskeletal symptoms).

**Reference:**

**Risk Of Arthritis After Acute Bacterial Gastroenteritis**

**Background and Objectives:** Reactive arthritis (ReA) is a known consequence of bacterial gastroenteritis. Previous research indicates that self-limiting ReA may develop within 4 weeks of an enteric infection (including *Campylobacter, Salmonella, Shigella,* and to a lesser extent *Escherichia coli O157:H7*). The prevalence of acute ReA following *Campylobacter* infection is estimated to be 7%; symptoms of chronic ReA may develop in 6% of cases following *E. coli* infection.

The purpose of this study was to evaluate the association between acute gastroenteritis and self-reported chronic arthritis within 4 years of the outbreak.

**Methods:** Participants with no known history of arthritis before the outbreak participated in a long-term follow-up study. Of the 2,299 participants, 788 were asymptomatic during the outbreak, 1,034 had moderate symptoms of acute gastroenteritis and 477 had severe symptoms that necessitated medical attention. The outcomes of interest were new arthritis by self-report and a new prescription of medication for arthritis during the follow-up period.

**Results:** After a mean follow-up of 4.5 yrs after the outbreak, arthritis was diagnosed in 454 participants for an age- and sex- standardized rate of 17.9% within 4.5 years of the outbreak. Arthritis was reported in 15.7% of those with no diarrhea, 17.6% in those with moderate symptoms of gastroenteritis and 21.6% in those with severe symptoms ( trend p = 0.009) (Figure 20). Compared with the asymptomatic participants, those with moderate and severe symptoms of gastroenteritis had an adjusted relative risk of arthritis of 1.19 (95% CI: 0.99 - 1.43] and 1.33 (95% CI: 1.07 - 1.66), respectively. No association was observed between gastroenteritis and the subsequent risk of prescription medication for arthritis (p = 0.49).
Interpretation and Discussion: This study’s findings support the hypothesis that either acute or chronic arthritic symptoms occurred in study participants who were exposed to *Campylobacter* or *E. coli* during the contaminated water outbreak. This is the largest study to date to suggest a ‘dose-response’ of diarrhea severity and report of subsequent arthritis.

Previous reports indicate a higher frequency of ReA following *Campylobacter* than *E. coli* infection; however, this study was unable to differentiate the rate of arthritis by infection type due to the small number of specimens collected during the outbreak. Many patients with diarrhea (especially dysentery) could have had contraindications to non-steroidal anti-inflammatory drug prescriptions, which may explain the lack of association with prescription arthritis medications.

Conclusion: Acute bacterial gastroenteritis necessitating medical attention was associated with a higher risk of arthritic symptoms, but not arthritic medications, up to 4 yrs following the outbreak. The nature and chronicity of these arthritic symptoms requires further study.

Reference:

**PATHOPHYSIOLOGY AND CLINICAL EXPRESSION OF POST-INFECTIONOUS IRRITABLE BOWEL SYNDROME.**

**Epidemiology Of Post-Infectious Irritable Bowel Syndrome**

**Background and Objectives:** Post-infectious irritable bowel syndrome (PI-IBS) is a common clinical phenomenon. Between 5% and 30% of patients who suffer an acute
of infectious gastroenteritis develop chronic gastrointestinal symptoms despite clearance of the inciting pathogen. Previous studies of the epidemiology of PI-IBS have assessed relatively small study cohorts with limited ability to statistically discern which risk factors affect the outcome. Few studies have assessed the long-term natural history of PI-IBS. To better define the incidence and epidemiology of PI-IBS, chronic gastrointestinal symptoms of WHS participants with no known prior diagnosis of IBS or inflammatory bowel disease (IBD) were examined.

Methods: The WHS cohort was divided into controls without gastroenteritis, subjects with clinically suspected gastroenteritis, and subjects with only self-reported gastroenteritis that could not be substantiated by another source. IBS was defined according to Rome I criteria using a modified Bowel Disease Questionnaire. The incidence and epidemiology of PI-IBS was characterized. Risk factors were assessed using multiple logistic regression.

Results: Of 2,069 eligible study participants, 488 (23.6%) met Rome I criteria for IBS at their first WHS visit in 2002 or 2003. The incidence of IBS was 10.1% among subjects with no gastroenteritis, 27.5% among those with self-reported gastroenteritis, and 36.2% among those with clinically suspected gastroenteritis (Figure 21). Independent risk factors for PI-IBS included younger age, female sex, bloody stools, abdominal cramps, weight loss, and prolonged diarrhea. PI-IBS was more likely than sporadic IBS to show diarrhea-predominant features.

Figure 21. Rate of newly diagnosed Rome I Irritable Bowel Syndrome (IBS) 2-3 years after acute gastroenteritis from exposure to contaminated drinking water (n=2,069).

Interpretation and Discussion: Within an interval of 2 years, a more than three-fold increase in the risk of developing IBS was observed among Walkerton residents who experienced bacterial gastroenteritis during the outbreak.

The prevalence of IBS in WHS participants with clinically suspected gastroenteritis is among the highest ever reported. This study has a number of methodologic advantages over previous reports, namely its access to a large, well-defined, at-risk cohort with a simultaneous and well-characterized acute enteric illness.
Conclusions: PI-IBS was more common among residents exposed to gastroenteritis than among those who remained well during the outbreak. Increased severity of the acute illness, female gender and younger age were independent predictors of IBS. The results of this study confirm a strong and significant relationship between acute enteric infection and subsequent IBS symptoms.

Reference:


Intestinal Permeability In Irritable Bowel Syndrome

Background and Objectives: Current scientific thinking suggests that post-infectious irritable bowel syndrome (PI-IBS) is the clinical expression of altered gut neuromuscular function due to persistent low-grade inflammation. Altered intestinal permeability can contribute to this inflammation by exposing the intestinal wall to luminal antigen. Increased intestinal permeability may also be a precursor to Crohn’s disease. The aim of this project was to learn about the pathophysiology underlying symptoms of PI-IBS. Specifically, this study’s purpose was to evaluate the association between intestinal permeability and IBS symptoms 2 years after the outbreak.

Methods: Consecutive WHS participants with Rome I IBS and controls without IBS attending a community clinic were enrolled in this study. Participants were invited to undergo measurement of intestinal permeability from fractional excretion of mannitol and lactulose after oral ingestion. Intestinal permeability was measured as the ratio of fractional urinary excretions of lactulose and mannitol, and compared among cases vs. controls. Predictors of abnormal intestinal permeability were assessed.

Results: A total of 218 subjects (132 IBS cases and 86 non-IBS controls) completed the study protocol. About 27 (12%) had been diagnosed with IBS before the outbreak and 115 (53%) were ill during the outbreak. Lactulose-mannitol ratios were increased among cases vs. controls and cases were more likely to have a ratio >0.020. Among cases, those with increased intestinal permeability were more likely to have increased stool frequency. Both IBS symptoms and male gender, but not diarrhoeal illness during the outbreak, were significant predictors of abnormal permeability.

Conclusions: IBS symptoms are associated with a subtle increase in intestinal permeability irrespective of prior gastroenteritis. This may improve understanding of the etiology of both sporadic and post-infectious irritable bowel syndrome.

Reference:
**Genetic Risk Factors For Post-Infectious IBS In The Walkerton Outbreak Of Waterborne Gastroenteritis**

**Background and Objectives:** The purpose of this study was to confirm and/or identify new post-infectious irritable bowel syndrome (PI-IBS) susceptibility genes. We selected a list of 78 variants as candidates to be screened on the Walkerton population cohort (Marshall JK, *et al.* Gastroenterology 2006; 131: 445-50), a well-characterized longitudinal study. These candidates can be classified in 4 categories: 1) reported IBS genes (including serotonergic pathway genes); 2) genes involved in intestinal epithelial barrier; 3) reported auto-immunity risk variants (including cytokines); 4) inflammatory bowel disease (IBD) genes.

**Methods:** Variants were genotyped using the Sequenom hME or Taqman assays. Analysis compared subjects who experienced GE but did not develop PI-IBS (889 controls) to those who experienced GE and reported PI-IBS 2-3 years after the outbreak (228 cases). Individuals included in the analysis were over 16 years old, had no prior history of IBS or IBD, were not newly diagnosed with IBD, had over 90% genotyping success rate, and had less than 5% Mendelian inconsistencies. Among the 1,098 successfully genotyped cases and controls, 739 (140 cases, 599 controls) do not have known relationship with any other individual. The remaining 359 samples (80 cases, 279 controls) belong to 120 families. Analysis was performed using a quasi-likelihood association test for cases and controls that accounts for known relatedness within the sample. The test is expressed as a chi-square statistic with 1df. After excluding variants with low success rate (<95%) or deviating from Hardy-Weinberg equilibrium (p<0.01), we analyzed 73 variants with a minor allele frequency >1%.

**Results:** Four candidates showed significant association with PI-IBS. Two are located in Toll-like receptor 9: the coding SNP rs352139 (P545P) (p = 0.0135) and the promoter SNP rs5743836 (-T1237C) (p = 0.0324). These 2 SNPs are in low linkage disequilibrium with each other (r2<0.14). The third is rs16260 (p = 0.0352), a promoter SNP (-C160A) of E-cadherin, and the fourth is rs1800795 (p = 0.0489), a promoter SNP (-G174C) of IL-6. After correction for multiple comparisons, none of these associations remained significant.

**Conclusion:** This study offered a unique opportunity to evaluate new susceptibility genes in PI-IBS. Further population studies will be needed to confirm and validate these potential candidate gene variants.

**Reference:**

**Future Research Projects Related To Irritable Bowel Syndrome (IBS) And Inflammatory Bowel Disease (IBD)**


Association between Diabetes Mellitus and IBD/IBS. Investigators: Marshall JK, Thabane M, Clark WF, Garg AX, Salvadori M, Suri R.

Exposure to intestinal infection in childhood/adolescence may result in development of IBS later in life. Investigators: Thabane M, Marshall JK, Simunovic M, Danesh NA.


Renal tubular proteinuria is increased in patients with post-infectious IBS. Investigators: Thabane M, Marshall JK, Simunovic M, Danesh NA.


CHARACTERIZATION OF A NOVEL FINDING OF HIGH VOLUME PROTEINURIA AFTER THE WALKERTON E. COLI O157:H7 MUNICIPAL WATER CONTAMINATION

Causes Of Reversible Nephrogenic Diabetes Insipidus: A Systematic Review

Background and Objectives: In nephrogenic diabetes insipidus (NDI), the kidney is unable to produce concentrated urine because of the insensitivity of the distal nephron to antidiuretic hormone (arginine vasopressin). In settings in which fluid intake cannot be maintained, this may result in severe dehydration and electrolyte imbalances. The risk for conversion of reversible to irreversible NDI seems to be a potential complication. This review summarizes the reversible causes of acquired NDI to facilitate earlier recognition and more effective treatment by clinicians.

