

"I THINK WE HAVE A PROBLEM IN VICTORIA": MDs RESPOND QUICKLY TO TOXOPLASMOSIS OUTBREAK IN BC

Anne Mullens

In Brief • En bref

More than 110 people, including 12 newborns, were infected with *Toxoplasma gondii* in Victoria last year. A team of doctors, researchers and public-health officials determined that the source of the world's largest recorded outbreak of the infection was the water supply. Anne Mullens looks at how the BC medical and scientific communities responded to a unique challenge.

L'an dernier, à Victoria, plus de 110 personnes, dont 12 nouveau-nés, ont été infectés par *Toxoplasma gondii*. Une équipe de médecins, de chercheurs et de responsables de la santé publique a conclu que la source de cette flambée d'infection, la plus grave jamais enregistrée au monde, était l'eau potable. Anne Mullens nous dit comment les médecins et les scientifiques de la C.-B. se sont attaqués à ce problème sans précédent.

For a team of British Columbia doctors, researchers and public-health officials, 1995 will go down as the year of *Toxoplasma gondii* because of a toxoplasmosis outbreak that kept them working day and night for months. More than a year after the unprecedented epidemic was identified in Victoria, data are still being tallied, ramifications studied and scientific papers written.

To date, 112 people have shown serologic evidence of infection by the parasite — the largest recorded outbreak in the world. The list included 37 pregnant women and 12 infants who were identified through a massive screening program. Others among the remaining 300 000 people who live on southern Vancouver Island may have been infected and don't know it.

"We have estimated that perhaps

as many as 3000 individuals were infected, but we have only identified 100," said Dr. William Bowie, a professor of medicine at the University of British Columbia. Bowie became coordinator of a "toxoplasma team" that has grown from a handful of people at the start of the outbreak to almost 50 people across North America today. Many will be studying the affected patients, conducting related research and writing about the outbreak for years.

The epidemic was made even more unusual by the team's conclusion that the crescent-shaped protozoa, *T. gondii*, was passed to people through the municipal water supply. Although some American soldiers were infected with *T. gondii* in the 1970s after drinking from a stream in Panama, the Victoria outbreak marks the first time municipal water has been suggested as the transmission route for the parasite. Infection most commonly occurs through contact with infected cat feces or

ingestion of infected, undercooked meat.

Dr. Andrew Burnett, a Victoria ophthalmologist, and Raj Gill, supervisor of the nonviral serology laboratory at the BC Centre for Disease Control in Vancouver, are credited with ringing the alarm bells in the third week of March 1995. They reported that the incidence of toxoplasmosis was extraordinarily high in the region.

Burnett, who specializes in diseases of the retina and vitreous, had seen his first patient in early January — an otherwise healthy 49-year-old man who complained of hazy vision and floaters in one eye. Internal examination of the eye revealed a tell-tale spot of creamy, yellow opacity against the retina, suspicious of acute acquired retinitis. There was no sign of any old toxoplasmosis scars — seen as a dark "punched out" ring on the retina — to indicate the reactivation of an old lesion. Burnett suspected acute acquired toxoplasmosis retinitis and ordered the blood work, but nevertheless was surprised when the test proved the diagnosis. "To see an eye with fresh retinitis, with no sign of a previous scar and proof in the blood showing an acute, first-time infection, is most unusual," he said. "I hadn't seen one in years."

Burnett became even more alarmed when over the next 8 weeks he and colleague Stan Shortt saw six other patients with the same diagnosis. When a seventh case was confirmed in mid-March, Burnett called

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Dr. Judith Isaac-Renton, medical parasitologist at the BC Centre For Disease Control. He told her he was seeing new cases involving eye lesions in numbers not seen before, all linked to toxoplasmosis. Almost simultaneously, laboratory supervisor Gill, who conducts all toxoplasmosis tests for the province, walked into her office carrying the results of 15 positive tests from the Victoria region. "I think we have a problem in Victoria," he said.

In coming months, many would remark on the good fortune that Victoria was a small enough city to have only two retinal specialists who saw all the first cases, and that only one laboratory handled all tests in the province. In a larger city the infections might have been more dispersed, and no alarms would have sounded.

