

Innovation from cell to society

Success Stories



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Making a Difference From cell to society

AllerGen NCE Inc. (AllerGen), the Allergy, Genes and Environment Network—one of Canada's Networks of Centres of Excellence (NCE)—proudly presents its eleventh issue of *Success Stories*.

Success Stories is written for Canadian families and healthcare providers. It provides up-to-date information on new research into asthma, allergies and anaphylaxis, and explores what causes these illnesses, how better to manage, treat and prevent them, and steps towards finding cures.

The Summer 2017 issue of *Success Stories* shares research and knowledge mobilization achievements of AllerGen researchers, students and partner organizations. This issue's feature stories include:

- the discovery that fruit consumption during pregnancy is linked to a baby's cognitive development;
- a unique immunotherapy treatment to shut off the immune response in asthma and allergies;
- the link between a mother's artificial sweetener intake while pregnant and her baby's risk of obesity;
- unproven asthma and allergy claims made by Canadian alternative medicine providers; and
- an AllerGen trainee at the helm of a national birth cohort study.

Now more than a decade into its mandate, the AllerGen network pursues its goals with mature and globally-connected research teams; a balanced portfolio across investments in discovery, development, commercialization and knowledge mobilization; and an integrated research strategy spanning three Legacy Projects and two Enabling Platforms that build upon core research investments established in 2005.

Legacy Projects:

- **Canadian Healthy Infant Longitudinal Development (CHILD) Study**

This globally leading birth cohort study follows the health and development of 3,500 Canadian children to uncover ways to predict, prevent and treat asthma, allergies, obesity and other chronic diseases.

- **Clinical Investigator Collaborative (CIC)**

This multi-centre, Canadian-based Phase II clinical trials group evaluates promising new drug molecules for biotechnology and pharmaceutical companies to enhance the treatment of allergic diseases in both the upper and lower airways.



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- **National Food Allergy Strategy / Canadian Food Allergy Strategic Team (NFASt-CanFAST)**

This innovative, nationally-networked research team provides new knowledge about the origins, causes, prevalence and treatment of food allergy and anaphylaxis, and informs the development of improved clinical management strategies and public health measures.

Enabling Platforms:

- **Gene-Environment Interactions**
- **Biomarkers and Bioinformatics**

By sharing our stories of research success, we aim to keep Canadians up to date on advancements in the science of allergy and asthma. We hope you find this issue of *Success Stories* to be interesting and informative. [A](#)

Judah Denburg, MD, FRCP(C), Scientific Director and CEO

Diana Royce, EdD, Managing Director and COO

Babies born to mothers who consumed six or more servings of fruit per day during pregnancy scored six or seven points higher on an infant development scale at age one compared to babies whose mothers ate less than one serving of fruit.



Fruits of Their Labour

Mothers who consume more fruit while pregnant may give their babies a brain boost

If a woman you know announces she's expecting, skip the cards and flowers—send her a fruit basket instead. If she eats enough apples, berries and bananas, she just may give her baby a head start in early brain development.

It may sound unlikely, but AllerGen researcher Dr. Piush Mandhane, an associate professor of pediatrics at the University of Alberta, has uncovered a link between a mother's fruit consumption during pregnancy and her baby's developmental test scores at one year of age.



**Dr. Piush Mandhane, Associate Professor
University of Alberta**

Dr. Mandhane made the discovery after analyzing data from AllerGen's CHILD Study (CHILD). CHILD is a national birth cohort study, with sites in Edmonton, Vancouver, Toronto and Manitoba, that is following 3,500 Canadian infants and their families to understand how early life experiences shape health and well-being in childhood. Dr. Mandhane leads the Edmonton study site.

For his research, Dr. Mandhane focused on a subset of nearly 700 mothers and children involved in CHILD, and analyzed the data after the children underwent a cognitive test at one year of age.

What he found took him by surprise: babies born to mothers who consumed six or more servings of fruit per day during pregnancy scored six or seven points higher on an infant development scale at age one compared to babies whose mothers ate less than one serving of fruit. "I wasn't looking for it, I wasn't expecting it, but I couldn't ignore it," Dr. Mandhane says. "The difference was significant."

Pregnant women are typically told what *not* to consume during pregnancy, with alcohol, caffeine and junk food topping the list. They're also advised to eat a balanced diet and ensure that they get enough of the nutrients (such as folic acid, iron and iodine) to support normal brain development.

Dr. Mandhane's research puts a new spin on nutrition during pregnancy. His results suggest that it's not just the nutrients that count, but their source. "Fruit juice did not have the same beneficial effect on infant development," he says, "nor did prenatal consumption of vegetables."

A sleepy start

When Dr. Mandhane designed his study, he didn't intend to look at fruit. "We wanted to learn how early childhood sleep duration and disruption affect an infant's cognitive development. Initially, I thought a mom's sleep pattern might have a bearing on her child's brain development and intellectual performance."

That's why he turned to CHILD: the study's database houses extensive information on each mother's prenatal habits and personal environment—her diet, medications, stress levels, and even the quantity and quality of her sleep.

The study children also complete the Bayley Scales of Infant Development (BSID III test), a standardized test of mental and motor development at age one. While not a true IQ test—one-year-olds are too young for that—the Bayley test takes inventory of things a young toddler can do, such as stacking blocks or finding hidden objects, says Dr. Mandhane.

A careful analysis of the data did not support Dr. Mandhane's hypothesis that a mother's sleep disruption affects her baby's brain development. But his research had also taken into account the mothers' eating habits—and that's when he uncovered the fruit effect.

"Each extra serving of fruit boosted the child's cognitive development, right up to six or seven servings a day," Dr. Mandhane says. Such a dose-response effect—the higher the dose, the greater the effect—is one of the hallmarks of a good study. "What surprised me most was the size of the effect—more than half a standard deviation, which is significant."

The gestational age of the child at birth also highlighted the effect: the earlier a child was born, the more obvious the fruit effect. In women who gave birth to preterm children, “having one extra serving of fruit per day gave the baby the same benefit as being born a whole week later,” says Dr. Mandhane.



