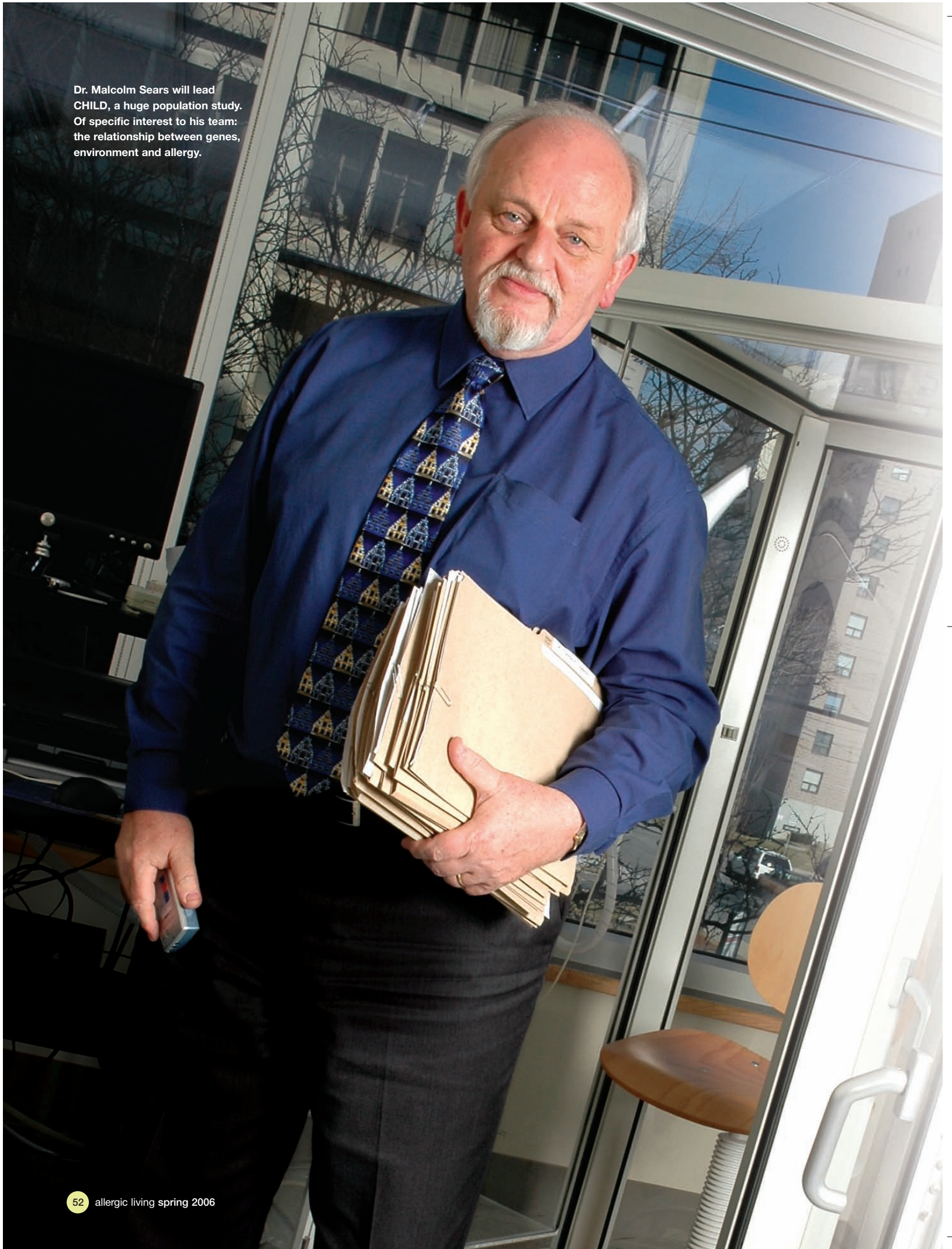


Dr. Malcolm Sears will lead CHILD, a huge population study. Of specific interest to his team: the relationship between genes, environment and allergy.



Every day, scientists are hard at work to crack the mystery of allergic disease. *Allergic Living* stops in for a progress report from three accomplished researchers, on three fascinating projects.



unlocking allergies

charting asthma's course

When he gets asked the question: "How can I avoid asthma?" Dr. Malcolm Sears will answer: "Choose your parents carefully." But Sears is today certain that our genes alone won't solve the riddle of why and how allergic disease develops and progresses.

