



By Katie Sweeney

CLEARING THE AIR

The lower incidence of allergic diseases in **developing** countries has had scientists speculate that better hygiene in the industrialized world leads to more asthma.

So why, then, do certain infections actually exacerbate or bring on the disease? Cedars-Sinai researchers think they've found the answer—and a new clue into the alarming rise of asthma in **developed** countries.

Walk into any grocery store and chances are good you'll find a handy box of disinfecting wipes waiting for you by the parade of grocery carts. When you get home, you'll likely wash your hands in antibacterial soap and clean your kitchen counters with antibacterial disinfectant. And when your kids scrape their knees, you'll promptly apply antibiotic ointment.

There's no doubt about it: We live in an ultra-clean world. And for the most part, clean is good. Modern sanitation systems, clean drinking water, and the advent of antibiotics and vaccines have all resulted in lower infant mortality and greater longevity.

But while all that cleanliness may be next to godliness, for the past 20 years, scientists have speculated that it could be causing an unintended side effect: an epidemic of allergies and asthma in the United States and other developed countries.

"In developing countries, children are exposed to more dirt, bacteria, and pathogens than in developed countries," explains Moshe Ardit, MD, vice-chair of research in the Department of Pediatrics and director of the Division of Pediatric Infectious Diseases at Cedars-Sinai Medical Center. "The theory has been that the resulting infections actually help protect you against developing allergies and asthma. With more hygiene, you get fewer infections—and therefore more asthma."

First proposed in 1989, this "hygiene hypothesis" has been commonly used to explain the increase in allergic diseases and asthma since industrialization as well as the higher incidence of allergic diseases in more developed countries. But there's a rub. According to the hypothesis, infections should protect you from asthma. And yet, certain infections not only don't protect you, they can actually exacerbate and even bring on the disease.

Understanding Asthma

It begins with just a mild cough. Soon, the child is coughing frequently, then wheezing as he struggles to breathe in and out. His small palms sweat, and his heart starts to race. It feels as if he is only breathing through a straw.

The child is having an asthma attack—and he is not alone. Rarely encountered in the 19th century, this chronic lung disease, which inflames and narrows the airways,

now affects 300 million people worldwide, including 22 million Americans—nearly 6 million of them children. Add in allergies, and the tally jumps to 60 million Americans. Compare that to the nation's 17 million diabetes patients and 7 million heart disease patients.

Although asthma can be managed, there is no definitive cure, and it leads to 5,000 deaths every year in the United States. Genetics also play a role (if one parent has asthma, chances are one in three that each child also will have asthma), as does the environment, but the exact cause of the disease remains unknown.



Dr. Arditi's discovery helps plug a key hole in the hygiene hypothesis. "It solves the question of why certain infections protect you from asthma, while others don't," he explains.

Enter Dr. Arditi, who in 1980 at the age of 25 emigrated from Turkey to the United States to study medicine. Dr. Arditi and his team had been conducting basic research into how inflammation—the immune system's normal answer to injury and infection—can get switched into overdrive and lead to chronic inflammatory diseases, including atherosclerosis. Now, they have turned to a different chronic disease—allergic asthma—which is triggered by allergens and accounts for 60 percent of all asthma cases.

The team set up a simple experiment, injecting groups of young mice with varying doses of bacteria called *Chlamydia pneumoniae*, which are associated with developing asthma. While infected, the mice also were exposed to a common antigen that normally does not cause allergies. Two weeks later, the mice were again exposed to the substance.

The results were clear. Mice infected with a high dose of the bacteria, which caused severe pneumonia, had no reaction to the antigen. The mice that had received a much lower dose of bacteria, resulting in a milder lung infection, had the opposite response: They developed allergic asthma.

Why would a mild infection cause an immune system to go awry? To answer that question, Dr. Arditi has developed a "modified hygiene hypothesis" that offers more clues into the alarming rise of asthma—and could help reverse the trend.

Balancing Act

Part of the thinking behind the original hygiene hypothesis has been that the antiseptic environment of the developed world causes the body's immune system to become unbalanced between two kinds of immune responses, Th1 and Th2.

Th1 and Th2 white blood cells release chemicals to fight


off perceived intruders. Bacterial and viral infections tend to require Th1 cells, while other assailants, such as parasites, stimulate the body to make Th2 cells. Although Th2 cells play an important role in immunity, they are also responsible for allergic responses.

Babies are born with more Th2 cells than Th1 cells. The hygiene hypothesis proposes that early exposure to infections can help develop the Th1 side of the immune system. Without this early "training," the Th2 side is at risk of becoming overactive, leading to asthma and allergies.

Dr. Arditi's discovery helps plug a key hole in the hypothesis. "It solves the question of why certain infections protect you from asthma, while others don't," he explains. His research emphasizes the importance of the severity of infections, rather than their number. "A mild infection, which is more typical in developed countries, doesn't require nearly as many Th1 cells. It is not sufficient to protect you from tipping over into that Th2, or allergic, pathway."

This discovery sheds more light on the intricate link between asthma and certain infections—knowledge that could help prevent the development of infection-related allergic asthma. In fact, scientists already are working on vaccines directed against certain viruses and bacteria linked with asthma.

Meanwhile, Dr. Arditi has turned his focus to better understanding how T cells protect the body from an overactive Th2 response. The team is also studying the link between air pollution, cigarette smoke, and allergic asthma.

"I think we have more clues now as to why we are seeing so many children with asthma in this country," he adds. "Hopefully, that knowledge can help us prevent certain individuals from ever developing asthma. We need to stop this epidemic." 

According to the Centers for Disease Control, the prevalence of asthma in U.S. children jumped by an astonishing 60 percent between 1980 and 2003. In Los Angeles County, approximately 1.2 million children and adults have been diagnosed with asthma, or nearly 12 percent of the population.