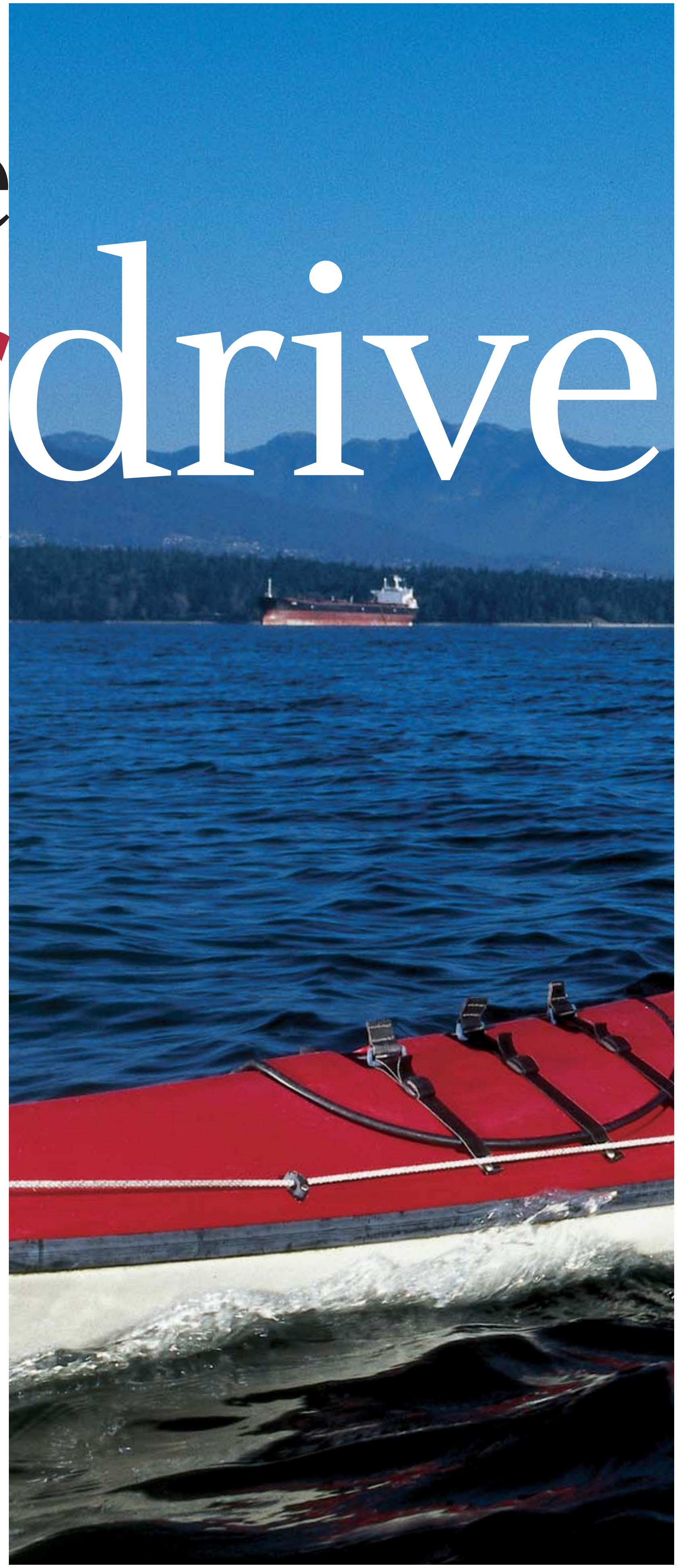
Science in Overdrive



The energetic Brett Finlay works hard to help solve global health problems but still finds time to be a husband, dad, boss, athlete, musician, cook, and grocery shopper. By William Dietrich