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When my data analyst showed me the figures, I couldn't believe it. I asked her to run the numbers again."

Digging deeper, Dr. Mandhane's team also looked into the specific nutrients the mothers had consumed. Two "stars" emerged: lycopene, a natural pigment that gives fruits and vegetables—such as tomatoes, grapefruit and watermelon—a red color, and fructose, the natural sugar found in most fruit and vegetables. The gestational age of the child at birth also highlighted the effect: the earlier a child was born, the more obvious the fruit effect. In women who gave birth to preterm children, "having one extra serving of fruit per day gave the baby the same benefit as being born a whole week later," says Dr. Mandhane. "That's a meaningful advantage."

But what if the women who consumed more fruit took better overall care of themselves than the fruit avoiders, and that's why their babies did better? Fortunately, Dr. Mandhane's study accounted for such differences. He also teased out other variables that could have skewed the results, such as family income and education. The fruit effect persisted. Still, Dr. Mandhane wasn't fully satisfied. "I kept wondering if we had missed a confounding factor that could explain the effect."

Fly guy adds to the buzz

In search of answers, Dr. Mandhane teamed up with pediatric neurologist Dr. François Bolduc, also an associate professor at the University of Alberta. A specialist in how genes affect the

memory and mental ability of both humans and fruit flies, Dr. Bolduc has been dubbed the "fly guy" because of the more than 300,000 fruit flies he keeps in his university lab.

Familiar to most of us as household pests circling over bruised bananas, fruit flies have a surprising capacity to learn. More than that, says Dr. Bolduc, "they have 85% of the genes involved in human brain function, which makes them a great model for studying our own learning and memory."

Would Dr. Mandhane's fruit effect hold up in fruit flies as well? To find out, Dr. Bolduc enhanced the diet of a group of pregnant fruit flies with a combination of orange and tomato juices. He then exposed their offspring to two different odours, one of them accompanied by a mild electric shock.

Two minutes later, he presented the young flies with the same odours and counted the proportion of those that steered clear of the scent associated with a shock—a measure of their ability to learn from experience. To test the flies' longer-term memory, he repeated the exercise a day later—a rather long stretch in the month-long life of a fruit fly.

The results echoed Dr. Mandhane's observations in humans: offspring of the flies who consumed a fruit-enhanced diet scored 30% higher on learning and more than twice as high on long-term memory tests than offspring of those fed a standard diet.

Dr. Bolduc repeated the experiment several times, each time with similar results. He also experimented with feeding fruit

juice directly to young flies after birth rather than to their pregnant mothers, “but this didn’t improve their learning,” he says. “It looks like the juice is doing something prenatally to enhance brain development.”

What happens next

EBioMedicine published the Mandhane/Bolduc study in May 2016. The news circled the globe and propelled Dr. Mandhane into the media spotlight, an outcome he credits largely to AllerGen. “Without AllerGen, CHILD wouldn’t exist, and without CHILD, my own study would not have been possible,” he says simply. CHILD has expanded its research scope well beyond its original thrusts of asthma and allergy, and “the data can be used to explore many other questions, as my study has shown.”

At the same time, Dr. Mandhane cautions against “over-interpreting” his findings. First, he must address a burning question: Does the fruit effect persist as the children get older? To find out, he plans to re-run his analysis using the children’s cognitive test scores at ages two, three and beyond.

“At age three, we can test higher cognitive functions like planning and multitasking,” he says. If prenatal fruit boosts these functions, “there may be a real benefit to promoting greater fruit intake during pregnancy, particularly if we can

improve outcomes for premature babies, who are at higher risk of intellectual delays,” he explains. “Going from an IQ of 100 to 105 may not make a significant difference in a child’s life, but moving from 85 to 90 certainly can.”

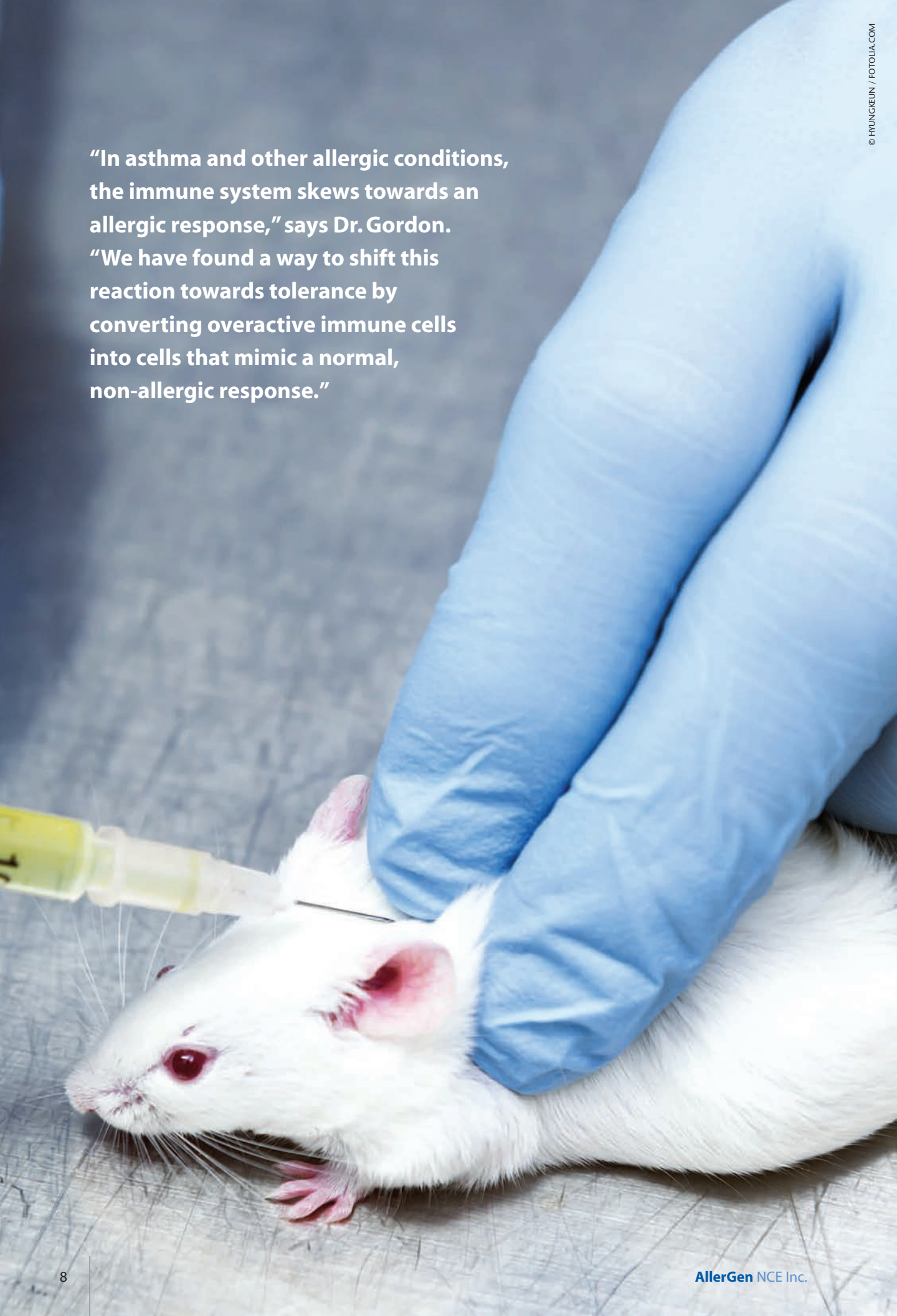
He and Dr. Bolduc aren’t finished working with fruit flies, either. They would like to understand, at the biochemical level, how and why prenatal fruit gives such an advantage to offspring. Perhaps something in the fruit boosts the growth of the brain’s neurons? Or perhaps the fruit switches on key developmental genes through an epigenetic effect? Identifying the stages of pregnancy when fruit intake has the most influence is also on the researchers’ to-do list. “When we know more, we may be able to develop targeted therapies that turn on the same pathways that the fruit is turning on,” Dr. Mandhane says.

