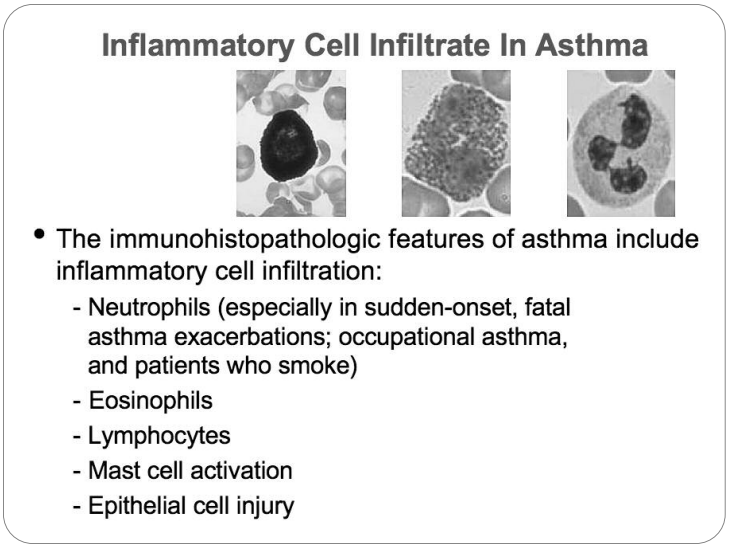
DR. SOPHOCLES: ***What does the chronic inflammation associated with asthma do to the lungs and does it cause permanent damage?***

DR. COX: For years, we've recognized that inflammation is a key feature of asthma, but we now recognize that there seem to be different types of asthmatics and they may not all respond to the same type of medication regimen. In some patients, certain medications may actually make their asthma worse. We'll talk a little bit about Beta-Agonists and some of the controversies around this.

We recognize that airway inflammation contributes to the hyper-responsiveness in asthma. Various different phenotypic patterns of asthma exist in the presence of underlying airway inflammation—which is variable and has distinct but overlapping patterns that reflect different aspects of the disease, such as making one intermittent versus persistent asthmatic. But airway inflammation is the key feature.



The inflammatory cell infiltrate in asthma includes a number of different cells: neutrophils, eosinophils, lymphocytes, mast cell, and as a result of this complex concert of cellular infiltration, there is damage to the epithelium of the lungs.

In biopsies of asthmatics that have had long-standing asthma, you can see a number of different pathological processes that we believe now contribute to a concept that we have referred to in the past as airway remodeling. (See slide on following page)

What happens is there is dysfunction of the cilia, the fine hair cells in the mucous membranes. There is sloughing off of the epithelium. There is increased mucin production. There is hypertrophy of the smooth muscle of the airway, increased blood vessel or angiogenesis growth, and a number of inflammatory cells that you can find in these biopsy specimens. (See slide on following page)

Airway remodeling in long-standing asthma. An airway from a 70-year-old patient with asthma is shown.

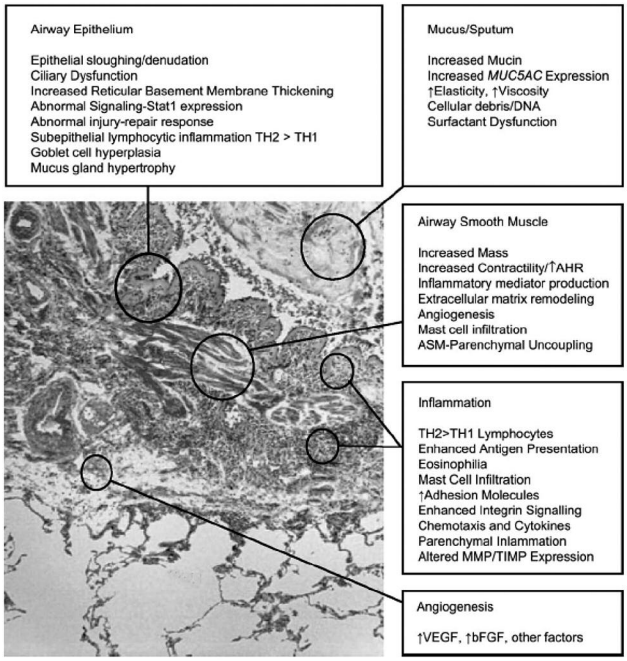


FIG 1. Airway remodeling in long-standing asthma. An airway from a 70-year-old patient with asthma is shown. Examples of the structural and functional changes of chronic asthma are highlighted and are discussed throughout the text. *MMP*, Matrix metalloproteinase; *TIMP*, tissue inhibitor of metalloproteinases; *bFGF*, basic fibroblast growth factor.

