Gesundheit! Patrick Holt smothers allergies and asthma

Drop the mop and play with Fido is Patrick Holt's recommendation for raising an allergy-free child. Although a tangled web of factors underlies allergies and asthma, Holt believes that preventing lifelong affliction could be simple.

Patrick with his wife and colleague, Barbara Holt.

Despite a flood of research on the topic, rates of allergy and allergy-induced asthma continue to climb in most industrialized nations. Holt, a professor at the Telethon Institute for Child Health Research in Perth, Australia, wants to reverse that trend. To accomplish this, he needs to know what triggers airborne allergy and asthma, starting at the moment babies draw their first breath. He's currently co-leading the first clinical trial to test a treatment that could prevent asthma in children who are genetically predisposed to the disease. The idea behind the treatment, consisting of daily drops of dust mite, cat, and grass antigen placed under the tongue, builds on his earlier studies showing that inhaled antigens can induce immunological tolerance (1), a process that involves regulatory T cells (2).

Dendritic cells (DCs) in airways feature prominently in Holt's research. These potent antigen-presenting cells help determine whether responses to inhaled allergens will be dominated by Th1 or Th2 cells (3). But even before DCs get involved, a bevy of factors—genetics, pre- and postnatal antigen exposure, and nitric oxide levels, to name just a few—determine whether exposure will lead to tolerance or hyperreactivity. Holt has studied these factors and believes many of them can be overcome. The main obstacle in taming asthma, he says, is an outdated mind-set.

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Is it true that Australia has one of the highest rates of asthma in the world?
It's true. Australia and New Zealand were on top for a long time, but now we've been joined by lots of European countries and the US, so we aren't as far in front as we used to be.

Why has Australia remained high?
Everyone has pet theories, but I think we're just an archetypal example of what has happened in the western world since World War II. Since the '60s, there has been a slow surge in the prevalence of allergic disease and allergic asthma in westernized countries. We see the same rise now happening in second world countries as they move into first world economies.

Are there any confounding factors in this trend?
There isn't anything major; this is a real thing. We're talking about 35 years of research. When we look at pediatric records starting in the '70s, we can see changes occurring in succeeding birth cohorts so that each new generation of children has a progressively higher risk for allergic sensitization and subsequent asthma. We're also seeing this trend in autoimmune disease.

Do you think differences in the way kids are raised now might account for this trend?
Sure. There are obvious differences like processed foods. But also, everything sparkles these days. You go into the supermarket and there are hundreds of cleaning products to spray on every surface to keep microbes away. That was unheard of when I was a kid. Clean houses used to be houses that were vacuumed and swept once a week.

There was a study done by a group in the UK that found that kids who basically lived in a bubble—whose families avoided every allergen they could—had higher levels of allergic sensitization by the time they were of school age.

Have changes in vitamin intake and nutrition influenced asthma prevalence?
I think so. Everything about allergy and asthma is multi-factorial. There's evidence that vitamin D deficiencies limit the rate at which the immune system matures. And the story here is that kids don't go outside as much as they used to, which could lead to vitamin D deficiencies. Epidemiologists have been mapping risk for asthma and allergy in relation to population levels of vitamin D, and they are seeing a connection.

There's also the omega-3 story. These fatty acids from fish have immunomodulatory effects that we don't completely understand, but if you look in populations that eat oily fish, the levels of asthma and allergic disease tend to be lower. A range of other dietary factors appear to contribute, but quantifying their effects is difficult because they vary in relation to how stressed an individual population is with respect to a particular set of components. For example, if a population lives in an environment where it's difficult to get green vegetables, vitamin deficiency may show up as a risk factor for allergy and asthma; whereas if the population is well nourished, it might not.

Do you think there's a way to reverse the rising trend without reverting back to less sanitary days?
This is basically what's at the heart of what we're doing now in our human studies. We think there are incredible opportunities for changing population patterns of lifelong asthma by attacking problems in early pediatrics instead of waiting until kids have permanent asthma. We know that the major changes responsible for the burden of disease in adult life

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occur in the first seven years of life. Plus, many of the tools we have could be revised only slightly to prevent the onset of disease. The real challenge is to convince the pharmaceutical industry and regulatory authorities like the FDA that young children should be the principle targets in controlling these diseases (4).