In the meantime, he cautions pregnant women against going overboard on fruit—especially if it leads them to gain excess weight, which could increase the risk of gestational diabetes. Instead, Dr. Mandhane suggests they turn to Canada’s Food Guide, choosing whole foods over processed ones whenever possible. “Whole foods provide an array of important nutrients, some of which we may not even know about,” he says. “It may take a little more time to peel an orange, but it’s definitely worth it.” [A](#)



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"In asthma and other allergic conditions, the immune system skews towards an allergic response," says Dr. Gordon. "We have found a way to shift this reaction towards tolerance by converting overactive immune cells into cells that mimic a normal, non-allergic response."



New research suggests our own cells may one day help us overcome asthma and allergies

Imagine if your cells could be “re-engineered” to reduce your asthma symptoms—or eliminate your food allergy. It’s not as far-fetched as it might sound: scientists at the University of Saskatchewan have found a way of doing this in mice, and they believe that the technique holds promise for humans, too.

Dr. John Gordon and his team developed a unique therapy that re-programs an individual’s immune cells to reduce—or possibly even reverse—allergic reactions.



Dr. John Gordon, Professor
University of Saskatchewan

“In asthma and other allergic conditions, the immune system skews towards an allergic response,” says Dr. Gordon, a professor in the university’s Department of Medicine. “We have found a way to shift this reaction towards tolerance by converting overactive immune cells into cells that mimic a normal, non-allergic response.”

Their innovative technique begins with dendritic cells—a type of immune cell found in tissues in contact with the outside environment, such as the lining of the nose and lungs, the walls of the digestive system and, of course, the skin. “If you could remove a sheet of skin from your arm, you would see the dendritic cells underneath—they look like a giant web,” Dr. Gordon explains. “A foreign particle entering the body through the skin, lungs or intestines runs into this web. Dendritic cells then signal to other immune cells to turn on or turn off the body’s immune response as needed.”

Flicking an “off” switch

Dr. Gordon’s interest in dendritic cells arose from breakthrough findings in cancer research. Early in 2000, cancer researchers discovered that the protein interleukin-10 (IL-10) causes dendritic cells to send a “turn-off” signal down the immune system pathway.

Dr. Gordon wondered: Might it be possible to use IL-10 to cause dendritic cells to shut off the allergic response in asthma and other allergies? His team devoted the next decade to answering this question.

Over several years, they developed and refined a technique to generate dendritic cells from the bone marrow of asthma-prone mice and expose the cells in a test-tube to a mixture of IL-10 or other molecules that promote tolerance. They then injected the modified dendritic cells back into “asthmatic” mice and exposed the mice to their triggering allergens (substances known to cause an allergic response): house dust or egg white protein. The mice initially responded with wheezing and other asthma symptoms.

But a few weeks later, something remarkable happened. “We continued to expose the mice to their allergen, but within two weeks their symptoms began to improve, and within three to six weeks their asthmatic response largely disappeared,” Dr. Gordon says. “What we found even more surprising was that this tolerance lasted for eight months or longer.”

In 2012, Dr. Gordon’s team published their findings in *The Journal of Immunology*. They also repeated the mouse experiment with different allergens, each time with similar results: dendritic cells altered with IL-10 appeared to trigger a “shut-off” mechanism further down the asthma pathway. Best of all, the treatment worked on human cells as well—at least in a petri dish: in a study involving dendritic cells from 25 asthmatic donors, the IL-10 technique reversed certain markers of asthmatic T cell responses.



There's an application for that

Recognizing the wider implications of this research, Dr. Gordon, who co-leads AllerGen's Biomarkers & Bioinformatics Enabling Research Platform, began collaborating with the Network's Canadian Food Allergy Strategic Team (CanFAST) to investigate the effect of the technique in a model of food allergy.

Dr. Gordon views food allergy as a "case of mistaken identity," where dendritic cells recognize certain foods as foreign, flip to the "turn-on" mode and transmit the signal along the immune pathway, producing an allergic response.