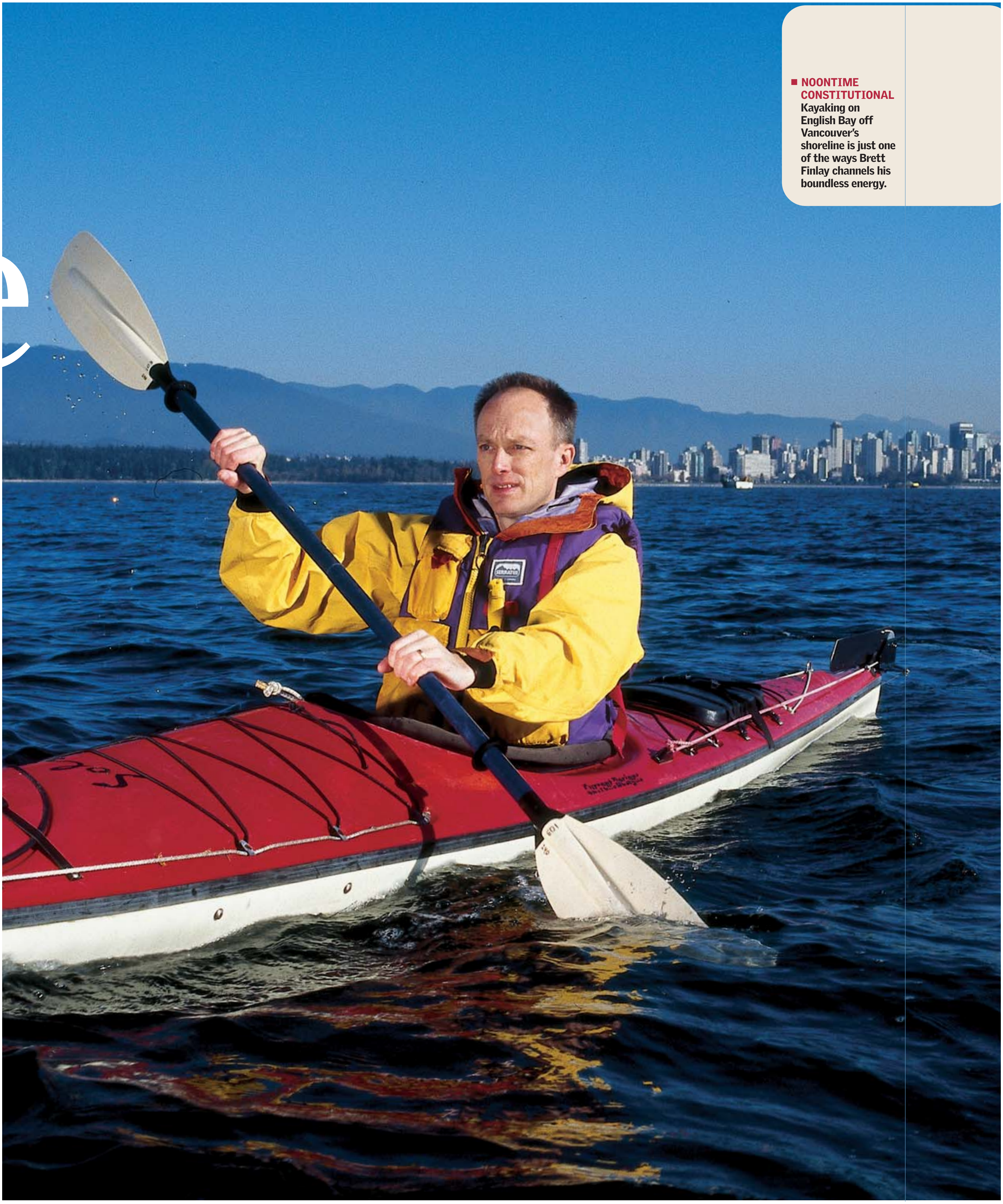
PHOTOGRAPH BY BRIAN SMALE

In May 2000, spring floods washed cattle manure into the water wells of Walkerton, Ontario, a farming community of 5,000 people about 90 miles west of Toronto, thereby contaminating the town's water supply. An epidemic of diarrhea followed, sickening half of the population and leaving seven dead. The culprit was *Escherichia coli* O157:H7, a strain of the common intestinal bacterium that was first detected from cases of severe bloody diarrhea in the late 1970s.

E. coli is now a significant health problem worldwide. According to the U.S. Centers for Disease Control and Prevention, for example, the microbe causes some 76,000 infections a year and kills an average of 61 people in the United States alone. Yet, this is just the tip of the iceberg. In developing countries, as many as 2 million people die annually from diarrhea-related dehydration.