Besides Burnett's and Shortt's seven patients, eight others in the region had come into their doctors' offices during the previous 2 months complaining of flu-like malaise and swollen lymph glands. Along with ruling out infectious mononucleosis and the lymphomas, the physicians had ordered blood tests for toxoplasmosis. All tests showed the presence of both IgG and IgM antibodies for *T. gondii*, indicating an acute infection.

Isaac-Renton determined that the same number of tests were being done around the province, but Victoria had more than five times the expected rate of positive results; normally one to four cases would be diagnosed in a year. She also checked the test protocol, because an epidemic might appear to arise simply because of test methodology. The test was the same.

T. gondii is a versatile parasite. A protozoa related to the *Coccidium* family, its oocysts are formed in the intestines of cats and shed in their feces. The oocysts can remain viable for months in moist, shaded soil, infecting rodents or birds, who reinfect cats and complete the cycle. Whether ingested by humans or ani-

mals as the intermediate host, the protozoa proliferates and spreads rapidly through the blood stream. It forms cysts consisting of bradyzoites, most commonly in striated muscle, the retina and the brain, where it can lie dormant and harmless for years. It may only re-emerge to cause harm if the host's immune system is compro-

had unusually high levels of antibodies to *T. gondii*, making Isaac-Renton wonder if the Victoria organism was a slightly different, perhaps more virulent strain. "We could see the positive result developing on the bench right before our eyes. It was a bright yellow and we'd say, 'Wow, here's another one.'" When two blood sam-

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— Dr. Andrew Burnett, Victoria ophthalmologist

mised. In Canada, 10% to 20% of people have been exposed to toxoplasmosis and developed immunity against it. The most common way to become infected is to ingest the oocyst directly or ingest the tissue cysts in infected meat from grazing animals.

In Victoria, the first challenge was to find the source of the outbreak. Isaac-Renton contacted Dr. Alison Bell, director of epidemiologic services for the province, and epidemiologist Dr. Arlene King, and they drew up a preliminary questionnaire. On Mar. 25 the three contacted all 15 patients who had tested positive to determine if they had cats, drank unpasteurized goat's milk, ate lamb or rare beef, enjoyed gardening or had other risk factors. The patients were also asked where they ate, shopped and bought their meat.

"We knew that the onset of symptoms had seemed to be late December so we were thinking eggnog, turkey, maybe a company Christmas party or community event — but there was no unifying factor that we could find," said King. "The ages ranged from 15 to 83 and there was no common link."

Over the next few weeks many new cases were identified by blood tests. The positive blood specimens

sent from other parts of BC showed the characteristic bright-yellow reaction, the scientists were sure the patients had spent time in Victoria — and indeed they had.

On Apr. 10, a case-control study began, designed by King, Bell and Dr. Denise Werker of the field epidemiology training program at Health Canada, currently working at the BC Centre for Disease Control. King, Werker and others conducted extensive home interviews that lasted more than 2 hours and involved 39 infected people and 88 controls. Still, no apparent mode of transmission emerged. "Once the awareness arose that there was no discernable connection between all these people, we began to realize we must have a very large outbreak, with many people whom we were not yet identifying," recounted King.

King, Isaac-Renton and Bell had to determine what should be done from a public-health perspective. Most at risk of acquiring infection were fetuses and newborns infected in the womb, 90% of whom would appear normal at birth. As the infants grew, however, *T. gondii* could cause sight-threatening lesions, deafness, hydrocephalus, seizures and mental handicaps. A woman who becomes infected in pregnancy has a 50%

chance of passing the infection to her fetus. The lowest risk of transmission, 15%, occurs in the first trimester, but that is also when the damage can be most severe and miscarriages most common. Later in pregnancy the chance of transmission increases — from 30% in the second trimester to 65% in the third — but infections tend to be less severe. "We knew we must put in place a screening program for all pregnant women and new mothers in the region," King said. The program would cover an estimated 4500 women.

Early support for the massive screening program came from Dr. Frank Jagdis, a pediatrician who would play a central role in treating the infected children, Dr. James Saffrey, head of family practice for the Greater Victoria Hospital Society (GVHS), and Dr. Patrick MacLeod, medical geneticist for the GVHS and the physician responsible for prenatal testing in the region.