Roughly 2.5 million Canadians report having a food allergy. Anaphylaxis, a severe, rapid onset allergic reaction to food and other substances, can produce dramatic and life-threatening symptoms—from flushed skin and hives to a swollen throat, fainting and difficulty breathing.

There is no cure for anaphylaxis, and treatment options are limited. Epinephrine autoinjectors work well, but are a band-aid solution at best: the medication may not reach the

bloodstream quickly enough to halt symptoms—and people with allergies may forget their autoinjectors at home. "We need therapies that prevent anaphylaxis from happening at all, rather than simply shutting off the symptoms after they've begun," says Dr. Gordon. His research, while still at an early stage, may open a path toward accomplishing just that.

With funding and support from AllerGen, he and his team concocted a new IL-10-like solution by blending a vitamin A-related acid that occurs naturally in the human gut with two common food allergens (peanut protein and egg white protein). They used the solution as a priming agent to "create an entirely new type of dendritic cell—one specialized in neutralizing the immune cascade of anaphylaxis."

Next, they injected allergic mice with the peanut or egg white proteins through a stomach tube until symptoms of anaphylaxis developed. They then separated the mice into two groups, treating one with the dendritic cells and the other with a simple saline solution.

A month later, researchers re-exposed the mice to the allergen, with striking results: within four weeks, the mice who received the dendritic cells had a 90% lower anaphylactic response than those treated with saline.

The immunotherapy did not simply reduce symptoms of anaphylaxis, but “caused the dendritic cells to react as they would in a healthy, non-allergic individual,” says Wojciech Dawicki, an AllerGen trainee and research associate in Dr. Gordon’s laboratory who was the lead researcher of this study. *The Journal of Allergy and Clinical Immunology* published the findings in November 2016.

While Dr. Gordon believes the dendritic cell therapy could one day help treat human food allergies, he cautions that an approved treatment is likely years away. “Our research team is good at the asthma model—we have shown that the treatment works in mice and in human cells in a test tube—so asthma is the first disease we will target as we move toward developing human therapies.”

Safety first

As a first step, Dr. Gordon has begun testing the treatment in a new project funded by AllerGen, the Canadian Institutes of Health Research (CIHR) and the Saskatchewan Health Research Foundation (SHRF). The model uses “humanized” mice who have had their immune systems knocked out and replaced with immune cells from asthmatic human donors.

If successful, the results could open the door to preliminary human trials the following year. Health Canada, which regulates the approval of new drugs and therapies, requires a “first-in-man” study showing the effectiveness of the treatment in a person who is close to the end of life, which paves the way for clinical trials to evaluate safety and effectiveness in healthy individuals.

The new project has generated promising collaborations across the country. Clinicians from AllerGen’s Clinical Investigator Collaborative, a multicentre clinical trials group, have expressed interest in experimenting with Dr. Gordon’s dendritic cells once Health Canada gives its approval. “That’s the power of AllerGen,” says Dr. Gordon. “We can all share our work, rather than toil away in silos the way researchers so often do.” Beyond

If the asthma treatment works in “humanized” mice, the results could open the door to preliminary human trials the following year.

Health Canada requires a “first-in-man” study showing the effectiveness of the treatment in a person who is close to the end of life, which paves the way for clinical trials to evaluate safety and effectiveness in healthy individuals.

the Network, a Canadian transplant physician hopes to test the therapy to prevent rejection of transplanted organs.

The technique could also be used to treat autoimmune diseases such as multiple sclerosis or rheumatoid arthritis. To make the therapy as versatile as possible, Dr. Gordon is broadening the palette of dendritic cells with which he works. “We are now assessing four distinct types of cell in the hope that different cells will ‘specialize’ in different diseases,” he says. Could one of them work best for asthma, another for food allergies, and another for multiple sclerosis? “That’s what we’re hoping to find out, so it looks like we have our work cut out for us,” he says.

“As for its use in food allergies, several individuals have volunteered to donate their immune cells to help move the research forward,” he adds. “This tells us just how badly people need and want a new treatment for anaphylaxis. We hope, one day, to be able to give it to them.” **A**

“Replacing sugar with artificial sweeteners in pop, or even in coffee and tea, may not be such a good idea. If a mom consumes diet drinks on a daily basis during her pregnancy, it may lead to— of all things— obesity in her infant.”



How Sweet It Isn't

Can a mom's intake of artificial sweeteners while pregnant make her child obese?

One day soon, a pregnant woman ordering a diet soft drink may elicit the same disapproving looks as if she had asked for a Scotch. As researchers continue to learn about the effects of sugar substitutes on health, diet drinks may join caffeine, raw fish and alcohol on a growing list of foods and drinks to avoid during pregnancy.

Recent studies have raised concerns about the association between artificially sweetened beverages (ASBs) and premature birth. In 2016, Dr. Meghan Azad, a young scientist at the University of Manitoba, hoisted another cautionary flag when she discovered that women who consumed one or more ASB per day during pregnancy were twice as likely to have a child who is overweight at one year of age, compared to women who avoided these beverages.



**Dr. Meghan Azad, Assistant Professor
University of Manitoba**

COURTESY OF CHIR

"Typically, we think of sugar as the 'bad guy,'" says Dr. Azad, an assistant professor in the Department of Pediatrics & Child Health at the University of Manitoba and a research scientist at the Children's Hospital Research Institute of Manitoba. "It turns out that replacing sugar with artificial sweeteners in pop, or even in coffee and tea, may not be such a good idea. If a mom consumes diet drinks on a daily basis during her pregnancy, it may lead to—of all things—obesity in her infant."

If it happens in mice...

As often happens in health research, Dr. Azad drew inspiration from animal studies. She took a particular interest in a 2014 study published in the journal *Nature*, which showed that giving artificial sweeteners to mice upset the normal balance of microbes in their guts. This disruption altered the way the mice metabolized sugar, eventually causing them to develop glucose intolerance—a pre-diabetic state in which the blood glucose is raised beyond normal levels.