Canada and the United States have developed four different approaches to preventing such tragedies, both at home and abroad, but what's remarkable is that a single Canadian scientist—B. Brett Finlay, a microbiologist at the University of British Columbia (UBC) and an HHMI international research scholar—is helping to lead all four:

- *Reform of water and health systems.* Finlay helped establish the Canadian Research Coalition for Safe Food and Water, a $13 million effort that supports research to increase food and water safety. Finlay is also a member of the advisory board for the Institute of Infection and Immunity, a group working to establish national priorities in that field and improve communication and coordination between Canadian health, food, and water agencies.
- *Vaccination of cattle that carry the bacteria.* The vaccine will help banish "hamburger disease" (as infection from O157:H7 is commonly called) by keeping it out of the meat supply in the first place. In a paper published in the January 2, 2004, edition of the journal *Vaccine*, Finlay and colleagues reported results of a clin-



■ **NOONTIME CONSTITUTIONAL** **Kayaking on English Bay off Vancouver's shoreline is just one of the ways Brett Finlay channels his boundless energy.**

ical trial of a cattle vaccine that successfully reduced the prevalence of O157:H7 in the feedlot. This promising finding suggests that it is indeed possible to vaccinate cattle to decrease the level of *E. coli*, which “could have profound benefits for human health around the globe,” notes Bhagirath Singh, scientific director of Canada’s Institute of Infection and Immunity.

- *Understanding how O157:H7 attaches to and disrupts healthy cells.* Discoveries from Finlay’s lab show how the microbe works so that new strategies can be developed to defeat it.
- *Boosting the body’s natural immunological defenses.* Finlay is a cofounder and member of the board of directors of Inimex Pharmaceuticals, a Vancouver company set up to develop and commercialize discoveries made by scientists at UBC. Inimex intends to use peptides to boost innate immunity against infections.

PREMATURE OPTIMISM

The past century appeared to be one of triumph over infectious disease. Antibiotic drugs such as penicillin as well as vaccines against a long list of bacterial and viral illnesses helped boost average American life expectancy by about 30 years. By 1969, the U.S. surgeon general declared, “It’s time to close the book on infectious diseases.”

But the optimism was premature. While human generations are about 20 years apart, bacterial generations are an hour or less apart. Bacteria trade and share genetic information, and this constant throw of the genetic dice means mutant strains rapidly arise that are resistant to our arsenal of antibiotics. In addition, new challenges—such as AIDS, Ebola, legionnaires’ disease, and SARS—continue to appear.

Meanwhile, only one new class of antibiotics, the oxazolidinones, has reached the market in the past 30 years, and finding drugs to combat each form of infection is difficult to justify. It can cost upward of $500 million and take 10 years to commercialize a new drug, but bacteria mutate so swiftly in response that drug-resistant strains can appear within a year and the new drug can be obsolete in three years.

Hospitals are breeding grounds for such resistance. For his 14-year-old daughter’s recent science project, Finlay helped her analyze bacterial contamination of coins collected from hospital cafeteria vendors compared to coins from an outside grocery store. Those that had passed through the hospital carried a far higher percentage of drug-resistant strains of microbes, demonstrating that these institutions’ heavy use of antibiotics has helped create superbugs.

“We need to rethink this,” he says. We are in a constant “arms race” with microbes and viruses that, he warns, “we will never completely win.” Because the germs mutate against every defense we throw at them, we need to develop other strategies.

Bacteria evolved on the planet first, long before plants and animals, and are found in almost every environment, from boiling hot springs to shafts thousands of feet below the ground. “They live everywhere,” Finlay observes, “and humans just represent another nice place for them to live.” We’re warm, wet, full of nutrients, and, in some ways, Finlay says, “more microbe than we are human.”

The human body has 10 times more microbes than cells, or an estimated 1,000 trillion bacteria for each one of us. A square centimeter of skin can have up to a million bacteria, and a gram of feces contains approximately 2 billion. The vast majority of these microbes are benign, helping digest food in our gut and crowding out their disease-causing brethren. But some of these bacteria develop parasitical strategies that make us sick.

Until recently, the two major counterstrategies were either to kill them with antibiotic wonder drugs or trick the body into beefing up its own defenses with the aid of vaccines. But given the current wealth of information on how cells, bacteria, genes, and biochemical pathways work in a complex microscopic ecosystem of mutual dependency and attack, researchers such as Finlay seek new approaches. They don’t try to kill the bacteria, thereby destroying our friends in the bacteriological ecosystem, but rather interfere with the processes that specifically cause illness.