MacLeod hadn't seen a case of congenital toxoplasmosis in 10 years. "I thought, 'This is a disaster, it is a dreadful disease,' and I was still thinking that, like 10 years ago, it was largely untreatable. I dreaded having to tell 30 or 40 women that their babies were infected."

To update his knowledge MacLeod spent a weekend combing online medical databases for recent information on congenital toxoplasmosis and its treatment, including promising studies from Chicago and France that detailed drug treatments that could give children what appeared to be normal outcomes. "By the time I was finished, I was thinking, 'This is winnable. Let's get going.'"

The team "started from scratch" to sort out the logistics of screening such a large population: it notified all doctors in the region, devised a method to track patients, drafted blood-requisition forms, found staff to test the samples as quickly as possible and prepared test kits. Isaac-Renton remembers the flurry of over-

seas phone calls after the French manufacturer sent only 1000 test kits instead of the 5000 that had been ordered.

At the height of screening the laboratory handled 600 samples a day, with staff working weekends and 15-hour days. Calls were made almost daily to toxoplasmosis expert Dr. Jack Remington at his Stanford University laboratory, where the amniotic fluid was sent for DNA testing and the blood was sent for confirmation and further testing. Daily calls were also made to Dr. Rima McLeod, a professor of medicine at the University of Illinois who is an expert in the diagnosis and treatment of infected babies. In Victoria, Patrick MacLeod arranged a toll-free information line for parents and doctors, assembled a toxoplasmosis information sheet, established a computer database of scientific information and set up a system to schedule appointments for infected mothers and infants.

On Apr. 24 Victoria's acting medical officer of health, Dr. Tim Johnstone, announced that all pregnant women or new mothers who had delivered since Oct. 1, 1994 — whether they lived in the region or simply had visited during their pregnancy — should be screened for toxoplasmosis. King remembers having a last-minute pang of doubt the night before the screening was announced: "What if this is all for nothing?" When on the first day of screening a positive test was revealed, the toxoplasmosis team, now numbering more than 30 people, knew the right decision had been made.

Nicole Barbondy was one of 37 women to test positive among the 4000 women screened in 2 months, her baby, Briane, was just 2 days old when she was found to be infected. She had a computed tomography (CT) scan, lumbar puncture and ultrasound. When tests revealed that the baby had a lesion affecting the periphery of her right eye, her par-

ents were devastated. "At first it was such a shock," Nicole Barbondy said. "I had been so careful during my pregnancy and I could not believe that somehow I had harmed my baby." On May 19, Briane started on a potent daily cocktail of drugs: pyrimethamine, a folic acid antagonist that disrupts the parasite's growth, sulfadiazine, which also inhibits the biosynthesis of folic acid, and leucovorin, which diminishes the impact of bone marrow suppression caused by the other two drugs. Every child shown to be infected was to take the drugs for 1 year.

"These drugs are not used lightly," said Rima McLeod, who has now collected data on 70 children treated by the regimen and is comparing it with the outcomes of 30 controls. "There is a substantial incidence of neutropenia that we have to monitor constantly and adjust the drug doses accordingly. We worry all the way through." Five of the Victoria newborns were enrolled in her ongoing study, which included being flown with their families to Chicago for tests. Briane Barbondy was one of the test subjects.

Pregnant women found to be infected were given a course of spiramycin to reduce the chance of infection of the fetus. As the months passed, the number of infected infants climbed to 12. Five were found to have eye lesions and CT scans revealed that two had brain calcifications. Every Thursday all 12 would have their white blood cell counts checked at the hospital. "It was worse for Jim and me than it was for Briane," said Nicole. "We found it very hard, but it was what was normal for her. She would see the blood nurse coming and stick out her arm." A support group was launched to help parents deal with the emotional impact and need for information.

Each night for almost 3 months during the pregnancy screening, Isaac-Renton in Vancouver and Patrick MacLeod in Victoria would

confer by telephone, going over the day's positive results so MacLeod could arrange the notification and management of infected patients. On Friday mornings a conference call let up to 20 team members update each other on progress and examine possible transmission routes.