At the time, Dr. Azad was mining data from AllerGen's CHILD Study (CHILD). Specifically, she was studying how various exposures during pregnancy and early life affect the gut bacteria of human infants, and whether or not those bacterial shifts lead to the development of chronic diseases, like asthma, allergy and obesity, down the road.

"CHILD is like a massive jigsaw puzzle," she says of the national project that has been following 3,500 Canadian children from before birth, tracking nearly every aspect of their health and development. "We are constantly looking at the babies' exposures during pregnancy and in infancy—like whether the mom had a caesarean section or vaginal delivery, what type of diet the baby was fed, whether the mom or baby received antibiotics, if there was exposure to household dust and mould, and even whether siblings or pets were present in the home—to try and pinpoint the environmental factors affecting gut bacteria."

After reading the *Nature* article, Dr. Azad wondered: Could a mom's consumption of ASBs during pregnancy affect her baby's weight? "Some animal research has suggested that consuming artificial sweeteners during pregnancy can predispose offspring to obesity, but we didn't know of any human studies looking at this outcome," she says. To answer the question, Dr. Azad went back to CHILD.

Mothers involved in the study had provided detailed information on what they ate and drank during pregnancy—including ASBs—and their children are regularly weighed, measured, and tested by CHILD researchers as they grow. As it happened, almost one in three CHILD mothers had consumed ASBs during pregnancy.



Comparing the moms' dietary patterns to their babies' physical development, Dr. Azad and her team generated one immediate finding: ASB consumption in pregnancy had no effect on the infants' weight at birth.

A deeper dive into the data, however, revealed something of interest: By the age of one, the children of moms who drank ASBs every day during pregnancy had twice the risk of being clinically overweight—defined as a body mass index (BMI) above the 97th percentile—compared to those born to moms who avoided ASBs altogether. “This suggests that a mom’s ASB consumption influenced her baby’s weight gain after birth, rather than during fetal growth,” says Dr. Azad. “This association persisted whether the artificial sweeteners came from soft drinks, coffee or tea.”

Filtering out the noise

In theory, the ASB consumption could mask another culprit. As Dr. Azad points out, “it is conceivable that pregnant mothers

who drink ASBs go on to feed their babies more unhealthy foods, which could explain the extra weight gain by the babies' first birthdays.” Or these moms may weigh more than average and pass on their genetic tendency for obesity to their children.

To make sure they had considered all of these variables, Dr. Azad brought in Dr. Russell de Souza, a nutritional epidemiologist from McMaster University, and Dr. Atul Sharma, an expert on infant growth curves from the University of Manitoba, to review the data. The team also factored socioeconomic status, maternal weight, total caloric consumption, and quality of the diet into the analysis. The link between ASBs and baby weight at one year of age held up. To Dr. Azad's knowledge, “this is the first human evidence that consumption of ASBs during pregnancy may influence a baby's BMI.”

One might ask: What's wrong with a bit of extra baby fat? Aren't squirrel cheeks part of what makes babies so adorable? As several previous studies have shown, however, “excess weight early in life predicts obesity later in childhood and even

in adult life,” says Dr. Azad, who plans to track the children’s weight as they grow to see if the trend towards obesity persists.

I can relate to that

Dr. Azad’s study illustrates CHILD’s scope and versatility. “No one had the link between ASB and baby weight in mind when CHILD was launched in 2008, and yet when we considered this question years later, we were able to answer it by looking at CHILD data,” she says. “CHILD is an incredibly powerful tool.”

The results of Dr. Azad’s research, published in *JAMA Pediatrics* in 2016, ignited massive media interest. Within days of publication, she was giving interviews across North America, and even appeared in an Australian documentary TV show. “It seems that having babies and drinking diet beverages are things that everyone can relate to,” she says.

Her findings popped up in dozens of print articles, with some headlines making exaggerated and misleading claims such as “sugary beverages during pregnancy cause childhood obesity,” or warning moms against making the “diet mistake that could make your kids overweight for life.”

The truth, says Dr. Azad, is far less clear-cut. For one thing, pregnant women who drank ASBs less often than once a week did not have heavier one-year-olds than other women—it was only more frequent consumption that put babies at increased risk. More fundamentally: “It’s very difficult to prove cause and effect. Our study has just exposed a link.”

To demonstrate that ASBs actually cause weight gain, researchers will need to show how the ASBs act in infants’ bodies. In this regard, Dr. Azad has several theories to explore.

Looking for an explanation


The first theory involves alterations in the gut microbiome, which mothers transmit to their children during birth. “We know that gut bacteria influence how much energy we absorb from food, and if you compare the microbiomes of obese and lean individuals, you will see differences,” she explains. It is possible that the ASBs consumed by pregnant women favour the growth of more obesity-inducing bacteria in their guts. When the mothers transmit this “obesity-prone” microbe profile to their babies, the babies go on to gain weight.

It is possible that the ASBs consumed by pregnant women favour the growth of more obesity-inducing bacteria in their guts. When the mothers transmit this “obesity-prone” microbe profile to their babies, the babies go on to gain weight.

Her second hypothesis has to do with metabolism. The human body has a programmed response to sugar, including the release of insulin and other hormones. But it’s not just sugar that triggers this cascade—the perception of sweet taste can also set one’s biochemical gears in motion. According to Dr. Azad, some evidence suggests that “routine consumption of artificial sweeteners may confuse and ‘reprogram’ our metabolism in a way that favours weight gain.”

Along a similar line, early exposure to ASBs may orient babies toward sweet-tasting things, including foods with real sugar. In fact, researchers have observed this phenomenon in mice. “If mice are exposed to artificial sweeteners as babies, they’re more likely to choose Froot Loops over regular mouse food when they reach adulthood,” says Dr. Azad. Currently, she is planning a study to see if an even earlier exposure to ASB—while mice are still in the womb—will produce a similar “sweet tooth.”