Methods: Two reviewers independently searched MEDLINE, Experta Medica (EMBASE), and ISI bibliographic databases. Human studies that described NDI caused by drugs, substances, or metabolic disturbances were included. To evaluate the causal role of the risk factor, data were abstracted according to Koch's postulates.

Results: One hundred fifty-five studies published between 1957 and March 2004 described 30 risk factors. Of 155 studies, 58 studies provided a "definite" diagnosis of NDI; 83 studies, a "probable" diagnosis; and 14 studies, a "possible" diagnosis. Nine factors were considered "definite" causes of NDI; 15 factors, "probable" causes; and 6 factors, "possible" causes. The most reported risk factors were lithium (84 studies), antibiotics (16 studies), antifungals (11 studies), antineoplastic agents (9 studies), antivirals (8 studies), and metabolic disturbances (8 studies). Duration of NDI reversal, as well as conversion to irreversible symptoms, seemed to depend on the duration of exposure.
**Conclusion:** Most risk factors for reversible NDI were medications, and their identification and removal resulted in resolution of the condition. Long-term treatment with lithium appeared to result in irreversible NDI.

**Reference:**

**Excessive Fluid Intake As A Novel Cause Of Proteinuria**

**Background and Objectives:** Proteinuria has been identified as a strong independent risk factor for the development and progression of renal disease. As part of routine screening in the WHS, urine protein levels in 24-hour collections of urine were measured in all adults who attended the annual follow-up clinic. We identified 100 adults who had proteinuria and polyuria (urine volume >3 L/24-hr), but no medical history or medication use to explain their condition.

In an attempt to discern the cause of the unexplained proteinuria and polyuria we conducted a series of studies to determine whether this observation was related to 1) urine osmolality 2) to examine the effect of fluid intake restriction on polyuria and proteinuria 3) to evaluate the effect of fluid intake on polyuria and proteinuria in healthy university students (non-WHS participants), and 4) to evaluate whether polyuria was independently associated with proteinuria in the entire WHS sample and to compare the magnitude of this association to other known risk factors.

**Methods:** In the initial study, which assessed objectives 1 and 2, participants underwent a confirmatory 24-hr urine collection followed by a urine osmolality measurement after overnight water deprivation. Participants were then asked to voluntarily reduce their total daily fluid intake to fewer than 8 large glasses (<2L/day) for one week, on the last day of which a third 24-hr urine sample was collected and tested for protein.

To address the third objective, 3 consecutive 24-hr urine samples were collected from 6 healthy university students and tested for protein (γ-globulin and albumin). Samples 1 and 3 were collected during usual fluid intake and the second during fluid loading.

**Results:** Fifty-six of the 100 WHS participants completed both initial and confirmatory urine concentration tests, which showed their urine osmolality could reach normal levels (meaning that diabetes insipidus was unlikely). Urine volume decreased from 3.7 L/24-hr at baseline to 1.8L/24-hr after fluid intake restriction. The amount of protein excreted decreased from 0.41 g/24-hr at baseline to 0.16 g/24-hr after fluid intake restriction.

In the study of university students, both proteins (γ-globulin and albumin) increased significantly following fluid loading and returned to baseline on day 3.

In the analysis of all WHS participants from year 1 and year 2, significant correlations were observed between 24-hr urine volume and 24-hr urine protein (Figure 22). In multivariable analysis, polyuria had the strongest association with proteinuria (adjusted...
RR=5.4; 95% CI: 4.8 - 6.1), followed by age ≥30 years, glomerular filtration rate <60ml/min, smoking, diabetes and female sex.

**Interpretation and Discussion:** In a small group of healthy WHS participants with polyuria and proteinuria, proteinuria was reduced following voluntary restriction of fluid intake. Similar results were observed in a study of university students, which demonstrated an increase in urine protein following increased fluid intake. Protein levels returned to baseline after normal fluid intake resumed. These results suggest that the increase in urinary protein excretion in healthy subjects is induced solely through acute fluid loading.

In analysis of the entire WHS cohort, polyuria was the strongest predictor of proteinuria. These results are relevant in assisting practitioners to interpret 24-hr urine tests for protein. These tests are commonly performed, and often lead to treatment decisions. Physicians should be aware that the strongest factor associated with proteinuria on a 24-hr urine in the general population is not in fact comorbid disease, but polyuria.

The long-term renal consequences of chronic exposure to mild proteinuria in polyuric individuals are unknown. Further research is needed to provide insight into the question of whether the proteinuria caused by polyuria is harmful to kidney function. Such a finding would have important public health implications given the silent nature of kidney disease and the widespread, but unsubstantiated belief that drinking eight glasses of water per day is healthy.

**Conclusions:** Further research is required to characterize the nature of the relationship between polyuria, proteinuria and kidney function. In the final year of the WHS, tests were conducted to assess the type of protein associated with polyuria and to determine whether polyuria is associated with a decline in kidney function. An analysis of the WHS data from year 1 to 7 will be designed to evaluate the long-term effects of polyuria on proteinuria and kidney function.

**References:**


**Future Research Related to High Volume Proteinuria**

The Long-term effect of polydipsia induced polyuria and proteinuria on kidney function. Investigators: Clark WF, Sontrop JM, Macnab JJ, Moist L, Salvadori M, Suri RS, Garg AX.
Figure 22. Correlation between 24-hr urine volume (L) and 24-hr urine protein (g).

Entire sample (n=2191; rho_sp = 0.70; p<0.001).

Sub-sample: Excludes participants with hypertension, diabetes, eGFR<60 mL/min, and kidney disease (n=1058; rho_sp = 0.72; p<0.001.)
THROMBOTIC THROMBOCYTOPENIC PURPURA/HAEMOLYTIC UREMIC SYNDROME (TTP/HUS): DEFINITION AND PROGNOSIS

TTP/HUS And Prognosis: The Syndrome And The Disease

**Background and Objectives:** Patients presenting with the syndrome of microangiopathic hemolysis and thrombocytopenia, without shiga-toxin associated colitis, have thrombotic thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS).

This paper will review recent developments in understanding prognosis from both a syndrome-level perspective and also a mechanism-specific perspective, and will use the term TTP/HUS to refer to the syndrome of microangiopathic haemolytic anemia and thrombocytopenia without a clinically identified cause.

**Vulnerability to Bias:** Prognosis for TTP/HUS is vulnerable to bias, including selection bias arising from inclusion of patients with secondary causes. Restricting analysis to patients with severe ADAMTS-13 deficiency does not remove this bias, as several investigators report severe ADAMTS-13 deficiency in secondary cases. Controlling for secondary causes remains important for prognostication even when restricting analysis to specific mechanisms.

A second form of bias relates to differences in the time at which mortality is measured. Prospective data demonstrate 4% mortality after the first cycle of plasma exchange but 22% mortality at 6 months. This difference illustrates the frequency of late deaths and the importance of clearly defining the time at which mortality is measured, which may vary from study to study.

Heterogeneous mechanisms: Preliminary assessment of prognosis by mechanism suggests that mortality varies by pathogenic mechanism. Among familial or recurrent cases, complement factor H mutation portends a worse outcome, while factor I mutation and membrane co-factor protein mutation, and cases not yet characterized, carry a relatively benign prognosis. Acquired severe ADAMTS-13 deficiency portends a similar prognosis as acquired idiopathic TTP/HUS without severe deficiency, demonstrating a mortality of approximately 20%.

**Relapsed Cases:** Emerging evidence illustrates the importance of first distinguishing idiopathic from relapsed idiopathic and secondary causes, given that prognosis varies appreciably between these groups. Specifically, the high survival rate of relapsed patients may represent evidence for the importance of early treatment initiation.

**Reference:**
Forzley BR, Clark WF. TTP/HUS and Prognosis: The syndrome and the disease (in progress).

**Treating TTP/HUS With Plasma Exchange: A Single Centre’s 25-Year Experience**

**Background and Objectives:** Thrombotic thrombocytopenic purpura/Haemolytic uremic syndrome (TTP/HUS) is a relatively uncommon disorder characterized by unexplained haemolytic anaemia and thrombocytopenia. Both disorders are examples of thrombotic
microangiopathies, but in the past have been differentiated on clinical grounds with HUS classically affecting the kidney and TTP affecting the brain, kidney and other organs. Although outcomes have improved with plasma exchange, modern treatment remains suboptimal with mortality rates of 16-29% in published randomized clinical trials.

Study objectives were to describe the clinical features, treatment regime and 6-month all-cause mortality rate of TTP/HUS patients at the London Health Sciences Centre (LHSC), Canada.

Methods: Data for this retrospective cohort study was obtained from inpatient and outpatient records for all patients referred for plasma exchange therapy at LHSC in Canada between 1981 and 2006.

Results: Patients (n=110) were categorized as: idiopathic primary (38%) or relapsed (16%), and secondary responsive (30%) or non-responsive (16%). Mortality data were available for all but three patients. The all-cause 6-month mortality rate was 19% overall and was 12% and 26% among idiopathic and secondary TTP/HUS patients, respectively. Zero mortality events occurred among the 17 idiopathic patients who relapsed. Relapsed patients had the least severe presenting characteristics, the fastest response time, and severity of clinical features decreased between the first and final presentation.

Conclusion: These findings suggest an excellent outcome for relapsed TTP/HUS patients. Patient education, surveillance, and aggressive plasma exchange therapy are hypothesized to improve the likelihood of survival: these hypotheses should be tested in a randomized controlled trial.


MEASUREMENT AND METHODOLOGICAL CHALLENGES IN OBSERVATIONAL RESEARCH

The aim of this research program was to evaluate some of the methodological issues particular to the WHS and to provide further insight into methodological challenges encountered in observational research in general.

Representativeness And Selection Bias

Background and Objectives: Differences between participants and non-participants is a potential source of bias in observational studies such as the WHS. Non-participation may results from denial, selective migration or differences in health seeking behaviours. If participants differ from non-participants in ways that are related to acute illness and long-term health outcome, then the measure of association may be distorted and the validity of the study results threatened. The purpose of this study was to evaluate the representativeness of the WHS sample and to discern whether the association between symptomatic gastroenteritis and health outcomes differed between early participants and those who agreed to participate after more intense recruiting efforts.
**Methods:** Using multiple data sources, including the 1996 and 2001 Canadian Census, and records from the Regional Health Unit, hospital and Walkerton Health Study, we determined both sample representativeness and the anticipated effects of intensifying study participant recruitment. Selection bias was assessed by examining for differences between initial and late participants, and their subsequent risk of having hypertension, proteinuria and reduced renal clearance.