As each case was identified, King placed a blue dot marking the patient's home address on a map of the region. Slowly a pattern began to emerge — almost all the cases were concentrated in Victoria's central core. Having worked there as a resident in community medicine, King recalled that there was something different about water distribution in the city compared with outlying regions. In June, King met with medical health officer Johnstone and Stewart Irwin, water-quality manager for the Greater Victoria Water District. Irwin detailed the system of reservoirs in the region and how those living in the southern part of the peninsula was served exclusively by the Humpback Reservoir, which had existed since 1913. Water from the three reservoirs was treated in two chloramination plants, in which a dilute solution of chlorine and ammonia is added to water before being delivered to residents.

"After they had explained how the water system worked, we brought out our map with blue dots and overlaid it on their map, and all of us looked at each other in a state of shock," King said. "We were all thinking — maybe there is a similarity here."

It still took more than 2 months of further study for the team to conclude, to its own satisfaction, that drinking water was the source of infection. A second case-control study of the pregnancy-related infections was mounted. Designed by King, Bell and Werker, it again looked in depth at possible transmission routes, such as eating habits and water consumption. Again, no link was shown to the usual sources of infection — meat and cats. However, this time,

when examining water links, there was a statistically significant finding that cases were more likely than controls to live or work in an area served by the Humpback Reservoir.

When two periods of heavy rainfall in December and February were plotted against the outbreak of the disease, it was found that turbidity incidents directly preceded, by a few weeks, the times when patients recalled experiencing the aches and malaise of probable toxoplasmosis infection.

The theory emerged that infected domestic or feral cats, or even an infected cougar, had defecated in the watershed and the heavy rains had washed a bolus of oocysts into the reservoir. As proof that this was possible, four of seven domestic cats caught in the watershed area were found to be positive for toxoplasmosis. Although no attempt was made to catch and test cougars in the Humpback watershed, each of five cougars caught in neighbouring Nanaimo, just 100 miles to the north, tested positive.

At a Sept. 8 press conference, Victoria's new medical officer of health, Dr. Richard Stanwick, announced that water was the suspected source. By that time, the outbreak was deemed to be over. Included in the tally were 51 cases of lymphadenopathy and 19 cases of eye lesions, one serious enough to cause blindness in one eye and others severe enough to pose a serious threat to vision quality. All of those known to be infected will be followed to see if more eye lesions appear in the years ahead. "We assume there will be some who go on to develop eye lesions whose retinas now, on examination, look perfectly normal," said Burnett. He also believes that he is going to see more toxoplasmosis-related eye lesions among Victoria residents who became infected during this outbreak, but did not know it.

Screening of all pregnant women in the region continued until Apr. 30,

1966, resulting in a final total of almost 8000 blood tests. The Humpback Reservoir, which had long been slated for removal from the water-supply system, was closed in September 1995 — 3 months early

Isaac-Renton developed the first test to detect *T. gondii* in water. Large amounts of water are filtered to isolate the oocysts, sporulating them. The isolate is then introduced into mice to see if they become infected. After 2 months, the mice are tested for antibodies to *T. gondii*. Although samples of Victoria water were tested in June and July of 1995, by that time oocysts had long since left the water and no positive confirmation could be found.

"We will never be able to say with scientific certainty that yes, this outbreak was passed in the water," says Alison Bell. "For some critics, the only way they will believe it really occurred is if viable oocysts are found directly in the water. It will be left to others to validate our hypothesis in future outbreaks."

Parents of infected children celebrated as the 1-year anniversary approached this spring and their children could stop the medication and the weekly trips to hospital. "We are so excited, we are counting down the days," said Nicole Barbondy in late April. For Briane, the protocol finally ended on May 19. Like the 11 other infected children, her development is normal and her prognosis good. Even the two children who showed brain calcifications are doing well and developing normally.

"They are pretty normal children," said Dr. Rima McLeod, but they may be at risk for eye disease in the future. "We will have a better idea about that by their 10th birthday. They will all be followed very carefully."

"The team in BC deserves a lot of credit for how this was handled. They worked with such alacrity and care. This should become a paradigm for how an outbreak like this should be managed." ■