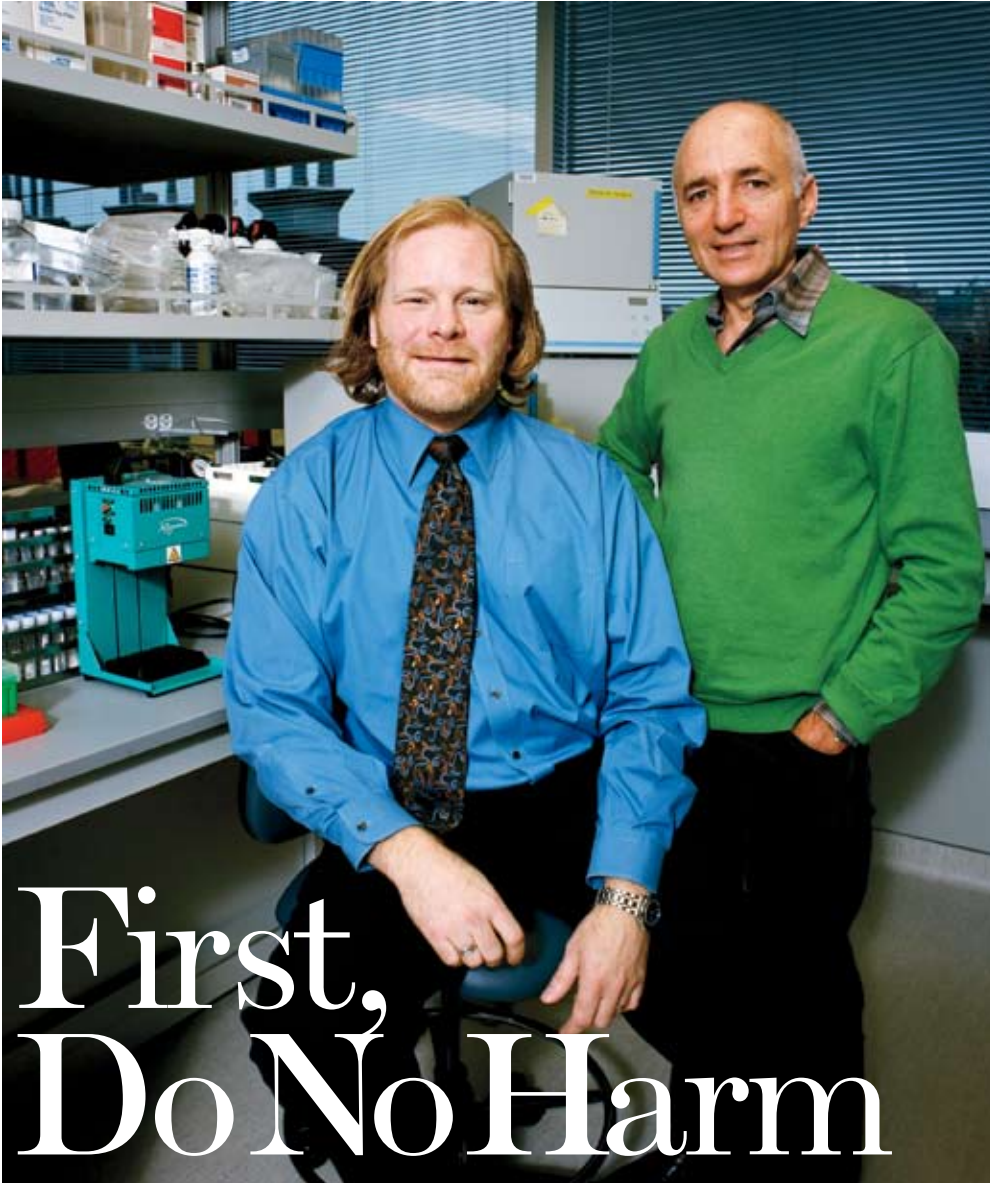


MEDICINE

By Roberta Staley



First, Do No Harm

5,400 Canadian children die each year from adverse drug reactions. Two Vancouver researchers are fighting for genetic testing that could save them

WHEN, JUST 12 DAYS after his birth, Tariq Jamieson died suddenly in Toronto, the coroner was puzzled. He suspected the cause to be Sudden Infant Death Syndrome but ordered laboratory tests to be sure. The test results solved the puzzle but deepened the mystery: Tariq Jamieson had died of a morphine overdose.

But how? The infant had not been administered any painkillers.

With no clues in the outside world, the investigation turned inward. A sample of Tariq's mother's blood was sent for testing. Technicians scrutinized her genes, using a process called genotyping, which involves looking for polymorphisms, or variations,

Dynamic duo Bruce Carleton (left), a pediatric clinical pharmacologist, and Michael Hayden, a geneticist, dream of a revolution in our approach to health care

among the genes responsible for drug metabolism. The mystery, finally, was resolved.