**Results:** Of the 4,315 participants, 2,756 were permanent residents of Walkerton, representing 55% of the town's total population. The sample was demographically similar to the population of interest, although statistically women were more likely to participate than men (55% of sample were women compared to 52% of population, p<0.01), and the proportion of both young and very elderly adults was smaller than expected (13% of sample were ≥ 65 years of age compared to 18% of population, p<0.01). Comparing the initial 3,959 participants to the 356 persons additionally recruited with substantial effort, the latter were more likely to be free of symptoms during the outbreak (21% vs. 7%, p<0.001), but were otherwise similar in terms of age, sex, the use of medical care resources and underlying health state predating the outbreak. The risk of long-term hypertension or renal sequelae did not significantly differ between initial and late study recruits.

**Discussion and Interpretation:** WHS participants appear to be representative of the population of interest. While those recruited through additional efforts were less likely to have been acutely ill during the outbreak, they were otherwise comparable to those recruited soon after the outbreak.

**Conclusion:** Participants of the WHS represent the population of interest, and comprise those who were acutely ill during the infected water outbreak. The available study sample should provide reasonably unbiased estimates of the associated risk between acute bacterial gastroenteritis and long-term health sequelae.

**Reference:**

**Recall Bias And The Accuracy Of Self-Report Data**

**Background and Objectives:** The validity of the association between acute infection and long-term health sequelae is dependent on the accuracy of exposure definition. Although positive stool cultures for known enteric pathogens would provide the best confirmation of acute enteric illness in an individual, the submission of stool samples during the outbreak was discouraged, in part because the local health services were overwhelmed and the outbreak source and causative organisms were already identified.

The accuracy of self-reported data with respect to severity of gastroenteritis symptoms was a major concern in the WHS and was further limited by the prospect of financial compensation from the government and the time lag of 2 years between the outbreak and study inception. Biased recall was empirically demonstrated in 405 participants who were questioned about acute symptoms by public health officials just after the outbreak and again by WHS.
personnel 2 years after the outbreak: 27% recalled acute symptoms that they denied just after the outbreak.

The overall effect of biased recall on study outcomes is uncertain. Misclassification of truly asymptomatic individuals as ill could attenuate or nullify any apparent relationships between acute gastrointestinal illness and chronic health outcomes. Alternatively, if individuals with long-term health problems exaggerated their recall of initial symptoms, any association between exposure and outcome would be artificially amplified.

The purpose of this study was to characterize and validate a gradient of acute gastroenteritis using prior health records to confirm recalled gastrointestinal symptoms at the time of the outbreak.

**Methods:** Participant survey responses were corroborated with health records at the time of the outbreak. Of the 4,135 participants, 1,388 were asymptomatic during the outbreak, 1,752 had symptoms of acute self-limited gastroenteritis that could neither be confirmed nor refuted by prior health records, and 995 had symptoms that necessitated medical attention (and thus were confirmed by prior health records).

To test the reliability of the exposure gradient, the relationship between each grade and five health outcomes were assessed, four of these represented plausible sequelae of acute gastroenteritis and the fifth represented a distracter, tinnitus, where an association was not expected.

**Results:** Compared to those with unconfirmed gastroenteritis, participants with confirmed gastroenteritis were more likely to describe fever, bloody diarrhea, and prolonged diarrhea (all \( p < 0.03 \)). The gradient also correlated with long-term plausible outcomes, including chronic gastrointestinal symptoms, chronic symptoms of arthritis or depression, and the avoidance of municipal water ingestion after the outbreak (\( p \) for trend consistently \( < 0.03 \)). Conversely, for the outcome of chronic tinnitus, an association was neither expected nor observed (trend \( p = 0.26 \)).

**Interpretation and Discussion:** The exposure gradient related to the severity of acute symptoms experienced during the outbreak. In addition, there was a clear dose-response relationship between the exposure gradient and five plausible health sequelae. Conversely, as expected, no association was observed for the distracting outcome, tinnitus.

Although the exposure gradient would be strengthened by the addition of a referent group who did not drink the bacterial contaminated water, an insufficient number enrolled in the study (<1%).

**Conclusion:** We were able to successfully characterize a gradient that can be used in future analyses assessing the risk of long-term health sequelae from the outbreak.

**Reference:**
Screening And Validation Of Laboratory Data

**Background and Objectives:** The Kidney Disease Outcomes Quality Initiative has recommended the use of GFR estimating equations to detect silent chronic kidney disease (CKD) in the community. The benefit of general reporting of CKD must be balanced with the harm of mislabeling people who do not have CKD.

The purpose of this study was to compare the popular Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) GFR estimating equations to the recently devised Rule equation in the Walkerton cohort, which represents a representative community-based sample.

**Methods:** The study sample (n=2,166) was divided into 2 sub-samples: those with (n=385) and without (n=1781) previous renal impairment.

**Results:** The prevalence of CKD was CG > MDRD >> Rule estimates. The magnitude of difference in prevalence of CKD as detected by the MDRD and CG versus the Rule equation increases markedly when the subsamples with (30.8 and 29.7 versus 17.5%) and without (12 and 11.3 versus 3.0%) previous kidney impairment are compared. General demographic and potential or known risk factors were used in a logistic regression model to assess the association with CKD. The MDRD estimates note female gender (odds ratio 2.19; 95% CI: 1.63 - 2.95) and both MDRD and the Rule equations identify hypertension and diabetes as significant CKD risk factors. All estimating equations identify age to be associated with CKD. The annualized serial decline in GFR was CG > MDRD > Rule estimates. Only the Rule GFR estimates detected a greater decline in renal impaired versus unimpaired populations.

**Interpretation and Discussion:** This study provides a direct comparison of the prevalence of CKD as detected by three different GFR estimating equations in a community-based sample. Adoption of the Rule equation to fulfill guidelines issued by the Kidney Disease Outcomes Quality Initiative is less likely to identify a large number of a community population as having CKD. Use of this GFR estimating equation dramatically reduces the number in the Walkerton cohort who are labeled with a diagnosis of CKD and the potential emotional, financial, and interventional burden that accompanies that diagnosis.

**Conclusion:** The calibrated Rule equation seems to perform better than CG and MDRD (CKD 3 versus 11.3 to 12%) but lacks validation against gold standards for community-based screening.

**Reference:**

Measurement, Validation, And Interpretation Of Blood Pressure Data

**Background and Objectives:** The accurate measurement of blood pressure (BP) in epidemiological studies requires standardized conditions, valid instruments, multiple measurement and accurate data capture. There are many published guidelines and recommendations for standardized conditions for BP measurement and guidelines for
interpretation; however, there is less information on established methods for ensuring data quality at the time of data capture.

When three BP assessments from the same visit are available, it has been recommended to drop the first measure to reduce systematic error introduced by initial anxiety. However, this assumes that all three measures were obtained using the same device. Because the observed BP can also vary with the type of instrument used averaging values obtained using different techniques may not result in an increase in reliability.

This study evaluated whether 1) upper and lower warning limits defined by the 2nd and 98th percentile of the sample distribution were adequate for flagging potential data entry errors across age and sex, 2) whether knowledge of the within subject variability could be used to flag potential data entry errors, and 3) whether reliability increases with the number of BP measurements in the presence of different measurement methods.

Methods: As part of the annual health survey, 3 BP measurements were obtained within a 30 minute period using both an automated oscillometric device and a standard mercury sphygmomanometer. Data was entered into a web-distributed data capture system. Information collected from the first 4,000 participants was used to refine the range and limit checks performed at the time of data entry.

The 98th percentile of the distribution of within subject variability was used to define a warning limit based on excessive within subject variability. This range was then graphically compared to the reference ranges for systolic and diastolic pressure.

The intraclass correlation coefficient was used to estimate the reliability of different combinations of BP measurements. Reliability estimates and 95% confidence intervals were calculated for mean pressure estimated by: all 3 measures, dropping the first measure, and 2 dinamap assessments and compared to the highest reliability of any single assessment.

Results: Simple upper and lower warning limits applied across age and sex were not adequate for flagging potential data entry errors. Age and sex-specific reference ranges should be used to minimize data entry error. Within-subject variability of >20 mmHg (systolic) and >13 mmHg (diastolic) can be used to flag potential data entry errors.

The first systolic BP was higher than subsequent measurements. Systolic BP was higher when measured with the Dinamap 1846sx. Diastolic BP was higher when measured using a standard mercury sphygmomanometer.

Conclusions: To minimize data entry error, age and sex specific reference ranges should be used rather than simple upper and lower warning limits. Repeated pressure measurements are more reliable than any single measure. When different measurement devices are used, the increase in within subject variability leads to a decrease in overall reliability.

Reference:
The Walkerton Health Study

This article was written by the clinical coordinator of the WHS, Arlene Richards, and describes the challenges, infrastructure support, staffing, and recruitment and retention efforts required to screen over 4,000 people in a yearly clinic visit. Also described are the clinical and laboratory algorithms used to identify participants requiring specialist assessment. The article discusses the design of the computer-based survey, advanced data entry and display control, and explains why these are essential to ensure accurate data entry.

Reference:

TTP/HUS: Observational Studies Generate Hypotheses That Lead To Randomized Controlled Trials

Thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS) is a disease syndrome whose history exemplifies how small observational studies can generate hypotheses that lead to randomized control trials (RCTs). Moschowitz’s original case report coupled with the case findings of Bukowski and Byrne led to an RCT and the Canadian Apheresis Group, which together proved that plasma exchange was superior to plasma infusion for the treatment of adults with TTP/HUS. In this study we present a single case report of continuous plasma exchange coupled with the observations about the pathogenic role of von Willebrand multimer protease.

In 1992 we saw a 72-year old patient with the diagnosis of TTP, who presented with a rapid progression to coma, a platelet count of less than 15,000, hemoglobin less than 71 and an LDH of greater than 3687, with a serum creatinine of 704 and oligoanuria. The patient had a low grade fever and received an initial plasma exchange with deepening in his coma and no response either in clinical or laboratory picture to the exchange. The patients low prognostic score coupled with his initial lack of response to his initial plasma exchange prompted us to embark on a 48-hour, 69 Litre plasma exchange with 179 units of cryosupernatant plasma and 14 units of fresh frozen plasma (2 units every 4 hours). Within 24 hours the patient awoke from his deep coma and was lucid. He had one further plasma exchange prior to his successful discharge from hospital, and he has remained in lasting remission from his TTP.

In 2008, we retrospectively reviewed our single centre experience with 128 cases of TTP/HUS and noted 12% mortality among idiopathic cases and zero mortality events among 15 patients with relapsing TTP. No association was observed between number of risk factors and mortality among patients in this study; however, sicker patients received significantly greater volumes of plasma exchange.

Based on results from our single case report and retrospective review, we hypothesize that improved outcomes in TTP/HUS may be possible through urgent initiation of therapy after diagnosis and more aggressive use of plasma exchange. We propose to test these hypotheses in a multi-centre randomized controlled trial that compares large volume high frequency plasma exchange with conventional plasma exchange, and also compares a patient education intervention and follow-up strategy to conventional follow-up management.
Reference:
Clark WF, Forzley BR, Sontrop JM, Kadri A, Moist L, Suri R, Salvadori M, Garg AX.