Pascual, J Allergy Clin Immunol 2005;116:477-86

Airway Epithelium
Epithelial sloughing/denudation
Ciliary Dysfunction
Increased Reticular Basement Membrane Thickening
Abnormal Signaling-Stat1 expression
Abnormal injury-repair response
Subepithelial lymphocytic inflammation TH2 > TH1
Goblet cell hyperplasia
Mucus gland hypertrophy
Mucus/Sputum
Increased Mucin
Increased MUC5AC Expression
↑Elasticity, ↑Viscosity
Cellular debris/DNA
Surfactant Dysfunction
Airway Smooth Muscle
Increased Mass
Increased Contractility/↑AHR
Inflammatory mediator production
Extracellular matrix remodeling
Angiogenesis
Mast cell infiltration
ASM-Parenchymal Uncoupling
Inflammation
TH2>TH1 Lymphocytes
Enhanced Antigen Presentation
Eosinophilia
Mast Cell Infiltration
↑Adhesion Molecules
Enhanced Integrin Signalling
Chemotaxis and Cytokines
Parenchymal Inlammation
Altered MMP/TIMP Expression
Angiogenesis
↑VEGF, ↑bFGF, other factors

FIG 1. Airway remodeling in long-standing asthma. An airway from a 70-year-old patient with asthma is shown. Examples of the structural and functional changes of chronic asthma are highlighted and are discussed throughout the text. *MMP*, Matrix metalloproteinase; *TIMP*, tissue inhibitor of metalloproteinases; *bFGF*, basic fibroblast growth factor.

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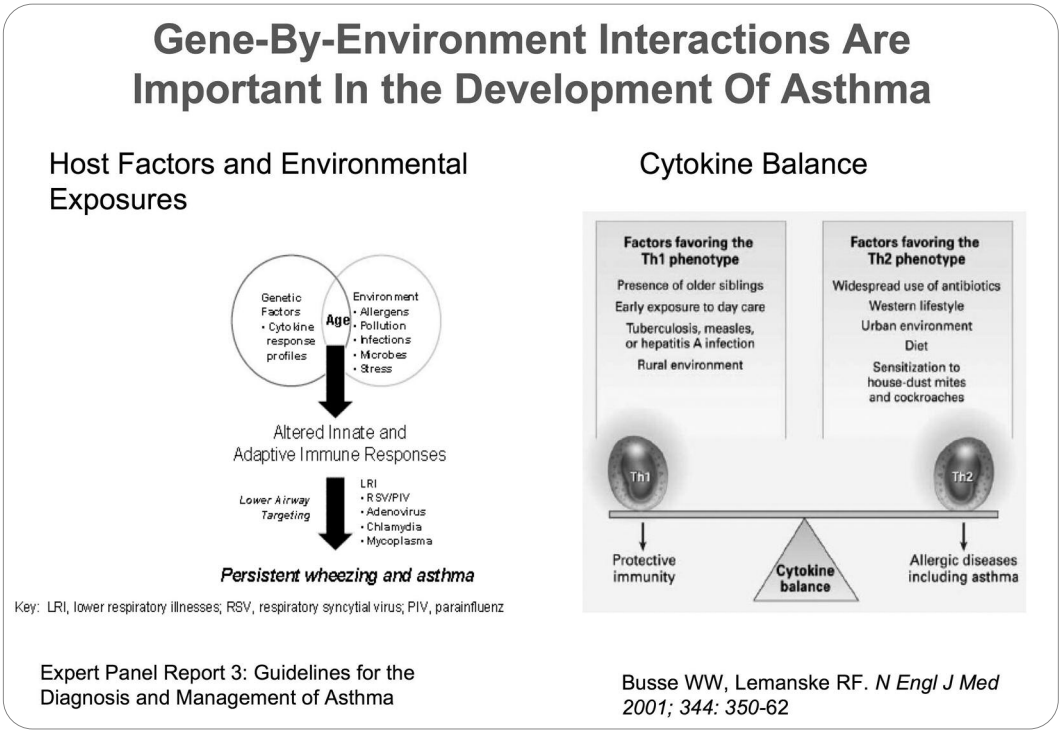
DR. SOPHOCLES: ***What are the predisposing factors for the development of asthma?***