Do you worry that the "bottom line" could get in the way of changing their approach to treatment?

No, because from a business modeling perspective this works too. If it is possible to safely treat early stage disease, the size of the market is large and the potential health benefits are extremely high. If industry management actually sits down and does the math, they'll find that there is plenty of potential to make the same amount of money by switching the emphasis to different age groups for treatment. The obstacle is getting people to change their mind-set. Since time immemorial, the pharmaceutical industry has specialized in treating chronic diseases—with the exception of infectious diseases. But now a new generation of people in pharma is starting to get the message, and these are the people we're trying to build relationships with so that we can help them make this transition.

The main thing is that information should not stay in the realm of mouse immunology, even though that's where it started. That's why I have stepped into the human arena too.

What are you doing there?

We have one NIH-funded trial, for example, based on the idea that if you can treat children who are at high genetic risk of allergic disease in a way that promotes the natural development of immunological tolerance, you'll take away their risk for long-term asthma. The trial was based on experimental animal data that we got back in the early '80s, which revealed the phenomenon known as inhalation tolerance—the equivalent of oral tolerance in the gut, which protects us from becoming allergic to proteins in the food we eat. Our immune system develops as it's exposed to airborne antigens like dust mite or cat proteins and makes up its mind about whether or not it's going to develop positive immunity or tolerance. Most children are non-allergic, and the capacity to generate IgE antibody to these proteins is permanently switched off by the successful development of tolerance.

We had also discovered that children who have the highest risk of asthma come from families with a history of allergic disease. And, at least in the animal equivalent of these children, they need more intense stimulation and longer stimulation by these everyday antigens in the environment [to become tolerant]. This led to our prediction that they would benefit from high levels of stimulation.

At this point, we've put 50 children through the trial, including children as young as 12 months of age. We gave the children a mixture of four major inhalant allergens in the form of drops under their tongues on a daily basis for a year.

Have there been adverse effects?

No, the children have had no symptoms of sensitization and there have been no increased levels of IgE. Therefore, the theoretical danger that we might do the opposite that we set out to do—sensitize instead of tolerize—does not seem to be a problem. However, we need to wait for a few years before we assess the efficacy of the treatment.

GRANDDAD'S GARDEN

Are there immune factors that are critical in determining tolerance or immunity?

Absolutely. There are probably about 10 cytokines that you would say are more important than the other 50 or so. These are things like IL-4, IL-5, IL-9, IL-13, interferon-γ, and TNF. What we really want to know is what are the master switches. We've found some gatekeepers, such as dendritic cells in the airway mucosa. They are the ultimate arbitrators in deciding whether an inhaled protein is going to induce tolerance or positive immunity. The Toll-like receptor system is probably involved too. And there are shared processes that determine the kinetics of postnatal maturation of immune competence in the preschool years. It looks like the faster your immune system matures, the lower your risk is of programming long-term allergic responses. To the extent that the hygiene hypothesis is concerned, microbial stimulation is probably the most important signal driving that maturation.

Do you have children?

I sure do. And grandchildren.

What is your fatherly advice with respect to avoiding allergies and asthma?

My kids are advised to breastfeed their children for the first six months of life because it's the best protection that we have now against early severe infection, which we know synergizes with allergy to create maximum risk for developing long-term asthma (5). And although I wouldn't go out and trumpet this, I'm personally convinced about the epidemiology data saying that early pet exposure is good for you. I also recommend a healthy diet and contact with the outside environment. We always allowed our kids to crawl around in the garden so that their immune system could say hello to the world out there.

There are incredible opportunities for changing population patterns of lifelong asthma by attacking problems in early pediatrics.

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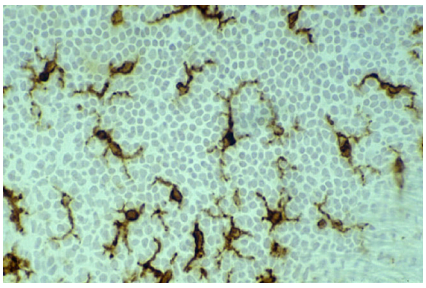

DCs in the airway mucosa (above) can respond to inhaled antigens in a way that triggers an asthma attack.