A media focus on sugar as a food to avoid has led many people to resort to artificial sweeteners as a substitute, says Dr. Azad. While Health Canada has stated that: “Consumption of sugar substitutes during pregnancy does not pose a health risk,” Dr. Azad’s research builds on a body of evidence suggesting there may be more to this story.

Until further research provides more definitive answers, Dr. Azad advises pregnant women to think twice before reaching for that can of Coke Zero. “It does no real good and, if it becomes a habit, could potentially be harmful. When you’re pregnant, unsweetened drinks like water are the best option,” she says. 



Professor Caulfield designed a study focused on the four most popular types of complementary and alternative medicine (CAM) provider in Canada: naturopaths, homeopaths, acupuncturists and chiropractors, to see what claims they were making on their websites about allergy and asthma diagnosis and treatment.

“Alternative facts” abound in the diagnosis and treatment of allergy and asthma. Timothy Caulfield would like to change that.

Which sources of health information can you trust? With health claims coming at us from all directions—from online ads promoting immune-boosting supplements to naturopathic clinics claiming to cure whatever ails you—the question has never been more relevant.

Timothy Caulfield is doing his part to keep the public abreast of, and forearmed against, misinformation that could jeopardize their health.



Timothy Caulfield, Professor
University of Alberta

A lawyer by training, a professor at the University of Alberta, and a writer and health policy expert, Professor Caulfield deals in evidence. He has nothing against “alternative” medicine, but he opposes claims being made about treatments that are unsupported by science. “I would be the first to herald an alternative form of medicine if it was proven to be effective,” he says. “Of course, if that happened, it wouldn’t be ‘alternative’ anymore! However, there is a sea of health myths and misinformation being pitched to the public and there is virtually no research to support these claims, which leads me to believe that most of it is pure ‘bunk.’”

Concerned about the rise in unproven health claims, Professor Caulfield set out to find out just *who* is saying *what*. The AllerGen network gave him the idea to hone in on allergy and asthma. “At an AllerGen conference, my clinical colleagues expressed concern about alternative medicine providers making claims for allergy and asthma treatments,” he says. “They saw a need for public education on what’s out there and what to trust, and they asked me if I would look into it.”

Professor Caulfield was just the person for the job. He is a Canada Research Chair in Health Law and Policy who has devoted years of research to “outing” health misinformation. His bestselling books *The Cure for Everything! Untangling the Twisted Messages about Health, Fitness and Happiness* and *Is Gwyneth Paltrow Wrong About Everything?* expose the “pseudo-

science” and false health claims dished up by celebrities and self-proclaimed experts.

To dig into the allergy and asthma issue, Professor Caulfield designed a study focused on the four most popular types of complementary and alternative medicine (CAM) provider in Canada: naturopaths, homeopaths, acupuncturists and chiropractors, to see what claims they were making on their websites about allergy and asthma diagnosis and treatment.

“We didn’t talk to clinic staff or patients,” he says, which he feels is both a strength and a limitation of the study. “We focused on what claims they were making online, so we were able to get clean data, but we didn’t capture the clinic experience.”

Professor Caulfield’s research team found a lengthy list of scientifically unsupported tests and treatments advertised on the websites of many of these practitioners. Published in the journal *BMJ Open* in 2016, their study concluded that over half of Canadian CAM clinics offer unproven allergy and asthma services.

Coding the right questions

The first step in the study was to create a “coding frame”—a list of simple survey questions—and to test the questions on a sample of CAM clinic websites. The researchers sourced CAM clinics the same way a patient might: using Google, and they

“We found a wide range of tests and treatments being offered—everything from pH testing to immunotherapy, intravenous hydrogen peroxide and even ionic footbath detoxification,” says Professor Caulfield. Some CAM websites pushed the envelope still further, claiming that ozone therapy, drinking broth, and even Bowen therapy (a type of touchless massage) could treat allergies and asthma.



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narrowed the list down to roughly 400 practices located in 10 of Canada's largest metropolitan areas. The researchers then applied the coding frame to each clinic's website and tallied up the numbers.

The coding frame was carefully constructed to generate consistent, unambiguous answers that would avoid subjective interpretation, “which would make the results less reliable,” according to Professor Caulfield. Questions in the coding frame included: Does the website mention allergy or asthma? Does the clinic claim to diagnose allergy or asthma? Is allergy treatment recommended? Are there any claims about efficacy or sensitivity?

For example, if a website claimed that a treatment “is effective for asthma” or simply that “it works,” it was counted as an efficacy statement. What the researchers did not consider was the tone of the claims. “It would be interesting to look at the tone—professional or fanciful,” says Professor Caulfield, “but that would add an extra layer of interpretation to the analysis, so we stayed focused on the statements themselves.”

Alternative facts

Professor Caulfield's team found that the majority of the CAM practices surveyed made frequent health claims about

allergy and asthma. Naturopathy clinics had the highest rate of treatment claims: 85% of naturopaths made claims about allergy treatment and 64% of them made claims about asthma treatment. Nearly 70% of acupuncture clinics offered services for allergy and 53% offered services for asthma, with homeopathy clinics following close behind (68% and 53%, respectively). Even chiropractors routinely made allergy (33%) or asthma (38%) claims.

“We found a wide range of tests and treatments being offered—everything from pH testing to immunotherapy, intravenous hydrogen peroxide and even ionic footbath detoxification,” says Professor Caulfield. Some CAM websites pushed the envelope still further, claiming that ozone therapy, drinking broth, and even Bowen therapy (a type of touchless massage) could treat allergies and asthma.

Food-specific immunoglobulin G (IgG) testing was also commonly advertised, despite the fact that the Canadian Society of Allergy and Clinical Immunology, an association representing Canadian allergists, has recommended that this test not be used due to the lack of research evidence supporting its efficacy.

Caulfield is quick to point out that “there's nothing inherently wrong about making claims.” Indeed, medical doctors do it all the time: they advise patients that a bronchodilator will keep

asthma from flaring up or that immunotherapy shots can relieve allergy symptoms. What concerns Caulfield is when claims are made without the support of science. Bottom line: “These CAM interventions are presented to the public as legitimate; however, for the most part they lack any evidence of efficacy, and some treatments—like spinal manipulation for asthma—could actually be harmful.”

