

Breath of Fresh Air

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What's Hygiene Got to Do with It? The Asthma-Dirt Connection

Here's the puzzle. Asthma and allergies have become more common in the last few decades ... dramatically so. Estimates suggest an 80% increase in the frequency of asthma over the last 15-20 years, and the prevalence of allergies, affecting 25-30% of all Americans, is also on the rise. The question is why.

The second piece of the puzzle is that this increase is not uniform around the world. In fact, it seems primarily confined to industrialized, "Westernized" nations (for example, the United States, Western Europe, Australia, New Zealand and Japan). In "third world" countries, asthma is far less common, although more common in their cities than in their rural areas.

How can we fit these puzzle pieces together? Is it simply a matter of greater air pollution in industrialized parts of the world? Some have suggested that our Westernized diet might contribute. More recently, scientists have become intrigued by the possibility that the increased cleanliness of our modern environments may have an unanticipated consequence: more allergies and asthma. The hygiene hypothesis suggests that we look to our decreasing exposure to germs as the cause for the rising frequency of allergies and asthma.

Linking fewer infections with more asthma

Certainly, we have seen a major decline in infections to which we are exposed in early childhood. Evidence confirms that, in general, those who have had infections such as tuberculosis, hepatitis, or measles are less likely to develop asthma. Perhaps related to their greater exposure to infections, children

who attend day care or who have older siblings were found in one study to be less likely to develop asthma.

In addition, our widespread use of antibiotics for childhood infections may lead to changes in the normal population of bacteria that live in our intestines. It was as if the immune system, no longer spending its time fighting germs, were then redirected to "defend against" allergens in the air that we breathe. Our homes, though freer of germs, are filled with plenty of allergens, whether from dust mites or cockroaches or pets, to serve as alternative targets for immune reactions.

In contrast to our modern, relatively germ-free environments, children growing up in farming communities are constantly exposed to farm animals and their droppings. Like our own feces, animal feces are full of bacteria ... the sort that our immune systems are designed to defend against. You can make an estimate of how much a child is being exposed to these bacteria by measuring in his/her home the amount of a protein, called endotoxin. Endotoxin is normally found in bacteria living in animal feces. The more exposure to farm animals, the higher the concentrations of endotoxin found in the home, including in the bedroom.

Asthma is less common in farming communities

Researchers conducted the following experiment in rural communities in Germany, Austria, and Switzerland, including both farming and non-farming areas. They measured the amount of endotoxin in children's mattresses, then determined which children (age 6-13 years) had allergies and asthma. For the most part, they found a direct

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Salmeterol (Serevent): Is It Safe?

In October, Merck Pharmaceuticals decided to withdraw its pain reliever and anti-inflammatory medication, rofecoxib (Vioxx), from the market. Post-marketing studies (that is, studies conducted after the medication had been approved for sale by the Food and Drug Administration [FDA]) found that use of Vioxx for 18 months or more was associated with a significant increase in the risk of heart attacks and strokes.

In the wake of this decision, the FDA is now being asked to review the safety of other prescription medications that were originally approved for sale in the United States but for which additional safety information has since become available. One of the five medications publicly mentioned for review is salmeterol (Serevent). Salmeterol is widely used to treat asthma and chronic obstructive pulmonary disease (COPD). Salmeterol is available for inhalation by Diskus device, either alone or in combination with an inhaled steroid, fluticasone (Flovent). The salmeterol-fluticasone combination inhaler, called Advair, is the most widely prescribed controller medication for asthma in the United States.

Studying the safety of Serevent

Why are there safety concerns about Serevent? In 1996, two years after FDA approval of Serevent, its manufacturers, GlaxoSmithKline, embarked on a large-scale experiment to assess the safety of Serevent. They felt the need to demonstrate its safety because of concerns that had been raised about potential harmful effects from regular use of this entire group of medications, called beta-agonist bronchodilators. Thousands of patients with asthma were asked to participate in this study, in which one group was given Serevent to take twice-daily and the other group received a placebo inhaler. Both groups of patients were advised to take their other usual asthma med-

ications as they had before. The study lasted just over 6 months, and the question asked was: were there any differences in harmful respiratory outcomes in the two groups; that is, did one group have more asthma deaths or near-deaths (respiratory failure requiring use of a ventilator) than the other group?