The mother was the inadvertent killer of her baby. Or rather, her genes were.

All cells in the human body contain two sets of identical genes, the twin serving as backup in case one gene is damaged. (Humans have about 30,000 genes scattered irregularly along 23 pairs of chromosomes, an inheritance bequeathed by both parents.) In the case of codeine, humans normally have a single gene (plus its twin) that transforms it into morphine. Tariq Jamieson's mother, however, had two genes (each with a twin) working to turn the narcotic into morphine. Four genes, rather than two, were instructing the body to manufacture morphine, turning breast milk into poison.

The Jamieson case was presented in a paper that appeared in Nature Publishing Group. It was co-authored by two Vancouver doctors, physician Michael Hayden and pediatric clinical pharmacologist Bruce Carleton, the principal investigators in the Canadian Pharmacogenomic Network for Drug Safety. (The study of the influence of genetic variation on drug toxicity and efficacy is called pharmacogenomics.) This network of physicians and clinicians across the country collates reports and initiates studies into adverse drug reactions, seeking to determine which genes are linked to the sometimes debilitating or even lethal effect of medications. It was thanks to the work of Hayden, Carleton, and several others that the extra copies

of the gene responsible for excess morphine production, CYP2D6, were identified. A worldwide warning about the possible danger of using codeine while breastfeeding was circulated in late 2008, saving probably thousands of babies every year from a coroner's scribbled "SIDS."

That discovery was part of a larger, more sublime goal that Hayden and Carleton set themselves: before a physician prescribes a drug, they want to see an inexpensive genetic test ordered to ensure that the patient doesn't harbour polymorphisms that turn good medicine bad. Called predictive diagnostics, this approach foretells a kinder, gentler medicine, in which drugs are prescribed based on a patient's unique genetic makeup rather than the generalized regimens currently given to patients

with ailments like cancer, heart disease, and psychiatric illness. "It's moving back to the roots of medical care," says Carleton. "It's about what this individual patient needs, not what health professionals think he or she needs."

"This," Hayden predicts, "is going to be a revolution in health care."

SLIGHT AND intense, the 59-year-old Hayden is a titan in the world of genetics, most famously having pioneered studies into Huntington's disease, an inherited neurodegenerative condition. His accolades are numerous—he was Canada's health researcher of the year in 2008—and colleagues, students, and patients around the world speak of him with awe verging on reverence.

He grew up in South

Africa, one of two boys born to Second World War British army veteran Roger Hayden and artist Ann Hayden. The pair divorced when Hayden was eight, his spirited mother and conservative father as compatible as fire and water. In a country gripped by the legislated cruelty of enforced racial segregation, Ann was an oddity. Jewish and poor—her modest house was the only one in her Cape Town neighbourhood without servants—she surrounded herself with music and laughter, welcoming artists, musicians, and individualists regardless of colour or religion.

Though young Michael was doted on by both parents, it was his mother who spurred him to push beyond boundaries, self-imposed or otherwise. She admonished him for studying too hard,

saying, "Come relax and listen to some good Portuguese music." The two would ride her Vespa to musical and theatrical events in nearby black townships, places whites were forbidden to enter.

Growing up in the rich soil of creativity and freedom seeded the lateral thinking that has been key to Hayden's innovation in the world of science. His mother also inculcated in him a strong belief that it is never too late to strive for what you believe in. Three years ago, the day before she died of cancer, she married her black lover, 20 years her junior. "I want to die happy," she told Hayden. "And I really want you to understand this: it's never too late for anything."

Carleton, too, had extraordinary influences growing up. In the town of

Kent, Washington, south of Seattle, his pianist mother, Patricia, orchestrated his musical education. His father, a Presbyterian minister, oversaw his son's moral development. A social-rights activist, William Carleton was inspired by Rosa Parks's refusal to give up her seat on the bus in Montgomery, Alabama, in 1955, a humble act of rebellion that sparked the civil-rights movement. In 1963, William joined the March on Washington, in step with 250,000 people who descended on the capital to support a new civil-rights bill. William also supported anti-Vietnam protests on the pulpit, antagonizing some of his parishioners.

"His sermons were steeped in research and focused on the integration of Christian ideals with contemporary

issues," says Carleton, whose father logged the 80-hour work weeks he now emulates. "This is very much a part of why I have a lot of empathy and feel responsibility to help solve medical problems like adverse drug reactions."