The appeal of flying carpets

Having accessed the services of naturopaths and acupuncturists for his research, Professor Caulfield has a sense of how they run their practices. “I don’t think they set out to dupe people: they seem to genuinely believe their claims and feel that they’re helping patients.” What’s more, some governments and private insurers have given these practices a stamp of legitimacy, so they’re not seen as “fringe” anymore.

He also believes that members of the public may embrace alternative practices because they are fed up with the hectic atmosphere often encountered in conventional healthcare settings. “Some people are disillusioned with time-crunched doctors who have them out the door in five or 10 minutes,” he says. “Then, they walk into a homeopathy clinic where the practitioner takes 45 minutes to find out who they are and what’s bothering them—body and mind. The patient leaves with a sense of validation and an action plan, so I certainly understand the attraction.”

In fact, Professor Caulfield maintains that alternative practices have something to teach mainstream medicine. Doctors would do well, in his view, to “take a hard look at their practices and ask themselves: ‘What’s missing? Why might patients be attracted to alternative practices?’” At the same time, he doesn’t see a nurturing bedside manner as a substitute for efficacy. “I find the lack of science supporting these claims alarming. Sure, there are problems with mainstream medicine, but that’s not a justification for resorting to unproven treatments. When the airlines mess up, do you turn to flying carpets?”

That’s not how some patients see it. “I have been accused of being narrow-minded and in the ‘pocket’ of the pharmaceutical industry,” Professor Caulfield says. “It’s clear that there has been a breakdown in trust between some patients and the medical system. We all need to work to repair that relationship.”

Truth in advertising

Professor Caulfield wants governments, not just individuals, to take notice. In an ideal world, “government policies would support evidence-based medicine and expose unproven claims,” he says. With support from the Health Law Institute, the University of Alberta think tank where he serves as research director, Professor Caulfield hopes to nudge federal and provincial governments to take action.


“Recent years have seen a push toward truth in advertising,” says Professor Caulfield, noting that watchdog organizations, such as Advertising Standards Canada, review consumer ads to make sure they’re not bamboozling the public. “Why shouldn’t this ethic extend to health practices?” In fact, this is starting to happen: The U.S. Federal Trade Commission recently put the brakes on homeopathy claims. Thanks to these efforts, labels of homeopathy products sold in the United States must include a disclaimer stating that the product makes no claims of efficacy.

According to Professor Caulfield, Canada could easily follow suit. “Health Canada and the provincial ministries could issue statements about what the science says and what it doesn’t say.” He would also like to see better regulation of health professionals. “Many alternative practitioner groups are self-regulated and claim that they’re science-based, but the onus should be on them to prove it.” To this end, the Health Law Institute “plans to talk to governments and regulatory bodies. Perhaps we can move a test case forward.”

Regulation of online information presents a greater challenge. “It’s like trying to regulate the world,” Professor Caulfield notes. On the other hand, “In this ‘post-truth’ era, there seems to be a rebound appetite for facts, so hopefully our message may resonate with a public that’s tired of being misled.”

Of course, no policy or grassroots movement can replace individual judgement. For media-weary consumers who don’t know what health information to believe, Professor Caulfield has two words: *Be skeptical*.

“Be skeptical of any test or treatment if it’s being proposed by a practitioner who is not science based. Accept nothing at face value and do your best to find independent, objective sources of information.”

In other words, “wear your scientist hat.” 

“By following these kids, our researchers have discovered links between early childhood exposures and the risk of asthma, allergies and obesity, and will potentially uncover early childhood links to more chronic conditions that develop later in life.”



HQP Profile—Diana Lefebvre

Taking care of CHILD—actually, more like 3,500 children

It's a typical day in Dr. Diana Lefebvre's office, which means the urgent emails—the ones with exclamation marks in the subject line—are piling up in her inbox and a grant application is sitting on her desk. She'll get to it all later, after she answers a call from a scientist hoping to get blood samples for his new research project.



**Dr. Diana Lefebvre, Research Manager
CHILD Study**

As the research manager for Canada's CHILD Study (CHILD), Dr. Lefebvre doesn't just wear many hats; on most days she wears one on top of the other. Her responsibilities include, among others: managing research staff, juggling finances, coordinating ethics approvals, helping to write grant applications and reports for funders, handling requests for biological samples and data, and communicating with the frontline coordinators and researchers who work directly with Canadian families enrolled in the study. "Actually, there's no such thing as a typical day," Dr. Lefebvre says. "The only thing I can predict about each day is that I'll be incredibly busy."

Technically a birth cohort study, CHILD has followed 3,500 Canadian children since before birth, with an eye to linking a child's early-life exposures to his or her health and development later on. Parents have completed detailed questionnaires about their lives and lifestyle since the second trimester of pregnancy, while the children have been undergoing physical assessments and providing samples of their blood, urine and feces for researchers to analyze.

The national study has four research centres—in Vancouver, Edmonton, Manitoba, and Toronto—and involves over 75 physicians, researchers, trainees and research staff. Dr. Lefebvre oversees the sites from the study's National Coordinating Centre at St. Joseph's Health Centre in Hamilton, Ontario, though she's in daily contact with people at all the sites, giving

her the sense that she's "travelling back and forth across the country every day."

"It's an exceptional scientific study," Dr. Lefebvre says of CHILD, which was launched in 2008. "Our oldest participating children are turning nine years old and the youngest are now turning five. By following these kids, our researchers have discovered links between early childhood exposures and the risk of asthma, allergies and obesity, and will potentially uncover early childhood links to more chronic conditions that develop later in life."

What links have been found so far? A few examples: A mother's fruit consumption during pregnancy can boost her baby's cognitive development at age one, and her intake of artificial sweeteners during pregnancy can increase her child's risk of obesity. Breathing in traffic pollution increases a baby's risk of developing allergies. A specific mix of gut bacteria in the first 100 days of life protects children against asthma, while the presence of furry pets in the household helps to train a baby's immune system.