He is about to lead a study that will explore the relationship between specific genes *and* environments. The hope of the research director of the Firestone Institute for Respiratory Health at St. Joseph's Healthcare in Hamilton, Ontario, and professor of medicine at McMaster University is to discover which of these gene-environment combinations result in the emergence of allergic disease. Sears will be examining these factors with a team of scientists from across Canada in an ambitious study being developed through AllerGen (the Allergy, Genes and Environment Network).

The study is called CHILD – for Canadian Healthy Infant Longitudinal Development study. Next year, the scientists involved in it will start recruiting participants among mothers in early pregnancy – as the aim of the study is to follow children through life, beginning even before they are born. The researchers will note the diet of each expectant mother, and check the breathing capacity and allergic history of both parents. But equally, they will measure the quality of the air inside and outside the mother-to-be's home. Ultimately, CHILD is expected to track

at least 10,000 Canadian children and their parents in a number of cities. Each child will be followed from the womb into infancy and childhood and, it is hoped, on to adolescence and right through to adulthood.

When it comes to the environmental aspects of the study, Sears says there are three big areas to consider: "The air we breathe, the food we eat, and the water we drink." Air is already recognized as one of the most likely sources of sensitization. "But then the question is: is it indoor air, which is where the cat dander is or the house dust or the cigarette smoke from the parent – or is it the outdoor air with the air pollutants and the factories down the street or the diesel trucks on the roads? Or is it the interaction between the diesel pollutants and grass pollens or animal dander?"

CHILD's environmental tests will be complemented by physical measurements, taken at different stages of life. Sears is optimistic about the potential of tests designed for young babies. Umbilical cord blood from newborns, for instance, could offer clues to the risk of allergies in the child's future. And his group will have sophisticated new technology available to measure infant lung function. After the newborn goes home, "we want to follow up by visiting the home environment, and sampling the indoor air and the outdoor air, looking at environmental issues that may or may not have a role," says Sears. "Then we'll follow up over time."

The long-term aspect is important because some allergies,

such as eczema or food allergies, tend to show up early, while he says that “the true allergic asthma may not be evident for five years.” The participants in the study will not necessarily have allergies; the idea is rather to draw from a general pool of children of diverse backgrounds, examine the genetic and environmental factors, and then watch for the patterns of asthma and allergies to emerge.

The concept of having a long-term population study that looks at asthma is not of itself new. There are already more than 20 such birth cohorts around the world. Sears, in fact, is well-known for his work on the cohort in Dunedin, New Zealand, which has, since 1972, tracked asthma and other health issues in a group of 1,037 people, who are now in their early 30s. But CHILD will have significant advantages. Most other studies did not measure lung function in very young children, whereas the Canadian study will start such tests soon after birth. This is important because the airway effects of allergic disease may appear very early in life. CHILD will offer the most sophisticated examination to date of the relationship between specific genes, specific environments and asthma. And it has size: the massive study recruitment effort will get underway next year and a battery of scientists will collect and analyze data. This is one large CHILD.

When asked which academic disciplines the study will include, Sears chuckles, then replies that “a host of disciplines are involved, from epidemiology, through statistics, pediatrics, obstetrics, allergy, immunology, physiology, environmental hygiene, psychology, geographic information systems, ethics.” He mentions having a presentation slide that lists about 30 disciplines, “and we’re probably missing some. This is a big undertaking.” —*Gwen Smith*

Dr. Hortense Dodo is silencing the allergy-causing proteins in the peanut plant.



peanut pioneer

The peanut has such power as an allergen that many react strongly to even minuscule amounts of its proteins. In a lab at Alabama A&M University, Dr. Hortense Dodo and her colleagues toiled diligently for five years to strip the peanut of its fearsome potency. Then in December, 2005, they announced to the world that they had done just that.

Dodo, a professor of food biotechnology, and her A&M team in Normal, Alabama, have managed to eliminate Ara h2, the main allergy-causing protein, in the peanut. She does so using a process called RNA interference technology, which was discovered by scientists trying to enhance different characteristics in plants and organisms. These scientists hypothesized that by layering multiple copies of the same gene they would get more of the dominant protein that the gene produced. The theory was akin to layering paint to achieve a richer colour.

But what happened, surprisingly, was just

the opposite. The genes instead self-destructed. “The cell feels that there is something basically wrong as far as that specific gene is concerned,” explains Dodo, “and then it just shuts down the whole system.”

Taking advantage of this discovery, Dodo set out to see if she could “shut down” Ara h2 in the peanut plant. And eureka, it worked. She is now growing peanut plants that are free of this one allergenic protein. In greenhouse studies so far, the Ara h2-free plants appear to be growing at the same rate as the unaltered plants. Dodo will soon start eliminating other proteins. Her hope is to create a truly allergen-free peanut.