SABOTAGING THE CELL

A key breakthrough of the Finlay lab was the discovery, in 1997, that disease-causing *E. coli* have a clever way of sabotaging human cells to create a place where they can anchor themselves. Each bacterium exudes a tube, like a syringe, into the cell surface and injects a protein called Tir that serves as a receptor, plus at least a dozen others that disrupt the host cell. The injections trigger rearrangement of the cytoskeleton, which underlies the cell wall like scaffolding under a tarp, and cause it to swell upward, forming a pedestal on which the bacterium can comfortably nest.

This insidious adhesion actually offers researchers an opportunity, Finlay says. If science could find a way to snip or block that syringe, bad actors such as O157:H7 would be unable to link to a cell and cause damage. Instead, they would be flushed out of the body. His lab, in fact, is working on this approach. “We tell pharmaceutical companies that you don’t have to kill the bugs, you just knock out the mechanism that causes the disease,” he explains.

Similarly creative thinking informs the Finlay lab’s development of the cattle vaccine against *E. coli* O157:H7, which is sure to attract a great deal of interest. Relatively simple to prepare and economical, the vaccine shows that it may be feasible to decrease human infections by vaccinating an animal population.

The lab is also working on *Salmonella*, a bacterium that sickens some 1.4 million people in the United States per year. In some ways, it is even craftier than *E. coli*, tricking the cell into opening up and absorbing it by chemically “ringing the doorbell.” Once it is inside, Finlay has discovered, it forms a protective coating to avoid being destroyed by cell defenses and starts feeding and multiplying until it explodes the cell. Is there a way to teach the cell not to open the door? If there is, Finlay is determined to find it.

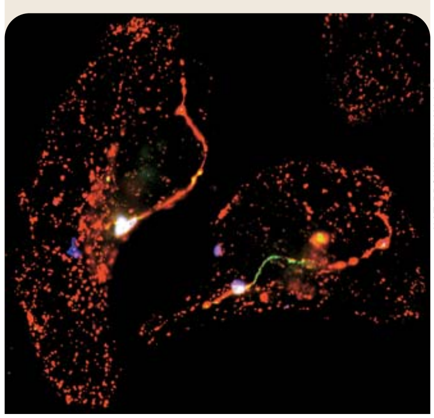
Still another tactic is to improve sanitation. The town of Walkerton, Ontario, had plenty of chloride on hand but didn’t use it to treat its water supply. If it had, the *E. coli* outbreak there might never have happened.

SUPER SCIENTIST

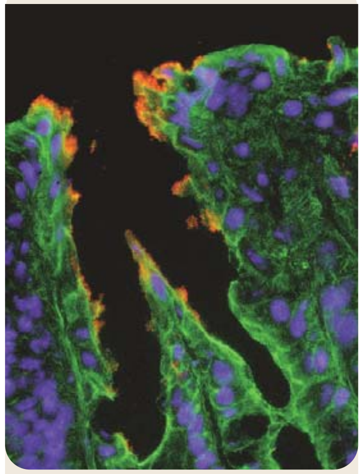
Finlay is one of those rare super scientists who somehow seems to have twice the energy and three

Sly Intruder

This image from the Finlay lab details one part of *Salmonella's* invasion of a cell. *Salmonella* injects proteins into the host cell, altering membrane traffic, which in turns leads host-cell organelles to form Sifs, or *Salmonella*-induced filaments. One of these proteins, PipB, is shown here in green, localizing to Sifs along with the host endosomal protein LAMP-1, shown in red. Bacteria are shown in blue.



NAT BROWN, FINLAY LAB.



BRUCE A. VALLANCE, WANYIN DENG, AND B. BRETT FINLAY

Enteric Entry

The Finlay lab uses the mouse bacterial pathogen *Citrobacter rodentium* to model *E. coli* infection in humans. This image shows immunofluorescence staining of mouse colonic tissue infected with the pathogen, at 10 days post-infection. During infection, *Citrobacter rodentium* expresses Tir, a receptor molecule for bacterial attachment (shown here in red), and translocates it into intestinal epithelial cells. The host cell protein F-actin is shown in green; host cell nuclei are stained blue.

times the accomplishments of most of the rest of us. As if he weren't busy enough, the 44-year-old was recently conscripted, as he calls the appointment by the British Columbian provincial government, to head a multidisciplinary effort to devise a vaccine for fighting the recently contained but still-threatening SARS epidemic. Within six months of Finlay's marshaling of scientific resources in April of last year, the Canadians were testing three different SARS vaccines in small animals, thanks to an emergency effort that emphasized coordination instead of competition between labs. "Brett led us through this complicated process with deftness and alacrity," says Robert Brunham, director of medical and academic affairs at the British Columbia Centre for Disease Control. "His can-do leadership made all the difference."