Future Research Projects Related To Measurement And Methodological Challenges In Observational Research

Selective attrition and the effects of loss to follow-up on potential cause-effect relationships in the Walkerton Health Study. Investigators: Macnab JJ, Sontrop JM, Moist L, Clark WF.

Sources of within-subject variability in serial blood pressure measurement. Investigators: Sontrop JM, Moist L, Clark WF, Macnab JJ.

POPULATION HEALTH

Elevated Blood Pressure In Relation To Overweight And Obesity Among Children In A Rural Canadian Community

Background and Objectives: Childhood overweight and obesity may result in premature onset of cardiovascular risk factors such as hypertension. Rural populations in North America may be at increased risk for overweight. We evaluated if overweight and obesity were associated with pre-hypertension and hypertension in a well-characterized population of children in rural Canada.

Methods: The study population for this cross-sectional study was comprised of children (4-17 years) who were participants of the Walkerton Health Study (Canada) in 2004. Prehypertension and hypertension were defined based on percentiles from the average of three blood pressure measures taken on a single occasion. Percentiles for body mass index and blood pressure were calculated using the 2000 Centers for Disease Control and Prevention growth charts. Multinomial logistic regression was used to evaluate the odds for prehypertension and hypertension from overweight and obesity.

Results: Of 675 children (98.7% white), 122 (18.1%) were overweight and 77 (11.4%) were obese. Prehypertension and hypertension were detected in 51 (7.6%) and 50 (7.4%), respectively. After adjustment for family history of hypertension and kidney disease, obesity was associated with both prehypertension and hypertension. Overweight was associated with hypertension but not prehypertension (Figure 23). These associations were observed across the genders and children aged <13 and >13 years, except that overweight was not associated with hypertension among girls.

Conclusion: In this population of children living in a rural community in Canada, overweight and obesity were strongly associated with elevated blood pressure. Whether blood pressure normalizes with improvements in diet, physical activity, and environment is an area for further study.
Reference:

Figure 23. Adjusted odds for pre-hypertension and hypertension from overweight and obesity in pediatric participants of the Walkerton Health Study (adjusted for family history of hypertension and kidney disease) (n=675). Reprinted with permission from the Journal Pediatrics.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR(^a) [95% CI]</th>
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<tr>
<td><strong>Odds of Pre-hypertension(^b)</strong></td>
<td></td>
</tr>
<tr>
<td>Overweight(^d)</td>
<td>1.6 [0.8, 3.5]</td>
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<tr>
<td>Obese(^e)</td>
<td>4.5 [2.2, 9.2]</td>
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<tr>
<td><strong>Odds of Hypertension(^c)</strong></td>
<td></td>
</tr>
<tr>
<td>Overweight(^d)</td>
<td>3.7 [1.8, 7.6]</td>
</tr>
<tr>
<td>Obese(^e)</td>
<td>7.0 [3.3, 14.9]</td>
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\(^a\)Reference category: Normal BMI: >5th to <85th percentile expected for age, sex. \(^b\)Average SBP or DBP levels >90th to <95th percentile expected for age, sex, and height or average blood pressure levels >120/80 mm Hg among adolescents. \(^c\)Average SBP or DBP levels >95th percentile expected for age, sex, and height, or previous medical diagnosis or use of hypertensive medications. \(^d\)BMI >85th to <95th percentile expected for age, sex. \(^e\)BMI >95th percentile expected for age, sex.

Factors that Led to the Walkerton Tragedy

In May 2000 bacterial contamination of municipal water in Walkerton, Ontario resulted in the worst public health disaster involving municipal water in Canadian history. At least 7 people died and 2300 became ill. This paper reviews factors that led to the Walkerton tragedy as described by the public inquiry led by Judge Dennis O’Connor, which examined the events and delineated the causes of the outbreak including: physical causes, the role of the Public Utilities operators, the Public Utilities Commissioners, the Ministry of the Environment (MOE) and the provincial government.

Improper practices and systemic fraudulence by the public utility operators, the recent privatization of municipal water testing, the absence of criteria governing quality of testing
and lack of provisions made for notification of results to multiple authorities all contributed to the crisis. The MOE noted significant concerns two years prior to the outbreak, however no changes resulted because voluntary guidelines as opposed to legally binding regulations governed water safety. The inquiry concluded that budgetary restrictions introduced by the provincial government four years prior to the outbreak were enacted with no assessment of risk to human health. The ministers and the cabinet had received warnings about serious risks. Budgetary cuts destroyed the checks and balances that were necessary to ensure municipal water safety.

Reference:

Environmental Prevention Of Human Disease From Verocytotoxin-Producing Escherichia Coli

Verocytotoxin-producing Escherichia coli (VTEC) haemolytic uraemic syndrome (HUS) is an important cause of mortality and renal failure worldwide. For those patients who need medical attention, no treatment aside from supportive care has proven effective for this disease. This has prompted a broader look at environmental prevention, with a particular emphasis on the transmission of bacteria from animal carriers to human beings. This paper reviews animal- and meat-handling strategies to reduce the burden of VTEC human disease.

Cattle are the main livestock reservoir for VTEC, particularly E. coli O157:H7. Its prevalence in the faeces of North American cattle ranges from 10 to 28%, with a recent study finding 96% of feedlots and 52% of pens having at least one positive faecal sample. Other farm animals and pets also shed VTEC. Efforts to reduce the survival and transmission of VTEC have focused on farm management and disinfectant practices, and strategies to increase animal resistance to infection, such as the use of antibiotics, vaccines and probiotics.

Trucks that transport animals between farms and processing plants can serve as a source of infection for cattle and processing plants. Universal contamination of truck sidewalls and floors with generic E. coli has been reported. Cleaning trucks with heat and sodium hypochlorite drastically reduces coliform numbers transported by poultry, and is most effective when it is performed after each load. When transport trucks do remain contaminated, it is often because procedures were not followed.

In Canada and the United States, mandatory performance standards for meat processing plants implemented through Hazard Analysis Critical Control Point (HACCP) systems. Since the mandatory implementation of HACCP in the United States, the incidence of E. coli O157 has decreased by >40%.

In the kitchen, special care is needed to avoid transmission of bacteria from meat to other foods being prepared. Organisms persist on kitchen surfaces if there is inadequate cleaning. Proper hand washing remains essential. The United States Food and Drug Administration recommends cooking ground beef to an internal temperature of 71°C (160°F).
Reference:

Local Water Diversely Known: Walkerton, Ontario 2000 And After

This study is a historian's analytical account of the water contamination outbreak in Walkerton, Ontario, in 2000-2002. The local priorities defining good water were considered. These vernacular understandings emphasized taste, softness, and thrift in municipal water, and they highly valued local sovereignty in matters of water quality, and solidarity as a quality of local citizenship. By using contemporaneous evidence from media reports and the judicial enquiry into the incident; the author traced how the qualities of good water were redefined, and with them community standards of safety, expertise, and risk. The emphasis on community consent to vernacular water monitoring practices and the implications of this shared responsibility differ from the journalistic and judicial accounts which emphasize individual culpability.

Reference:

Future Research Projects Related To Population Health

The Walkerton longitudinal study on the effects of aging on renal function. Investigators: Clark WF, Garg AX, Macnab JJ, Moist L, Salvadori M, Sontrop JM, Suri RS.

Impact of surveillance on blood pressure control in the Walkerton Health Study. Investigators: Moist L, Sontrop JM, Macnab JJ, Clark WF.

Longitudinal study of body mass index and hypertension in children in a rural community. Investigators: Salvadori M, Sontrop JM, Macnab JJ, Suri R, Clark WF.

Community perception of the Walkerton Health Study. Investigators: Parr J.

SUMMARY OF RESEARCH ACCOMPLISHMENTS

3. Absence of renal sequelae after childhood Escherichia coli O157:H7 gastroenteritis. Garg AX, Clark WF, Salvadori M, Thiessen- |
|-----------------------|-----------------------------------------------------------------------------------|

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<thead>
<tr>
<th>Manuscripts for Imminent Submission</th>
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<tr>
<td><strong>1.</strong> Long-term risk of dysglycemia after <em>E. coli</em> O157:H7 gastroenteritis: The Walkerton Health Study. Suri RS, Mahon JL, Clark WF, Garg AX.</td>
</tr>
<tr>
<td><strong>2.</strong> Risk of pregnancy-related hypertension within five years of exposure to bacteria-contaminated drinking water. Moist L, Sontrop JM, Garg A, Suri R, Salvadori M, Gratton R, Clark WF, Macnab JJ.</td>
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<tr>
<td><strong>3.</strong> TTP/HUS and prognosis: The syndrome and the disease. Forzley B, Clark WF.</td>
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<tr>
<td><strong>4.</strong> Polyuria is associated with mild proteinuria in the general population. Sontrop JM, Suri R, Sultan N, Macnab J, Moist L, Clark WF.</td>
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<tr>
<td><strong>5.</strong> Fluid loading causes an increase in urinary protein excretion. Weir MA, Sontrop JM, Kortas CM, Clark WF.</td>
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<tr>
<th>Presentations</th>
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<tr>
<td><strong>2.</strong> American Society of Nephrology Annual Meeting 2004. Association of Common Measures of Kidney Function; Year 1 and 2 of the Walkerton Screening Clinic. Clark WF.</td>
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| **4.** Proceedings of Canadian Cardiovascular Congress: Canadian Hypertension Society 2004. Poster presentation: Improving the...
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<tr>
<th>Quality of Blood Pressure Data through the Use of Age and Sex Specific Reference Ranges and Repeated Measurements. Macnab JJ and Clark WF.</th>
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<tr>
<td>7. Faculty of Epidemiology, McGill University, The Walkerton Health Study. Clark WF.</td>
</tr>
<tr>
<td>17. The 40th Annual Meeting of the Canadian Society of Nephrology, 2008. Poster presentation: Fluid Loading Causes an Increase in Urinary Protein Excretion. Weir MA, Sontrop JM, Clark WF.</td>
</tr>
</tbody>
</table>
External Grants - Funded
1. Kidney Foundation Grant ($100,000) 2002 – 2004
2. Canadian Diabetes Association Grant ($65,000) 2003 – 2005
3. High Volume Proteinuria, DAF ($15,000)
4. Crohn’s and Colitis Foundation of Canada ($360,000) 2005-2008
5. Hypertension during Pregnancy after exposure to water contaminated with *E. coli* O157:H7 and Campylobacter, LHRI ($13,000)

DISSEMINATION OF RESULTS

An important goal of the Walkerton Health Study was to disseminate research findings to a wide audience that included both the Walkerton community and the research community. Dissemination of results to the Walkerton community was primarily accomplished through newspaper articles and Town Hall meetings, which were held annually in Walkerton. During Town Hall meetings, WEL investigators presented results from the previous year, highlighted any new initiatives for the upcoming year and answered questions from the public.