The study, called the SMART study as an acronym for Salmeterol Multi-center Asthma Research Trial) was stopped in 2002 after approximately 26,000 persons with asthma (of the intended 60,000) had been enrolled. The study was stopped because of difficulty enrolling patients and the findings in African-Americans (as described below). Analysis of the results to that point found a trend toward more asthma deaths (13 vs. 3) and life-threatening asthma events (37 vs. 22) in the Serevent-treated group. When the scientists conducting the study examined subgroups of patients, they found the following concerning results:

- among African-Americans, 5 times as many deaths and near-deaths from asthma occurred in those given Serevent than in those given placebo; and
- among patients with asthma not using an inhaled steroid as a preventive (controller) medication, again more deaths and near-deaths from asthma occurred in those given Serevent than in those given placebo. Only 38% of the African-Americans who participated in the study used an inhaled steroid.

Before continuing with our interpretation of these results, we need to acknowledge that publication of this newsletter, *Breath of Fresh Air*, is made possible in part

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Breath of Fresh Air

Editor-in-chief

Christopher H. Fanta, M. D.

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News About Asthma

Congratulations to Partners Asthma Center nurse, Elaine Carter

Elaine Carter, R.N., Nurse Educator at Partners Asthma Center for the last 6 years, has been awarded the Human Needs Service Award by the Massachusetts Nurses Association.

Ms. Carter has a background in asthma education at community health centers. At Partners Asthma Center she performs numerous roles, including patient care, nursing education, pulmonary function testing, and allergy skin testing. At the Center for Chest Diseases at Brigham and Women's Hospital, she runs the program for administering anti-IgE monoclonal antibody therapy (Xolair) to patients with severe asthma. She was among the first nurses in the state to become a certified asthma educator, after passing the National Asthma Educators' Certification Examination.



We are very proud of her talents and her kind and gentle ways in helping patients with asthma and their families. Congratulations to Elaine on this outstanding recognition from the Massachusetts Nurses Association!

Repeat release of zileuton (Zyflo)

In December, 2003, the manufacturer of the leukotriene blocker, zileuton (Zyflo), withdrew this drug from the market. There were no safety concerns; the reason was sluggish sales.

Since then another pharmaceutical company, Critical Therapeutics, has purchased the rights to manufacture and market Zyflo. Pending FDA approval of its production facilities, Zyflo will likely reappear on the market in 2005.

Like montelukast (Singulair) and zafirlukast (Accolate), Zyflo works by blocking leukotrienes from causing bronchial muscle contraction and inflammation of the bronchial tubes. Different from Singulair and Accolate, Zyflo works to decrease production of the leukotrienes rather than blocking their effects once formed. A major disadvantage of Zyflo is that it needs to be taken four times per day. Critical Therapeutics is working to develop an extended-release formulation for Zyflo, making twice-daily dosing possible in the future.

Predicting drug effects based on our genes

A recent study of persons with mild asthma has given further proof that our genes affect how we are likely to respond to certain medications. In this case the medication was the commonly used short-acting bronchodilator, albuterol. And the study was conducted in part by researchers at Partners Asthma Center, including Drs. Elliot Israel (lead investigator), Jeffrey Drazen, Aaron Deykin, and Michael Wechsler.

Because of differences in our genes, we make slightly different proteins on our bronchial



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muscles to which albuterol binds when it works its bronchodilating effects. The slight differences in these proteins turn out to influence how albuterol affects our lungs. Dr. Israel and his colleagues was able to characterize the genes of persons with mild asthma and prove that, based on these genetic differences, some persons improved after using albuterol four times a day on a regular basis, whereas others appeared to worsen. Their most striking finding was that some persons with mild asthma – because of their genetic make-up – showed overall improvement when they stopped using albuterol and substituted a different type of bronchodilator.

Many questions remain to be answered before we reach the day when knowing the particular pattern of your genes will influence which medications your doctor recommends for treating your asthma. But this important research brings that day one step closer.

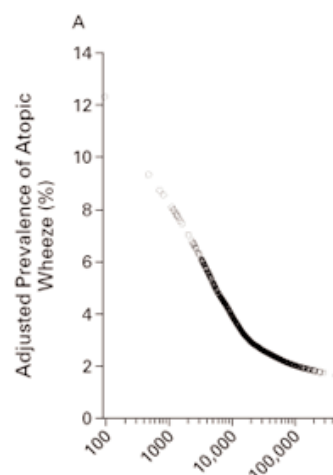


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relationship: the greater the exposure to endotoxin in the home, the less likely that the children would have allergies or asthma (Figure 1). Conversely, “cleaner” homes (having less of this protein found in animal droppings) were associated with a greater likelihood of allergies and asthma.