“The goal is not to try to force people who are allergic to peanuts to eat the transgenic [allergen-free] peanut,” says Dodo. “The goal is to have this peanut replace existing peanuts in the food industry.” Doing so would reduce the risk of accidental ingestion, and therefore the number of peanut-induced anaphylactic reactions – and ultimately – deaths. “At most, even if there was a reaction, it would be milder,” says Dodo.

It took years to silence the first protein, but Dodo hopes that a hypoallergenic peanut will be available to food manufacturers within the next five to 10 years. And since the RNA interference technology can be used on any number of allergens, she’s already got her next target in sight: the walnut.

— *Dory Cerny*

code cracker

Dr. Tom Hudson has a full plate, but likes it that way, as he's an unrepentant enthusiast for his work in the field of genetics.

Besides being the founder of the Genome Quebec Innovation Centre at Montreal's McGill University, Hudson is also a project leader with AllerGen (the Allergy, Genes and Environment Network), working with scientists from the University of British Columbia, the University of Manitoba and the University of Quebec on research that is opening the door to understanding allergic disease across the globe.

Hudson's AllerGen study focuses on identifying genes that may predispose a person to developing allergies and asthma, and determining how they are affected by the environment. It's a tall order, but he's used to those. The eminent geneticist was a key member of the International Haplotype Map Consortium (HapMap) – the famous “gene mappers” who catalogued common genetic differences in three of the world's populations.

A raft of studies in allergy and asthma have identified hundreds of genes that “might” be associated with the diseases, and much of Hudson's work involves narrowing the focus to the genes that merit further scrutiny. “The fact is that a lot of studies have been done to date,” says Hudson, “and they were very small and underpowered, and produced false positives.” The small sample sizes made it appear as if there was a link between certain genes and allergy, but that relationship wasn't borne out in other studies; the pattern just didn't hold up. Hudson hopes to avoid the false positives problem by examining the genes of a large group – 3,600 people who belong to three separate study cohorts in Manitoba, British Columbia and Quebec.

From this big pool, genetic data has been collected from children with asth-



Dr. Tom Hudson is discovering the genes which predispose us to allergy.

ma, allergy or both, their parents and even some grandparents. Hudson's team is analyzing their DNA to look at 165 genes that have been implicated in allergy or asthma, or that have to do with immunity. Each gene contains strings of four-letter codes. Aberrations in these codes are called Single Nucleotide Polymorphisms (SNPs). There are more than 1,500 SNPs

In 150 years we learned 200 causes for fever. “That's the type of killer medicine I'd like to do for asthma.”

associated with the genes that Hudson's lab is looking at, and these “markers” are what alter the genes in a way that may determine whether a person is predisposed to a certain disease.

“If the gene has to do with immune cells, we'll have an idea that it has to do with the immune response” or allergy, says Hudson. “If it's a gene that we see in the smooth muscle, then we start thinking that it has to do with the airways being more reactive” (as seen in asthma). Knowing that the SNPs are there, the next step is to figure out the mechanism by which they affect the genes to form allergic or asthmatic predisposition.

In this unique study, Hudson and his col-

leagues are not only analyzing the relationship between genes and allergic disease, but also how the identified genes are affected by their environment. Scientists have tracked the three study groups' exposure to (or avoidance of) pet dander, cigarette smoke, traffic pollution, dust and viruses. They've also taken down information on breastfeeding, noted the results of lung-function tests and levels of IgE (the antibodies found in those with allergies). This research will also be useful to AllerGen's CHILD Study.

Understanding the connection between genes and environment will help in developing future treatments. For Hudson, it is also opening the door to the exploration of allergic disease worldwide. Groups in Australia, Germany and the United States have asked his

team to test the same identified SNPs in their cohorts. In doing so, Hudson and his colleagues will keep expanding their sample size and gaining more precise knowledge of the genes and how they function in differing circumstances. “The fact that we might have the same genes but they have a different effect in another environment is something we're very keen to

explore,” says Hudson. Even changing the environment from urban to rural may have an impact on how the genes function.

Ultimately, Hudson's goal is not to find every gene responsible for allergy and asthma: “But it's important that we know, in our families, what these genes do,” he says. With the analysis of the Quebec cohort's data well underway and the Manitoba and B.C. samples not far behind, Hudson is simply hoping to understand the diseases better. “Just 150 years ago, fever was a disease. Now we know there are 200 causes for fever and we can treat the right type,” he says. “That's the type of killer medicine I'd like to do for asthma and allergy.” —D.C.