Participants received an annual summary report, and highlights of the previous year’s findings were reported in the Walkerton Herald Times in January and/or February of each year (see examples in Appendix I). These articles also contained information on participation, recruitment, and upcoming specialty clinics. Finally, a monthly series of articles written by WEL investigators appeared in the Walkerton Herald Times providing a lay-description of hypertension, diabetes, dyspepsia, arthritis, irritable bowel syndrome, *E. coli* O157 and *Campylobacter* (see Appendix I).

Dissemination of results to the research community occurred primarily through publications in peer reviewed scientific journals and presentations at conferences. Presentations were also made to both faculty and students at both the University of Western Ontario and McGill University. In addition, highlights from the study were shared with the medical community at a special symposium that focused on thrombotic thrombocytopenic purpura / haemolytic uremic syndrome (TTP/HUS). This symposium took place in London, Ontario (June 1-2, 2008) and was planned to coincide with the Canadian Society of Nephrology 40th Annual Meeting (London, Ontario, May 28 to June 1, 2008).

The purpose of the HUS/TTP symposium was to present findings on the long-term outcomes following exposure to *E. coli* O157:H7. A half-day session was reserved for the presentation of results from the Walkerton Health Study. Additional topics included 1) the presentation of recent scientific advances about thrombotic microangiopathies to improve therapeutic and diagnostic strategies, 2) a comparison of current models of care in the treatment of HUS/TTP, and 3) a discussion of some of the basic controversies surrounding treatment of HUS/TTP. Symposium presenters included WEL investigators as well as researchers from Health Canada, University of Oklahoma Health Science Center, Washington University School of Medicine, and the Canadian Apheresis Group. The symposium was attended by 120 people from Canada and the United States and included physicians, nurses and academics. Summaries of the presentations will be published in the journal *Kidney International*. The symposium agenda is provided in Appendix II.
DISCUSSION AND COMMENTARY

The most serious case of water contamination in recent Canadian history occurred in May of 2000, when the municipal water of Walkerton, Ontario, was contaminated with E. coli O157:H7, campylobacter species and salmonella resulting in 2,300 cases of gastrointestinal illness, more than 750 emergency room visits, 65 hospital admissions, 27 recognized cases of haemolytic uremic syndrome (HUS) and seven deaths. The Walkerton Health Study (WHS) was funded by the Ontario Ministry of Health and Long-Term Care to meet both the needs of the community and provide a unique opportunity to characterize the association between acute bacterial gastroenteritis and chronic diseases, including arthritis, hypertension, renal disease, diabetes, post-infectious irritable bowel syndrome, and inflammatory bowel disease. Over seven years, more than 4500 citizens of Walkerton and surrounding area have voluntarily participated in the health study. In the clinical realm, a wide range of undetected health problems were identified. The major concerns identified in the initial screening related to complications that primarily addressed four (4) major clinical groupings:

1) hypertension and kidney disease
2) irritable bowel syndrome
3) diabetes mellitus
4) acute reactive arthritis.

Among participants with hypertension, the number that received treatment increased substantially from 18% in 2002 to 70% by 2008, with over a 50% decline in uncontrolled hypertension from the inception of the study to its last clinic in 2008. The screening process identified 459 adults with potential renal disease and 436 were seen at least once by a nephrologist in Walkerton. Although the majority required only one assessment for specific diagnostic advice and treatment, 126 were reassessed up to 6 times for specific further treatment and advice. In terms of children with kidney disease, 245 of the 250 identified were seen by a paediatric nephrologist and the minority that had renal disease at the time of this assessment or those who had experienced HUS at the time of the outbreak were provided with annual follow-up appointments and specific treatment where necessary. Over 811 patients were identified by our screening questionnaire and invited to attend yearly information sessions on the Irritable Bowel Syndrome. The Walkerton Health Study clinic was responsible for creation and distribution of 1200 copies of a booklet outlining treatment strategies for Irritable Bowel Syndrome and 555 participants received an individual consultation with a gastroenterologist for specific diagnosis, treatment and advice.

Concerns about the increased incidence of Diabetes Mellitus noted in a systematic medical literature review of haemolytic uremic syndrome, the most severe complication of the water contamination led to a widespread screening program and identified over 783 patients who had dysglycemia and almost 619 agreed to glucose tolerance testing, which resulted in the identification of 45 new diabetics requiring follow-up and treatment with 51 being in the pre-diabetic range and asked to visit their family physician for annual monitoring. In the area of acute reactive arthritis, over 260 participants were identified after screening and were assessed by a rheumatologist and provided with specific advice on what to do with their mechanical or musculoskeletal complaints. As in most generalized screening programs, the majority of clinical assessments and interventions by specialists who came to the Walkerton area community were thought to be unrelated to the water contamination but could be considered non-specific detection benefits of a screening study. In the last year of the study over 88% of the participants reported their health as being good to excellent.
Research from the Walkerton Health Study has spanned a number of clinical problems, but among the most salient findings was the 30% increased risk of hypertension and renal impairment observed in those who experienced the gastroenteritis thought due to *E. coli* O157:H7. This is important not only for the citizens of Walkerton but also for the long-term follow-up of individuals who experience gastroenteritis secondary to *E. coli* O157:H7 every year in Canada. The very low incidence of long-term complications among children who suffered haemolytic uremic syndrome is also an important new finding that suggests that the prognosis in water borne *E. coli* O157:H7 cases of haemolytic uremic syndrome may be milder, but requires even longer term observation in a minority that have early signs of progressive impairment. The negative findings of an association of incident cases of Diabetes Mellitus secondary to gastroenteritis is important since this alleviates concerns raised by several studies that noted an increased incidence of Diabetes Mellitus in those with the most severe form of illness related to *E. coli* O157:H7 that resulted in haemolytic uremic syndrome. The finding that Irritable Bowel Syndrome is associated with increased permeability has major import in terms of the pathogenesis of the Irritable Bowel Syndrome and also its potential association with Inflammatory Bowel Disease has opened up a new area of research investigation.

The WEL Investigators and the Investigators of the Irritable Bowel Syndrome Group have been highly productive with 24 current peer reviewed publications, 6 in press and 10 undergoing preparation following the final compilation of the 7-year longitudinal results. Although the Walkerton Health Study appears to have had a productive clinical and research output not all participants have had resolution of their health related problems. The study has benefited from the dedicated efforts of the screening team in Walkerton as well as a diverse group of clinical and research investigators from the University of Western Ontario, London Health Sciences Centre and McMaster University. Major recognition for the success of this seven year longitudinal study must be directed to the participants. These members of the Walkerton community and surrounding area have freely given of themselves to participate over an extended period of time in an intrusive and invasive clinical and experimental study, following a tragic set of circumstances. The annual town hall meetings and daily interactions in the clinic provided the opportunity for community input that shaped the focus of the annual screening study. It has been a privilege to participate with these individuals, whose efforts will result in improved clinical outcomes and significant new research findings that will benefit not only their community but many others.
APPENDIX I: DISSEMINATION OF RESULTS AND EFFORTS TO ENCOURAGING RETENTION AND RECRUITMENT IN THE WHS

An important goal of the Walkerton Health Study was to disseminate research findings to a wide audience that included the Walkerton community as well as the research community. Dissemination of results to the Walkerton community was primarily accomplished through newspaper articles and Town Hall meetings, which were held annually in Walkerton. During Town Hall meetings, WEL investigators presented results from the previous year, highlighted any new initiatives for the upcoming year and answered questions from the public.

Participants also received an annual summary report, and highlights of the previous year’s findings were reported in the Walkerton Herald Times in January and/or February of each year. Two examples of articles highlighting study results from the previous year are provided below.

EFFORTS TO ENCOURAGE RECRUITMENT AND RETENTION

Recruitment and retention were essential for the success of the WHS. Before the screening clinic opened each year, an extensive advertising campaign was mounted in the local newspapers, radio, and Cable TV. Posters were displayed in hospitals, physician offices, pharmacies, the library and other strategic locations around town and flyers were inserted into all of the town’s post office boxes. Every opportunity was taken for interviews with the local and national media.

An example of a flyer used to advertise the WHS is provided below. This is followed by an example of a newspaper advertisement highlighting the study and participation opportunities.
Results of Year 1 Walkerton Health Study (2002)

In 2002, the first year of the Walkerton Health Study, 4,420 people registered and 3,959 completed the screening. Listed below are graphs indicating

- the prevalence of illness and diarrhea among the participants and
- the number of participants referred for further investigations.

### Exposure Diarrhea

- **did not drink water**: 1.74%
- **drank water - well**: 32.28%
- **drank water - mild illness**: 10.71%
- **drank water - mild diarrhea**: 32.26%
- **drank water - severe diarrhea**: 17.86%
- **drank water - bloody diarrhea**: 5.15%
Referral Clinical Care Pathways

Walkerton and surrounding area

Registered Year 1
4420

Participated Year 1
3959

Clinical Algorithms
1140

*Neph 300
*Nephrology or Kidney

*Neph 98

*Neuro 98
*Neurology

*GI 402
*Gastrointestinal

*Rheum 109
*Rheumatology

*Counsel 231
*Counseling

Adult 197

Child 103

213

21

428

130

46

*Neph Nephrology or Kidney
*Neuro Neurology
*GI Gastrointestinal
*Rheum Rheumatology
*Counsel Counseling
Results of Year 2 Walkerton Health Study (2003)

In year 2, an additional 356 people joined the study for a total of 3,373 who completed the screening. Almost 80% of the participants from the Walkerton area returned for the year 2 screening while some deferred their scheduled reassessment until the following year. Based on the 2001 Census, approximately 57% of the residents of Walkerton have participated in the Walkerton Health Study.

Exposure History:
Ninety-eight percent of the participants reported drinking the water and 66% reported being ill at the time of the outbreak. The most common complaint was diarrhea, followed by cramps. Compared to year 2 participants, participants entering the study in year 1 were only slightly more likely to have been sick at the time of the outbreak. As well, they were significantly more likely to have experienced bloody diarrhea, cramps and/or fever. They were also significantly more likely to have visited a doctor or hospital for blood or stool testing. Overall 28% of participants made a phone call to a doctor while only 19% visited a hospital or Emergency Department.

Previous Health Conditions:
Approximately 16% of the participants had previously been diagnosed with hypertension (High Blood Pressure) and approximately 10% with affective disorder, such as stress and anxiety disorder. Other conditions and diseases previously diagnosed were kidney disease, diabetes, heart attack, stroke, irritable bowel syndrome, Crohn’s disease, ulcerative colitis, gallstones, and bloody diarrhea.