Our immune systems are meant to help defend us from the innumerable germs in our environments. The hygiene hypothesis suggests that if we are exposed to fewer germs, whether in the form of common infectious diseases, bacteria in our own intestinal tracts, or bacteria from animal feces, our immune system is more likely to be re-directed toward making allergic reactions against harmless allergens in our environment. Allergies become more common in a world that has been made too germ-free.

Before you go out and buy a sheep to live in your basement in the hopes of protecting your children from developing asthma, remember that the hygiene hypothesis is just that ... a hypothesis. It offers one possible explanation for the observed increase in allergic diseases, but it is far from the only explanation; and it has not been proven unequivocally true. What it does offer is a potentially exciting avenue for future asthma research. Might it be possible to find harmless proteins or bacteria to which children’s immune systems could be exposed at an early age, thereby directing them away from making allergic responses. Many questions of course remain: Which bacteria or proteins would be safe? At what age might children be exposed? How much of an exposure to the protein or bacteria is needed? You too can probably think of many other questions that would need to be answered? Nonetheless, scientific research begins with a “testable hypothesis,” and the hygiene hypothesis offers a wealth of testable ideas about how one might begin to reverse what has been called our modern “asthma epidemic.”



This graph illustrates that the more endotoxin found in the children's homes (units of endotoxin on the horizontal axis), the less often the children had allergic wheezing (percentage of children on the vertical axis). From the New England Journal of Medicine, 2002.



Salmeterol (Serevent): Is It Safe?, from page 2

by a generous educational grant from the makers of Serevent, GlaxoSmithKline.

What accounts for these findings?

The explanation for the findings in the SMART study – why Serevent was associated with more bad asthma outcomes – is unknown. Some have speculated that taking an effective bronchodilator (to open the breathing passageways by relaxing the bronchial muscles) without taking an anti-inflammatory medication (to prevent swelling of the walls of the bronchial tubes and excess mucus production) can lead to life-threatening asthmatic attacks because one is deceived into feeling that one's breathing is satisfactory while all the while the breathing passageways become more swollen and clogged. Other explanations are possible, however, and future research will be needed to answer this question of "why?"

As a result of the findings from the SMART study, a warning was added to the informational insert provided with each package of Serevent and Advair inhalers.

WARNING: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179).

Additional advice in the package insert suggests that

Patients should not stop SEREVENT or ADVAIR therapy for asthma or SEREVENT for COPD without physician/provider guidance since symptoms may worsen after discontinuation.

The question that may now go before the FDA is: should anything more be done to

ensure patient safety, including potentially removing Serevent and Advair from the market?

What would you recommend?

Imagine that you are a member of the advisory board reviewing this information. You know of the concerns about the safety of Serevent, and you know too of the benefits of its use in combination with anti-inflammatory medications — fewer symptoms, improved lung function, fewer asthmatic attacks, and avoidance of the need for higher doses of inhaled steroids. You know that literally millions of people feel that they have been greatly helped by these drugs. What would you advise?

We at Partners Asthma Center continue to prescribe Serevent and Advair. We feel that the benefits outweigh the potential risks. We do not recommend that Serevent be used unless a patient with asthma is also taking a regular anti-inflammatory medication. And we believe that the best protection against life-threatening asthmatic attacks is not removal of long-acting beta-agonist bronchodilators from the market but good medical follow-up, knowledge about asthma and warning signs of severe asthmatic attacks, and a plan of action in the event that you suffer a severe asthmatic attack. Remember that the bad outcomes in the SMART study were life-threatening asthmatic attacks. You can remain safe from such attacks with good medicines and good medical care.



Donors' Corner

Partners Asthma Center proudly acknowledges the generous monetary contributions of its patients:

Fay Mittleman
Patricia Barbour
Carol Lippia-Tenney
Anonymous

We also appreciate the strong support expressed along with one of these donations:

“I have enjoyed the quarterly publications of the asthma newsletter (*Breath of Fresh Air*) and have shared some of the information with health teachers. I look forward to visiting the Partners Asthma Center website.

“I am making this contribution with the hope for your continued success as you grow as a great support and fund of information for people with asthma.”

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