Carleton, younger than Hayden by eight years, presents an air of cheerful calm typified by his bright-blue silk tie and blue dress shirt. Youthful and fit, he's cool in a surfer-dude kind of way. (Surfing happens to be his favourite sport.) He too is widely published and internationally respected. What these two men share, in addition to the drive that leads to intense overtime, is an almost priestly devotion to the physicians' dictum, credited to Hippocrates over 2,300 years ago, *primum non*

nocere: "First, do no harm." Despite breathtaking advances in health care, medicine today balances on a knife edge of ethics that sometimes disavows this ancient oath. Of the more than 180,000 admissions every year at BC Children's Hospital, 22 percent, says Hayden, are for adverse drug reactions. ADRs, he adds, cost the Canadian economy billions every year. "Drugs are an environmental insult causing all kinds of problems, and sometimes the problems are greater than the disease."

Adverse drug reactions are among the top half-dozen leading causes of death in the United States and Canada, costing upward of \$130 billion a year and killing as many as 5,400 children in Canada annually, according to a 1998 report

in *The Journal of the American Medical Association*. In 2001, *The American Journal of Pharmacology* reported that ADRs claimed 100,000 to 218,000 lives every year in the United States, putting it within striking distance of heart disease, cancer, and lower respiratory infections. Carleton says that a lack of reporting of ADRs to regulators like Health Canada—only four percent a year according to Drug Safety—accounts for the disparate statistics.

CARLETON'S ROUNDS at BC Children's Hospital start at 7 a.m. Each morning, he looks in on kids like Dana Tent's son, five-year-old Stefan, who was diagnosed at age 14 months with a malignant brain tumour called a medulloblas-



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Carleton's advice: Incurable loss of sight is not.



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toma. In a nearly five-hour operation, a neurosurgeon removed the baseball-sized mass. Afterward, Stefan faced six cycles of chemotherapy to kill off remaining cancer cells. The medications kill all fast-growing cells, including the white blood cells that fight infection. Stefan was hospitalized numerous times with soaring fevers; he stopped growing and eating. He was so physically traumatized by the month-long rounds of chemotherapy that he had to learn to walk again.

The drugs used in oncology are some of the most dangerous given to human beings. Two common oncology drugs are cisplatin, an effective treatment for many cancers, and anthracycline. Cisplatin causes hearing loss and kidney damage in some children, while anthracycline

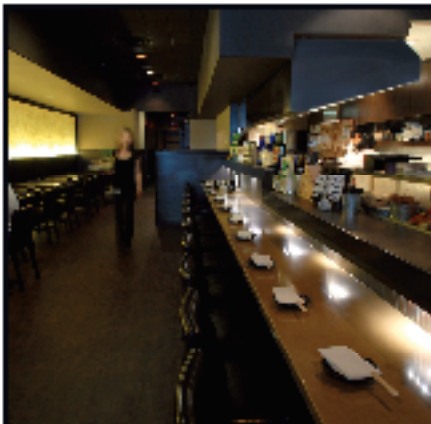
can cause cardiac failure. But not all children suffer these side effects, and geneticists in the pharmacogenomics laboratory next to Hayden's office in the glittering new glass and concrete Child & Family Research Institute on the BC Children's Hospital grounds are busy finding polymorphisms in those who do suffer hearing loss and heart complications. This study is especially important, says Hayden, for children in the Third World. The same drugs are used to fight childhood cancers in poor nations, whose undeveloped infrastructures do not support state-sponsored care for long-term heart, kidney, and hearing ailments. Families can be plunged into lifelong poverty trying to care for children with such problems.

After Stefan's sixth round of chemo, which included cisplatin, Dana Tent received some bad news: auditory tests showed that her son could no longer hear high-frequency sounds such as the "t" in "can't." Today, the active little boy with lustrous hair and wide brown eyes is taking speech therapy. He's happy and healthy, and for this Tent is profoundly grateful. That does not alleviate her heartbreak over his hearing loss. "It's just not fair," she says, blinking away tears. "Didn't he fight enough? Didn't he have enough already?"

Carleton, the father of three sons, never developed the thick skin of some clinicians. The salve of cancer's 82 percent cure rate in children doesn't take away the pain of knowing that

two-thirds of patients will suffer long-lasting after-effects of the cancer therapy. He says that when parents like Tent "look me in the eye and say, 'How can this happen to my child?' I need a more satisfying response than, 'Well, it's an adverse effect and fortunately it occurs rarely, but your child was the rare one.'" He takes a deep breath. "Someday," he says, "kids, and the public, will ask for accountability."

He flips open his phone. He's changed the Telus logo in the upper corner of the question "Kids Better?" It's not a statement of doubt. It's a daily reminder, a moral kick, to work harder, do more. "I try to remember every day why I'm getting up, why I'm answering this call, why I'm at that meeting. It's to make children better." **VM**



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