Diabetes Study:
In year 2, the Walkerton Health Study concentrated on identifying the long-term risk of Diabetes Mellitus after exposure to E. coli. All participants over the age of 10, who did not have a diagnosis of diabetes, were asked to withhold eating and drinking for 8 hours prior to their appointment. A fasting blood sugar was performed. Eight new cases of diabetes were identified. In addition, 283 participants were identified as requiring more in depth testing (Oral Glucose Tolerance Testing). Because of this intensive testing, a further 10 people (6%) were identified as having sugar diabetes bringing the total number of diabetics to 18. Another group of 25 (15%) were identified as having borderline sugar levels and have been provided with lifestyle modification recommendations. All newly identified diabetics have been referred back to the care of their family physicians.

Gastrointestinal Health Problems:
In addition to offering specialty consultations, participants were offered Educational Group Sessions with a Gastroenterologist. As well, an information booklet on Irritable Bowel Syndrome was specifically developed by Dr. Howard for the people of Walkerton and area. Approximately 550 participants with on-going bowel complaints received the booklet. In addition, the booklets were distributed to the local family physician’s offices and to the local library. 171 participants were identified as requiring a Gastrointestinal consultation and 95 an Educational Group Session.

Nephrology (Kidney): 141 adults and 82 children were identified as requiring follow-up with a kidney specialist.
THE WALKERTON HEALTH STUDY
YEAR 7 FINAL SCREENING CLINIC

Open
Monday, March 10th to
Friday, July 25th 2008

WHO SHOULD ATTEND?

ALL PREVIOUS PARTICIPANTS
ALL who lived in Walkerton during the Year 2000
ALL who drank the contaminated water

WHY?

To reassess all previous participants
To identify risks and treat those with medical complications
To make medical history

Stay Involved

Keep Healthy

Prevent Complications

This is the last year of screening for the
Walkerton Health Study
Don’t miss your chance for a final health check

To schedule your appointment, please call
(519) 881-1476
The Walkerton Health Study (WHS) Year 4 screening clinic opened on March 14th, 2005 and will remain open till July 22nd, 2005. The screening clinic hours are from 7:30 AM to 3:30 PM with limited evening and weekend appointments.

**Goals:** The Year 4 goals remain very similar to those of previous years:
- To treat people with illness related to the water contamination in May 2000
- To identify the silent and long-term complications
- To refer those identified for more complete investigation and treatment
- To reduce and prevent long-term complications

**The Screening Clinic:** The appointment includes weight, height, blood pressure measurements and a short interview followed by laboratory testing. The main focus this year is on sugar diabetes. Therefore, we are asking all non-diabetics, over the age of 10 years, and non-pregnant women to provide a blood sample after an eight hour fast.

**Pregnancy after the Water Contamination:** The people of Walkerton have expressed concerns about the impact contaminated water could have on future pregnancies. This year the WHS will retrospectively investigate whether women who drank contaminated water have an increase risk of developing hypertension (high blood pressure). We will find these answers by comparing the outcomes of women who had severe diarrhea at the time of the outbreak to women who were well. Also, we will compare Walkerton women with women from rural, Southwestern Ontario. **We encourage all women who became pregnant after May of 2000 to attend the screening clinic so that we can answer these questions.**

**What is Happening Now**
- Booking Year 4 screening appointments
- Booking educational group sessions on irritable bowel syndrome with a Gastroenterologist
- Booking Adult Nephrology consults

**What is Happening Next**
- Performing a more sensitive diabetic test on those whose tests indicate they may be pre-diabetic
- Paediatric Nephrology consults
- Nephrology follow-up consults with all HUS children
- Newly diagnosed sugar diabetes consults
- Town Hall Meeting with the WEL Investigators in November, 2005 to report Year 4 findings

**Why Screening is Important**
- Early detection of sugar diabetes
- Early detection of kidney disease and subsequent treatment and prevention of progression
- Intervention for gastrointestinal illness related to the water contamination
- Monitoring for high blood pressure
- Monitoring for many other illnesses like heart disease, stroke, arthritis, inflammatory bowel disease, etc

Please consider this your personal invitation to stay involved with the Walkerton Health Study. Book your appointment today by calling (519) 881-1476.
A series of articles were written by WEL investigators appeared regularly in the Walkerton Herald Times. The purpose of these articles was to provide a lay-description of WHS research foci and medical conditions related to the outbreak including hypertension, diabetes, dyspepsia, arthritis, irritable bowel syndrome.

Diabetes and the Walkerton Water Contamination of May 2000.

By Dr. William F. Clark, MD, FRCPC, WEL Investigator

What does sugar diabetes (diabetes mellitus) have to do with the water contamination of 2000 in Walkerton? This is a question that Dr. Rita Suri and the WEL Investigators of the Walkerton Health Study, through the participation of Walkerton and area citizens, have attempted to answer.

*E. coli* O157:H7, a contaminant in the municipal water in the Spring of 2000, is known to cause Hemolytic Uremic Syndrome (HUS) in less than 2–7 % of those who develop acute gastroenteritis. Kidney involvement is a major feature of HUS. Small blood vessels in the kidney are occluded (blocked) by blood clots resulting in scarring and loss of function. In a minority of people, isolated case reports have also shown that the blood vessels supplying the Islets of Langerhans in the pancreas are occluded by blood clots resulting in loss of function. The Islets of Langerhans supply insulin and the loss of function can cause diabetes mellitus. Dr. Suri and the WEL Investigators carried out a systematic review of the medical literature to determine the incidence of diabetes mellitus following HUS. This review, which was published in Diabetes Care in 2005, revealed a major increase in the incidence of diabetes mellitus in children who had suffered from severe HUS.

Dr. Suri and the WEL Investigators wished to determine if all individuals, not just the small number with HUS who suffered severe gastroenteritis, were at an increased risk of developing diabetes mellitus. This concern resulted in two years of studies looking at the glucose metabolism of participants in the Walkerton Health Study. These investigations resulted in the diagnosis of many silent (undiagnosed, pre-existing) cases of diabetes mellitus and others in the pre-diabetic stage. Since 2002, the Walkerton Health Study has identified 71 new diabetics and 144 in the pre-diabetic stage. The advantage of diagnosing silent diabetes and those in the pre-diabetic stage is that it gives individuals the opportunity to make significant lifestyle changes, which will benefit them and prevent or reduce future complications. As well, there is encouraging news. It appears that, at this time (preliminary results), there may not be an increase in diabetes mellitus in the general population of Walkerton who suffered severe gastroenteritis at the time of the water contamination in May 2000. Dr. Suri, on behalf of the WEL Investigators, thanks all who participated in this study, the first of its kind in the world.
**Dyspepsia**

By Dr. Alex Ford MBChB, MD.,MRCP in association with Dr. J.K. Marshall MD, MSc, FRCPC, WEL Investigator

**What is Dyspepsia?**
Dyspepsia is a term that doctors use to describe a variety of symptoms that are thought to come from the esophagus (stomach tube), stomach and duodenum (upper, small bowel). Symptoms can include heartburn, acid reflux and pain in the upper part of the abdomen. These symptoms are very common in the general population, with almost half of people experiencing them at one time or another. Some sufferers will make an appointment to see their family physician as a result of symptoms, and may be sent for tests to find a cause.

**Testing and Diagnoses**
The most common test ordered is an endoscopy, a telescopic camera examination that allows the doctor to look inside the esophagus, stomach and duodenum. This may help diagnose certain conditions such as gastro-esophageal reflux disease (where acid refluxes out of the stomach and damages the lower end of the esophagus by causing inflammation), peptic ulcer disease (stomach or duodenal ulcers), or more seriously, but very rarely, a cancer of either the stomach or esophagus. Usually, the endoscopic examination offers no obvious explanation for the symptoms of dyspepsia. In this situation, the patient is said to suffer from a condition called “functional dyspepsia”. Their physician may offer medication to relieve their symptoms.

An endoscopic procedure also allows the doctor to take samples of the lining of the stomach (these are called biopsies) to look for infection in the stomach caused by a bacterium called *Helicobacter pylori* (*H. pylori*). *H. pylori* can cause peptic (stomach) ulcer disease, stomach cancer, and also functional dyspepsia. If a person is found to have *H. pylori* infection, it is usually treated with a week-long course of antibiotics. The purpose of the treatment is to improve dyspepsia symptoms and to prevent ulcers or stomach cancer from developing in the future.

**Investigation**
Over the past few years, researchers have been working to find the cause of functional dyspepsia. Some doctors have proposed that, just like in irritable bowel syndrome, an acute infection of the gut (such as infectious gastroenteritis) can provoke functional dyspepsia due to chronic inflammation of the stomach and duodenum post infection. There have been several studies published that have reported on this phenomenon, but most of these studies are very small, and they have only reported this possible association up to one year after the infection.

It is now eight years since the water was contaminated in Walkerton. This year, as well as the usual information collected at the screening clinic, we ask all participants, over the age of eighteen, about dyspepsia symptoms, by means of a very short questionnaire. The intent is to see if we can show an association between previous infectious gastroenteritis and dyspepsia. This will allow us to determine whether dyspepsia symptoms are more common in those who had acute gastroenteritis in 2000. We look forward to sharing these results of this latest Walkerton Health Study investigation with you at the Town Hall Meeting on Thursday, October 16th at the Victoria Jubilee Hall.
Healthy Blood Pressure and Kidneys

By Dr. Amit Garg MD, FRCPC, PhD, WEL investigator

What Is Blood Pressure?
Blood is carried from the heart to all parts of your body in vessels called arteries. Blood pressure is the force of the blood pushing against the walls of the arteries. Each time the heart beats (about 60–70 times a minute at rest), it pumps out blood into the arteries. Your blood pressure is at its highest when the heart beats, pumping the blood. This is called systolic (sis-TOL-ik) pressure. When the heart is at rest, between beats, your blood pressure falls. This is the diastolic (di-a-STOL-ik) pressure.

Blood pressure is always given as two numbers, the systolic and diastolic pressures. Usually, they are written one above or before the other, such as 120/80 mmHg (measured in millimeters of mercury, a unit for measuring pressure). When the two measurements are written down, the systolic pressure is the first or top number, and the diastolic pressure is the second or bottom number (for example, 120/80). If your blood pressure is 120/80, you say that it is "120 over 80."

Blood pressure changes during the day. It is lowest as you sleep and rises when you get up. It also can rise when you are excited, nervous, or active. A blood pressure of 140/90 mmHg or higher, when present over multiple readings, is considered high blood pressure. Both numbers are important. If one or both numbers are usually high, you have high blood pressure. If people live into their seventh, eighth, or ninth decades, most will develop high blood pressure.

Why Blood Pressure Is Important
When high blood pressure is not found and treated, it can cause arteries throughout the body to "harden" faster, especially those in the heart, brain and kidneys. This can cause a heart attack, stroke or kidney failure.