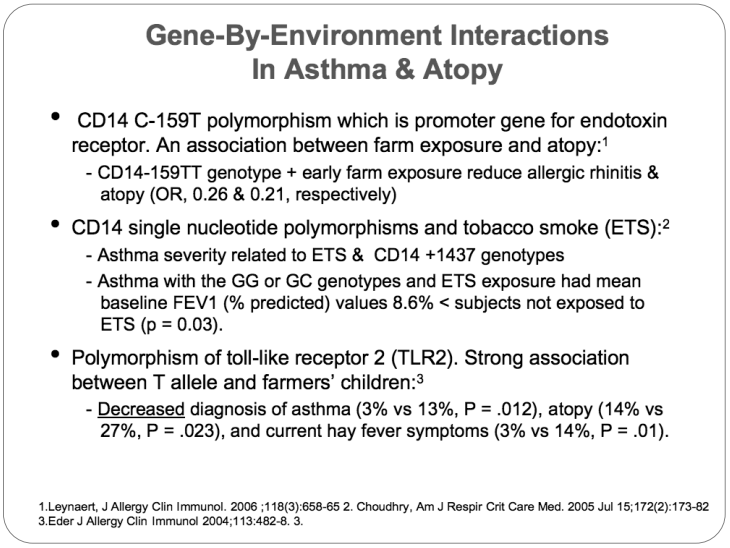
DR. COX: We believe the three main predisposing factors are genetics—and that is genetics and the interaction with environmental influences—atopy, which is the genetic predisposition for the development of IgE, the antibody involved in allergic reactions, and viral respiratory track infections which are the most important cause of asthma exacerbations but they may also contribute to the development of asthma.

DR. SOPHOCLES: ***How does genetics play a role in asthma?***

DR. COX: We think that you're born with certain genetic phenotype that make you more susceptible to certain environmental exposures. There are a number of different relationships that have recently been discovered that seem to contribute to the development of asthma. And one of the examples that we've seen is children that grow up on farms appear to have less incidence of asthma. But when you look a little more carefully, it may be a subset of individuals that carry a certain genetic profile that seem to benefit from growing up on the farm. So gene-by-environment is a combination of that individual's phenotype and then the environmental exposures that come along after birth.



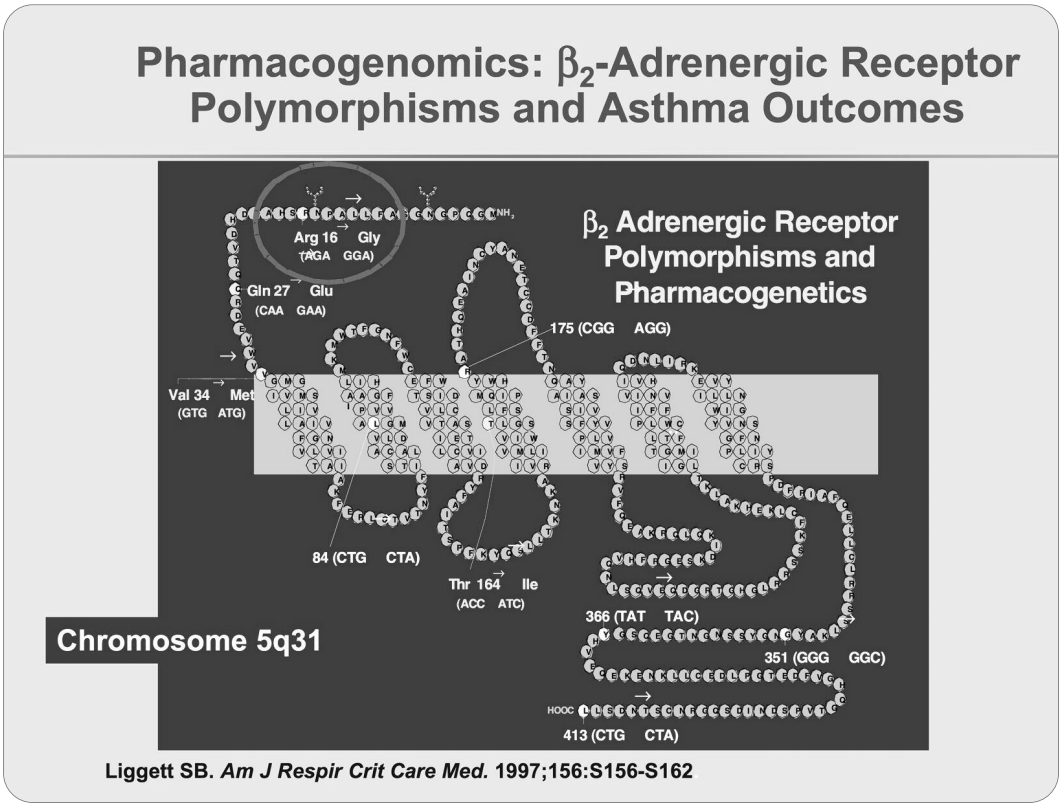
There is a CD14 polymorphism at the C-159T, which is a promoter gene for endotoxin receptor. One of the reasons for the theory behind the children growing up on farms having less asthma, is that they're getting a greater amount of endotoxin exposure. The early endotoxin exposure in individuals that have a certain polymorphism for this receptor reduces the incidence of allergic rhinitis and atopy, and what we believe occurs is that the endotoxin shifts the TH2 towards a TH1 which is a non-allergic pathway.