Master troubleshooter

Running a long, multi-centre project like CHILD is a tricky business. No sooner is one challenge resolved than another surfaces. Indeed, Dr. Lefebvre sees the bulk of her job as "anticipating problems before they arise." Challenges like a

Why do they stay? “Our families want to help advance science and medical research—to know that their participation has led to a health discovery or a new medication or treatment that will help all kids live healthier lives. For CHILD families, it’s the idea of ‘putting a brick in the wall’ to help others in the future.”



CHILD Study family. Photo courtesy of CHILD Vancouver site.

CHILD family moving overseas: will they still be able to complete the questionnaires? Or a research assistant who leaves just before a new data collection phase begins. Or a researcher who needs blood or urine samples... yesterday.

How did she get the job in the first place? Dr. Lefebvre calls it serendipity, but her trajectory was dictated by more than chance.

After graduating with a bachelor's degree in biology from McGill University, Dr. Lefebvre worked for six years as a lab technician. All the while, she watched graduate students come and go through the lab on their way to an advanced degree. "At one point I realized: I can do that," she says.

Dr. Lefebvre completed her doctoral studies in three and a half years. Her molecular endocrinology thesis examined the role of oxytocin receptors in preterm labour. Her first post-doctoral appointment took her to Mt. Sinai Hospital in Toronto, her second to a protein kinase lab in Vancouver. Back in Toronto, she put in eight more years running a research lab, followed by two years at the Dana Farber Cancer Research Institute in Boston and a year at the Ontario Institute for Cancer Research (OICR) in Toronto.

By the time the CHILD Study research manager position came up, Dr. Lefebvre had a solid resume and, perhaps more importantly, the confidence to manage a complex research project. "Good thing I had that broad base," she reflects. "I'm pretty sure it helped me get the job."

Why families stay

Keeping participants in the study is especially vital in a long-term project like CHILD. Families may be asked to stay involved for a decade or longer, participating in interviews, undergoing physical examinations and clinical testing, and completing questionnaires. In CHILD, 92% of the original cohort is still taking part eight years on, which is an uncommonly high figure for a cohort trial, according to Dr. Lefebvre.

Why do they stay? "Our families want to help advance science and medical research—to know that their participation has led to a health discovery or a new medication or treatment that will help all kids live healthier lives," she says. "For CHILD families, it's the idea of 'putting a brick in the wall' to help others in the future."

That, and the special relationships that CHILD research coordinators have developed with the families at each centre. “Our senior coordinators—Linda Warner, Joyce Chikuma, Rishma Chooniedass, and Aimée Dubeau—know that if families are happy and engaged, they’ll stay on, and if they stay on, the study can continue to generate important health findings as the children grow up.”

In addition to regular newsletters, “the staff members send birthday cards to the children and get on the phone to talk to parents. The personal touch makes all the difference.” The families, in turn, “send us pictures of their kids, which we include in the newsletters—with their consent, of course.”

Keeping it real

So what is so special about CHILD? For one thing, the participants reflect the general population: some rich, some poor, some healthy, some less so. Many cohort trials focus on populations that are at risk for a particular medical condition, but CHILD provides a snapshot of what’s happening in the real world, making it an ideal study for unearthing Canada-wide health patterns.

CHILD also stands out in terms of the scope and detail of its participant questionnaires. When it comes to nutrition, for example, parents report on every aspect of a mom’s prenatal diet, their child’s diet, including breastfeeding, infant formula, and, as the children get older, the introduction of solid foods, and diversity and amount of specific foods consumed. Detailed health and medication questionnaires form the foundation of the study, not only for the children, but for the parents as well.

Parents also provide detailed information about their indoor and outdoor home environments: What kinds of pets do they have? Do they live near a highway? Is the house made of wood, brick or stone? How many people live in the home? Is the furniture made of wood, leather or plastic? What is the “emotional temperature” inside the home? How much time do kids spend watching TV or playing video games? Since the study began, parents have filled out over 400 questionnaires, some of them spanning 10 or more pages. “It’s not just the number of questions that stands out, but their level of detail,” says Dr. Lefebvre.

Not surprisingly, collecting such copious amounts of data poses ongoing challenges. To ease the burden on families,


CHILD has created a web-based portal allowing parents to complete questionnaires from their homes. “Some families move overseas yet they continue to send in their questionnaires, and they come for clinic visits when they are back in the country,” says Dr. Lefebvre. “That’s dedication.”

Staying afloat

The rich storehouse of CHILD data helps not only the researchers directly involved with the study but also other scientists, in Canada and elsewhere, who can mine the data to answer their own unique research questions. Dr. Lefebvre is usually the first point of contact for investigators requesting access to the data and biological samples that have been painstakingly collected over the years. To date, CHILD samples and data have fuelled 41 research grants with funding valued at over \$39 million. As Dr. Lefebvre sees it, “CHILD has become a scaffold to support dozens of new projects.”

While AllerGen and the Canadian Institutes of Health Research (CIHR) have supported CHILD for the past eight years, Dr. Lefebvre sees continued funding as the study’s biggest ongoing challenge. “Understandably, most politicians have short-term priorities, but CHILD is a marathon. To conduct a world-class study like this, you need funds to support experienced staff, store the 500,000 biological samples, and conduct complex tests and assessments. Funders don’t always appreciate that.” Which means the CHILD team can never put the funding issue to bed. “We’re always writing the next grant application and the one after that.”

For all of the study’s accomplishments to date, Dr. Lefebvre maintains that CHILD’s greatest promise still lies ahead. “We want to know what happens to the CHILD kids as they reach puberty,” she says. How will they do in school? How does screen time affect their health and development? Will the kids who have asthma now outgrow it later? Will new cases pop up? Will any of the kids will start showing signs of obesity and cardiovascular disease?

“Many adult diseases start in childhood, and CHILD gives us an opportunity to find out why and how. Having this incredible Canadian resource that can predict and possibly prevent chronic disease—we absolutely have to keep it going.” 



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Success Stories

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