Blood Pressure in Walkerton after the 2000 Water Contamination
We have noticed that adults, who became ill during the Walkerton outbreak, have been more likely than others to develop high blood pressure four years after the outbreak. There may be a few reasons for this. Escherichia coli O157:H7 infections can affect the kidneys that regulate blood pressure in the body. Also, the outbreak may be an ongoing source of stress for some people, which can sometimes raise a person’s blood pressure.

Treatment for High Blood Pressure
The good news is that many people can prevent or control high blood pressure by changing to healthier habits. This includes following a balanced diet, loosing excess weight, being physically active, quitting smoking, and limiting alcohol intake. Sometimes, blood pressure stays too high even when a person makes these kinds of healthy changes. In that case, it is necessary to add medicine to help lower blood pressure. There are many effective medications to control high blood pressure, which can help people live longer, healthier lives.

We thank everyone for ongoing participation in the Walkerton Health Study. We hope to assess your blood pressure and kidney function in our clinics, which will take place in the years 2007 and 2008. Together, we can better understand outcomes from the outbreak, and use this information to maximize health in the community.
Irritable Bowel Syndrome
By: Dr. John K. Marshall, MD, MSc, FRCPC

History and Diagnoses of IBS
Irritable bowel syndrome (IBS) is a common and frustrating problem, characterized by intermittent discomfort in the abdomen and irregular bowel habits (diarrhea, constipation or both). Surveys in most Western countries suggest that between 10% and 20% of adults suffer from IBS, but not everyone seeks help from their family physician.

IBS is more common in women than men and usually presents in early adulthood. However IBS can appear and affect anyone at any age. Making a diagnosis of IBS can be frustrating for both patients and doctors, as there is no single test to prove the diagnosis. Instead, doctors look for the right symptom patterns and may do tests to rule out other possibilities. IBS is, therefore, a diagnosis of “exclusion”.

Treatment
Treatment of IBS is less than perfect, but a number of options exist. First and foremost is careful attention to diet and lifestyle to identify “triggers” that induce symptoms or make them worse. Triggers can relate to diet (e.g. lactose, fatty foods, spices), stress or any change in routine. While not all triggers can be avoided, recognizing and understanding their effects on gut function can be helpful and even reassuring. Most people don’t need or want medication to treat IBS. For those that do, medications are chosen to ease the most troubling symptom(s) of IBS. Unfortunately, current therapy isn’t effective for everyone. However, new treatments are being developed to give future IBS patients more options.

Post-infectious IBS
Post-infectious IBS is a specific form of IBS where symptoms begin after an episode of infectious gastroenteritis. While most people recover fully from such an infection, between 10% and 30% continue to suffer altered bowel habits (usually diarrhea) and stomach pain despite getting rid of the bug. Although doctors have recognized this phenomenon for decades, there has been relatively little research to help us understand what happens to people with post-infectious IBS. Small studies have suggested that symptoms gradually improve in most patients, possibly over years.

Post-Infectious IBS in Walkerton
Unfortunately, some Walkerton residents became all too familiar with post-infectious IBS following the water contamination of 2000. The Walkerton Health Study is underway to identify and treat people with health problems related to the outbreak, and to learn more about those problems in order to help other people in the future. Among our findings so far is that people, who got sick during the outbreak, were three times more likely to have IBS than those who stayed well. Young adults, females and people with particularly severe bouts of diarrhea were most likely to have post-infectious IBS. And among people who have returned to the clinic for their annual visits, many have reported a gradual improvement in their bowel habits.
What We Hope to Learn
As the Walkerton Health Study continues, we hope to learn more about what happens to people with post-infectious IBS over time. The current medical thinking is that most will return to full health, and that post-infectious IBS does not lead to any other digestive problems. We are looking specifically to see whether infectious diarrhea and IBS increase the future risk of inflammatory bowel disease (Crohn’s disease and ulcerative colitis). We are also looking to see if genes (DNA) can predict who gets sick when water is contaminated, and who develops long-term problems.

All members of the Walkerton Health Study team look forward to learning the answers to these important questions, and are grateful to residents who continue to visit the clinic in the wake of an awful human tragedy. Your efforts will undoubtedly help other people who face similar situations in the future.

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Dr. John Howard, a WEL Gastroenterologist, will be conducting information sessions on IBS Tuesday, September 19th at 12:00 noon and 4:00 P.M. If you wish to attend, please call (519) 881-1476 to reserve a place.

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Inflammatory Bowel Disease

By John Marshall MD, MSc. FRCPC

Definition
Inflammatory bowel disease (IBD) is a chronic medical condition characterized by an inflammation in the wall of the digestive tract. Because of its similar name, IBD is often confused with IBS (irritable bowel syndrome) but is a very different condition.

Types of IBD
IBD has two major forms, Crohn’s disease and ulcerative colitis. In both, the inflamed bowel lining can cause abdominal pain, diarrhea and rectal bleeding. However, there are important differences between the two. Crohn’s disease can affect any part of the digestive tract “from bum to gum”, while ulcerative colitis affects only the large bowel (also called the colon). In ulcerative colitis, inflammation is limited to the innermost lining of the bowel. However, patients with Crohn’s disease can have inflammation that goes deep into the intestinal lining. This can produce tunnels from the intestine to the skin or other organs (called fistulas) and infected fluid collections outside the bowel (called abscesses).

Etiology
IBD can appear at any age, but most often arises in young adults in their 20s and 30s, with men and women affected equally. The cause of IBD is not known, but a number of interesting theories have been put forward. It is well known that people can inherit a predisposition to the disease from their parents, and it is not unusual for patients with IBD to have other affected family members. However environmental factors are also important. For example, the “hygiene hypothesis” suggests that IBD develops because we are kept too clean as children, and overreact to bacteria or other particles in the digestive tract as adults.
Our intestinal flora (the bacteria that live in our bowels) play a key role in the development of IBD, but our understanding of their interaction with the intestine remains limited.

**Prognosis**
Many people with IBD have few symptoms and live normal lives. However, it can be a frustrating condition where patients alternate between flares (where symptoms appear) and periods of remission, with relatively few symptoms or none at all. Quality of life can suffer, and patients can have trouble functioning fully at work or in social situations.

**Treatment**
The treatment of IBD is changing, with the development of new medications and surgical techniques. Traditional medications include anti-inflammatories and steroids that turn off or reduce inflammation. There is growing interest in the potential role of probiotics and prebiotics, which change the mix of bacteria living in the colon. New “biologic” therapies like Remicade (infliximab) are costly, but can help patients who don't respond to other options. When medications fail, some patients with IBD undergo surgery to remove affected parts of the digestive tract. For patients with ulcerative colitis, removing the colon prevents the disease from coming back. However, Crohn's disease often comes back after surgery in other parts of the intestine.

**In Conclusion**
In some ways, a diagnosis of IBD can be devastating for young adults more interested in attending school, beginning their career, or starting a family. However, I often tell patients that there has never been a better time to develop this condition. There is exciting research underway to understand what causes Crohn's disease and ulcerative colitis, and there are many new novel treatments being studied in clinical trials. The Crohn's and Colitis Foundation of Canada has had huge success in raising funds for research, advocating for patients, and providing both education and support to patients and their families. Indeed, I encourage everyone to visit their website at www.ccfc.ca.

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**Effect of Exposure to Contaminated Water on Pregnancy Complications**

By Dr. Louise Moist, MD, MSc, FRCPC, WEL Investigator

**Shifting Focus**
The Walkerton Health Study is now shifting its focus towards the potential for unrecognized long-term health effects after exposure to contaminated water. This gives us the unique opportunity to study the complications of pregnancy in women exposed to contaminated water compared to women without exposure.

**Preliminary Analysis**
Preliminary analysis of the Walkerton Health Study data indicates that high blood pressure during pregnancy was self-reported by 14% of women who conceived after the contaminated water outbreak. This is above the reported range in the literature of 5-12%. This self-reported increase in high blood pressure highlights the need to confirm the incidence, explore potential mechanisms of injury, and document subsequent outcomes in both the women who become pregnant and the baby delivered, after exposure to contaminated water.
Why?
The scientific explanation for the increase in blood pressure may be due to the injury from the water contaminant (E. coli verotoxin), which decreases the ability of the vessels to dilate by a decrease in the synthesis of vasodilatory prostaglandins. Therefore, the initial blood pressure drop, which usually is seen in pregnancy, may not occur, and there may be a further increase in blood pressure as the pregnancy progresses.

Ongoing Investigations
The Walkerton Health Study is collecting health information on over 5000 people who were exposed to contaminated water during the outbreak in May 2000. This pregnancy study will identify women who became pregnant after exposure to the contaminated water. With their permission and in those women only, hospital charts will be reviewed to document a history of elevated blood pressure during pregnancy. The rate of pregnancy related high blood pressure will be compared to the rate reported in age matched women who were not exposed to contaminated water. We will also be collecting information on other factors that can influence the development of high blood pressure during pregnancy such as diabetes, smoking history and a previous history of high blood pressure.

This study will involve collaboration with the WEL Investigators of the Walkerton Health Study as well as Dr. Robert Gratton, an expert in pregnancy and perinatal outcomes. The results of this study are expected after the completion of the 7-year observational study in 2009.

Your continued support of the Walkerton Health Study is essential for us to identify long-term health risks to those who drank the contaminated water.

Reactive Arthritis

By: Dr. Janet Pope MD, MPH, FRCP and Dr. Amit X. Garg MD, FRCPC, FACP, WEL Investigator

Year 5 Focus
This year, the Walkerton Health Study is focusing on reactive arthritis. In the Year 1 screening survey, 131 participants indicated that they had a red, hot, swollen joint(s) shortly after the water contamination in May of 2000. All were assessed by Dr. John Thompson and Dr. N. le Riche, rheumatologists. Upon examination, the vast majority did not have reactive arthritis. Those with reactive arthritis were treated and follow-up continued as deemed necessary by the rheumatologist.

In subsequent years, additional questions in the survey identified other participants who may have experienced reactive arthritis.

Reactive Arthritis and Water Contamination
In many studies, contaminated water has been associated with reactive arthritis. However, more common bacteria that cause reactive arthritis are salmonella (such as in food poisoning). There are other types of bacteria such as campylobacter (from undercooked chicken) and Yersinia that cause inflammation of joints, particularly one or two joints. The
symptoms are usually transient caused by a reaction where the body thinks that it is fighting off bacteria, but instead it attacks the joint lining (synovium).

As many of you are aware, the contaminants in the Walkerton water supply were primarily *E. coli* and *campylobacter*. *Campylobacter* and even less so, *E. coli*, have only rarely been associated with reactive arthritis.

**Intervention**

We have received a grant from the Canadian Institute of Health Research to determine:
- the frequency of reactive arthritis in the affected community
- and the subsequent precipitation of chronic, reactive, inflammatory arthritis over time.