Outside the lab, Finlay is a whitewater-kayaking champion, ski instructor, clarinetist with the Pacific Symphonic Wind Ensemble, and a daily runner who sometimes holds Inimex staff meetings during jogs along Vancouver's English Bay. He is also a devoted husband, loving father to two bright children, an accomplished cook, and even the family grocery buyer.

"Brett manages his day in 15-minute blocks," says his wife Jane, a pediatrician, who both marvels at and endures his drive and perfectionism. An example of Finlay's organization is his approach to grocery shopping, which he insists on doing himself because it is faster and eliminates impulse buying. He has a computerized list of products, keyed to the layout of a favorite store, on which family members circle what they want. He charges the aisles in a blitz.

> Despite Finlay's fast pace and unwavering focus, his approach to science is also refreshingly down-to-earth.

"To say he's high-energy is putting it mildly," says Stanford University microbiologist Stanley Falkow, who oversaw Finlay's work as a postdoc. "He has no fear of a subject. He'll focus on multiple subjects, but focus on them one at a time. He kept a to-do list at his lab bench. It was when every item on it was crossed off that I knew he had gone home."

Finlay also works hard to make science accessible to the general public. A skillful speaker, Finlay gave two of the four HHMI Holiday Lectures on Science in 1999 ("The Microbes Strike Back" and "Outwitting Bacteria's Wily Ways"), which were shown in 15,000 U.S. and Canadian high school classrooms. (See *www.hhmi.org/biointeractive/disease/lectures.html.*) At lectures for high school students, he has been known to use animations and everyday items such as Jell-O and bagels to help students visualize the microscopic world. His laboratory's Web site (*www.biotech.ubc.ca/faculty/finlay/homepage.htm*) uses cartoons of bacteria besieging castles—an analogy for cells—to explain the lab's research.

Despite Finlay's fast pace and unwavering focus, his approach to science is also refreshingly down-to-earth. If science is complex in its details, the questions it asks and problems it tackles are fundamentally simple, he says. "If you can't explain to your mom what you're working on, you shouldn't be working on it."

GREAT EXPECTATIONS

In fact, it was Finlay's parents who explained much to him. A lot of his energy and seriousness of purpose comes from a relentless curiosity fostered during childhood by scientist-parents. His father, Cam, was an ornithologist who worked at Elk Island National Park of Canada, near Edmonton. His mother, Joy, was an accomplished botanist. Finlay's parents gave him the opportunity when growing up to, for example, clean dinosaur bones, build bird shelters, and measure the contents of a dissolved magpie nest.

"Their attitude was to expose us to many things and let us do what we wanted," he recalls, but there was also an expectation to excel. His mother once disconnected the doorbell so that Finlay had the time to complete projects instead of being tempted to go out and play. His parents taught him to start keeping detailed scientific notebooks. And when his parents were working, Finlay cooked the family's meals.

Finlay found his calling when he first looked into a microscope. "Once I stuck my face in the microscope, it was a whole new world. You're an explorer. You're after what no one has found before. The North Pole has been conquered, but microbial science is uncharted territory."

Ask Finlay today about his work and he'll describe it as "playing in the lab" while trying to solve problems that can help people lead better lives. Much of his inspiration came from touring labs and seeing sick children in Vancouver, Brazil, and Indonesia and noting the real human agony that can come from our constant struggles with the microbial world. "I can see the utility of it," he says. "I want to do science of use to humanity."

The scientist is also helping to streamline the process of science itself. When British Columbia's government asked him to oversee the crash effort to find a vaccine for SARS, it was not just the problem but the approach that intrigued him. Instead of confining the research to individual labs, each of them often operating in competitive semisecrecy, scientists from an array of disciplines were brought together to propose and try ideas quickly.

"I leaped at the opportunity," says Finlay. "This has been a chance to put in rapid research in response to a real threat—a 'commando science' attitude—and it's incredibly refreshing because the enthusiasm [of researchers] is unbounded. It breaks down barriers. You leave your ego at the door. You leave money concerns at the door."

Leaping at opportunity. Rapid response. Unbounded enthusiasm. That's how it is, day in and day out, in Finlay's supercharged world. To the casual observer of Finlay's brand of science in overdrive, it's clear that he wouldn't have it any other way. H