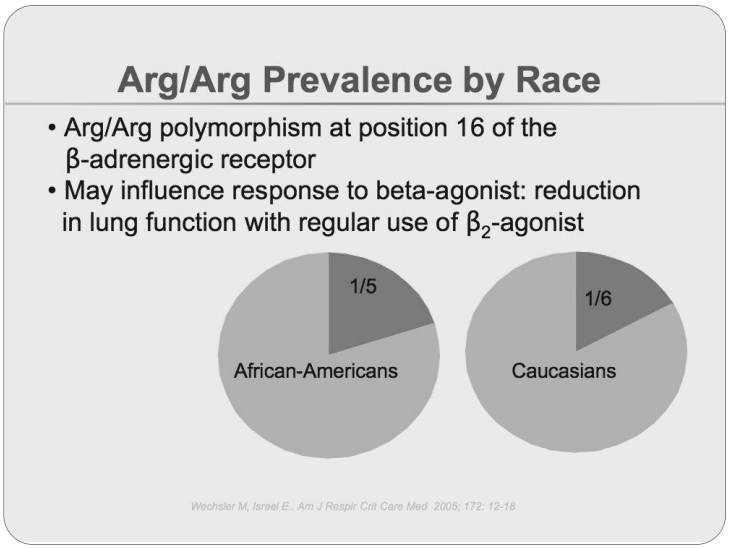
Another polymorphism that's been identified on the CD14 nucleotide is related to tobacco smoke exposure. And what was found is individuals with GG or GC genotypes and environmental tobacco smoke exposure had lower FEV1's than individuals who were not exposed to environmental tobacco smoke.

And the third polymorphism that's been identified that's linked with asthma development, and again in children growing up on farms, is toll-like receptor 2. Individuals that have a certain polymorphism for toll-like receptor 2 had a decreased incidence of asthma and atopy and current hay fever, compared with children who did not. So in summary, there appears to be different polymorphisms and phenotypes that, when interacting with certain environmental exposures, lead to a decrease or increase in asthma and atopy.

One example that probably has received a lot of attention, even outside of the asthma specialty arena, is polymorphism of the beta 2 receptor. Now the beta 2 receptor is a receptor that is required by a beta- agonist which asthmatics use as their rescue medication. And it is believed that insertion of Gly at position 16 will alter the way the receptor finds the Beta-Agonist medication in an unfavorable way. (See slide on following page)



Now there's a higher incidence of Arg/Arg polymorphism at position 16 in the African-American population, about one fifth of this population has this polymorphism, where as about one sixth of Caucasians have this polymorphism.



One study was designed to look at the response to regular use of Albuterol versus placebo to see if it did indeed have a harmful effect and they looked at it based on the individual phenotype. So they were divided into the Arg/Arg and the Gly/Gly groups and there was a crossover leg where they received either Albuterol four times a day or placebo four times a day, and then they measured pulmonary function tests, peak flow measurements and their outcome. (See slide on following page)

And what they found was the group who were Arg/Arg phenotypes, when they were placed on regular Albuterol, they actually had a deterioration in their lung function. So this would suggest for those individuals who have that phenotype, Arg/Arg, that they would not respond well to regular use of Albuterol.

This is an example of gene-by-environment interaction and in particular how it affects response to medication. And there's also been some studies that have shown that there are certain individuals that do not respond to inhaled corticosteroids and that may also have a genetic basis. This explains some of the information that is coming out about interactions between medications and some individuals responding well and some not responding well and the possible role genetics may play in this.

Maybe in the future what we'll be seeing is we'll be phenotyping our patients and selecting a medical regimen based on their particular phenotype — sort of like finger printing. And I really do believe that this is the future, because this is where there's a lot of interest in asthma research, and I know in other diseases, research is going on. So not all asthma drugs are going to be effective for all asthma patients.

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