We expect to find few cases of ongoing inflammation in joints caused by the contaminated water. Of course, other joint complaints are common in the general population, such as degenerative arthritis, muscle strains and back pain. Through the great community participation in the screening questionnaires, we are hoping to identify and treat people with reactive, inflammatory arthritis. To further select those with reactive, inflammatory arthritis, an initial assessment will be done by a musculo-skeletal physiotherapist. People with positive findings for reactive, inflammatory arthritis will then be offered a consult with Dr. Janet Pope, a rheumatologist.

We will also look at the costs associated with chronic, reactive, inflammatory arthritis. However, we are optimistic that the disease burden in the community, from contaminated water, causing chronic, reactive, inflammatory arthritis, will be small. However, this investigation is important, for it will help the community and the scientific researchers better understand chronic, reactive, inflammatory arthritis as it relates to water contamination.

We thank you for your continued participation in the Walkerton Health Study.

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**The Story of another Contaminant in the Water on May 2000**

By Marina Salvadori, MD, FRCPC, WEL Investigator

*Campylobacter*

When the Walkerton municipal water was contaminated with bacteria in May of 2000, *E. coli* O157 became a household name. There were, however, other bacteria in the water and some people became sick with bacteria called *Campylobacter*. *Campylobacter* is a spiral shaped bacteria that can cause disease in humans and in animals. Most people get *Campylobacter* from handling raw poultry or eating raw or undercooked chicken. It only takes a very few of these bacteria to make you sick. Even just 500 organisms can make someone sick. That can be the amount in one drop of juice from raw chicken. You can also get the infection from drinking un-pasteurized milk or drinking contaminated water. *Campylobacter* can live in the intestines of many animals including chickens, cows, pigs, sheep, dogs and cats.

**Symptoms**

Most people, who become ill, get diarrhea, cramps, belly pain and fever within 2 to 5 days. It is rare to get sick more than 10 days after you have been exposed. You can have no
diarrhea, mild diarrhea or bad diarrhea which may be bloody. Some people get nausea and vomiting. The illness typically lasts for about 1 week. Some people, who are infected, never have any symptoms at all. The infection is usually diagnosed by sending the stool for special cultures in a laboratory. It is very rare to have long term consequences from Campylobacter. Some people may get arthritis following Campylobacter and this is called reactive arthritis. It usually gets slowly better over about 6 weeks to 2 years. There is also a very rare disease that affects the nerves of the body that can begin several weeks after the diarrhea. This disease is called Guillain-Barré Syndrome and occurs when your immune system attacks your body’s own nerves. This can lead to paralysis that can last several weeks. Most people get better from this. As far as we know there were no cases of Guillain-Barré Syndrome associated with the Walkerton outbreak.

**Treatment**
Virtually all people affected with Campylobacter recover without any specific therapy. Most people should just drink plenty of fluids to keep their body hydrated. Sometimes antibiotics, such as erythromycin are used.

**Prevention**
Campylobacter does occur in Ontario, especially in rural populations. Currently there are about 30 cases per 100,000 people living in Ontario. The most important ways to avoid Campylobacter infection are to drink clean, chlorinated, drinking water, avoid un-pasteurized milk and be very careful with food handling practices. In your own kitchen, you should make sure all poultry and beef is thoroughly cooked; you should wash your hands with soap after handling raw foods and before touching anything else; you should be particularly careful to use a separate cutting board for cutting meat and make sure the cutting boards, counter tops and utensils are carefully cleaned with soap and hot water. Never be afraid to send undercooked poultry back in a restaurant for further cooking. Campylobacter is a reportable disease in Ontario and all cases that are cultured in stool are reported to public health for investigation.
What really is an *E. coli* O157:H7?

By Marina Salvadori, MD, FRCPC, WEL Investigator

Walkerton residents are only too familiar with the term *E. coli* O157, the bacteria that caused most of the illness in May of 2000. Participants of the Walkerton Health Study have been interested in learning more about this bacteria. Bacteria, made up of one single cell, are the most primitive of life forms. *E. coli*, or Escherichia coli, are a family of bacteria. They are a gram negative rod, which means their shape is oval and they do not stain with a particular dye that is routinely used in a microbiology laboratory to identify bacteria. *E. coli* usually live in the stomach and bowels (or gut) of humans and animals. Most cause no harm and are part of the “good” bacteria that we need to help us live in normal health. Outside of the gut, in the bladder, *E. coli* are the commonest cause of urinary tract infections. Rarely, they can cause diarrhea. As everyone in Walkerton and area knows, *E. coli* O157 can cause severe, bloody diarrhea and hemolytic uremic syndrome (HUS).

**When Discovered**

*E. coli* have different types of bodies (“O”) and flagellae (or tails, “H”). So *E. coli* O157:H7 has the body type of 157 and the tail type of 7. It is unique because it secretes a toxin that damages different cells in the human body, particularly the cells that line the blood vessels, the kidneys, and the lining of the gut. Since the laboratory can grow *E. coli* from all stool, until the late 1970s people thought that there must be something besides *E. coli* in the stool causing bloody diarrhea and HUS. Then, in the late 1970s, a group of Americans discovered that *E. coli* O157:H7 eats a different type of sugar from other *E. coli*. With a special culture they were able to grow it in the laboratory and show *E. coli* O157:H7 was a cause of bloody diarrhea. In 1982, an outbreak of HUS occurred in Pickering Ontario. Doctors at the Hospital for Sick Children in Toronto tested for *E. coli* O157:H7 in these children with HUS. Tests were positive and for the first time *E. coli* O157:H7 was identified as causing HUS.

**Source of Infection**

*E. coli* O157:H7 normally lives harmlessly in the gut of cattle. It is known to cause “hamburger disease” (bloody diarrhea leading in a minority to HUS). When cows are slaughtered, fecal material, including *E. coli* O157:H7, may get on the meat. When it is ground up the bacteria spreads through the meat, but cooking kills all the bacteria. Inadequately cooked meat gives “hamburger disease”. You can also get this infection from eating vegetables, fruit, or water (Walkerton May 2000) that has been contaminated with the fecal material from cattle.

Most Escherichia coli are your friends. We need them to have normal stool, produce Vitamin K, and to keep our bodies in balance. *E. coli* O157:H7 is a very unusual and infrequent type of *E. coli* that is harmful to people.
APPENDIX II - HUS/TTP UPDATE 2008 SYMPOSIUM

HUS/TTP UPDATE 2008 SYMPOSIUM

Sunday June 1st & Monday June 2nd, 2008
At the Delta London Armouries in London, Ontario Canada

AGENDA
HUS/TTP Symposium (Following CSR)
Sunday June 1, 2008 Afternoon Session 1:00 PM – 5:45 PM
Dr. D. Sutton & Dr. D. Burch, University of Toronto – Chair

Welcome
1:00 Greetings
Dr. V. Hsu, University of Western Ontario

1:05 Introduction to Symposium
Dr. W. Clark, University of Western Ontario

Pathogenesis of HUS/TTP
1:10 V - TEC in HUS
Dr. M. Karmali, Health Canada, Quebec

1:20 Overview of Pathogenesis of HUS/TTP
Dr. J. A. George, University of Oklahoma Health Sciences Center

1:30 Mechanism of Microthrombosis in TTP
Dr. A. Sood, Molecular and Medical Sciences Center Albert Einstein College of Medicine

1:40 Mechanism of Microthrombosis in HUS
Dr. D. Rock, Canadian Rheumatology Group

2:00 Molecular events in vascular injury in HUS/TTP
Dr. P. Manders, University of Toronto

2:10 Question Period

2:30 Refreshment Break (10 minutes)
Dr. R. Foley, McMaster University & Dr. B. Singh, University of Western Ontario – Chair

Experiences with HUS in Canada
3:10 What Have We Learned About HUS in Canada?
Dr. R. McLean, University of Ottawa

Experiences with HUS in the United States
3:30 Outbreaks of HUS/TTP
Dr. R. Ten, Washington University School of Medicine

3:45 Walkerton Outbreak and Long-term Follow-up
Dr. W. Clark, University of Western Ontario

3:50 How did it happen in Canada, eh?
Dr. M. Sakkas, University of Western Ontario

4:10 Pediatric HUS in Walkerton in May 2000
Dr. D. Mattalini, University of British Columbia

4:25 Outcomes of Gastroenteritis & Pediatric HUS following Water Contamination
Dr. A. Gang, University of Western Ontario

4:45 Diabetes and E-coli 0157:H7
Dr. R. Sari, University of Western Ontario

5:00 Hypertension and Pregnancy Following Water Contamination
Dr. L. Mold, University of Western Ontario

5:15 Post-Infectious Diarrhea - Irritable Bowel Syndrome – Inflammatory Bowel Disease
Dr. J. Marshall, McMaster University

6:15 Following Water Contamination
Dr. C. Whiteside, University of Toronto

4:55 Summary

The London Club
7:00 Cocktails
8:00 Dinner and DEBATE

Differential Diagnosis of HUS vs. TTP for Optimal Treatment
Dr. R. Burch & Dr. G. Rock vs. Dr. Taref & Dr. Ten, Dr. W. Clark to moderate

10:00 Close meeting

Sunday June 1, 2008 Evening Session 7:00 PM – 10:00 PM

Monday June 2, 2008 Morning Session 9:00 AM – 11:00 AM
Dr. J. Ball, University of Western Ontario & Dr. M. U. Qureshi, University of Alberta – Chair

8:00 Continental Breakfast

A discussion of specialists’ experiences as it relates to prognosis, treatment, complications and late outcomes.

9:00 TTP/HUS
Dr. G. Rock, Canadian Rheumatology Group

9:20 TTP/HUS
Dr. W. Clark, University of Western Ontario

9:40 TTP/HUS
Dr. J. A. George, University of Oklahoma Health Sciences Center

10:00 Relapsing TTP/HUS
Dr. D. Rock, McMaster University

10:20 Prognostic Factors Affecting Treatment
Dr. B. Foley, Children’s Hospital, Calgary

10:40 Treatment Options for HUS Secondary to E-coli 0157:H7
Dr. Martin Bitton, McGill University

11:00 Question Period

11:30 Closing Comments
Dr. W. Clark, University of Western Ontario

LEARNING OBJECTIVES
• Utilize recent scientific advances about thrombotic microangiopathies to improve therapeutic and diagnostic strategies.
• Become aware of the most recent findings about long-term outcomes from one of the world’s largest outbreaks of E-coli 0157:H7.
• Identify and compare current models of care in the treatment of HUS/TTP.
• Understand some of the basic controversies about treatment in HUS/TTP.

Registration Information: Attendance limited to first 150 registrants. Information is available online at www.csco.ca
Registration fees include dinner during the evening session on June 1, 2008 and a Continental Breakfast before the Morning session on June 2, 2008.
Fees are $150.00 per person and $100.00 per non-physician, Technician and/or Other. Please make cheques payable to: Walkerton Health Study.
Please contact the Delta London Armouries if you require accommodations Toll-Free: 1-877-844-7706

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