

Evidence for the Transmissibility of Atopy*

Hypothesis

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The etiology of atopy is unknown. Its family distribution suggests transmissibility. Populations moving from countries with a low incidence to those with a high incidence increase to the higher rate. African and New Guinea village groups developed asthma with return of individuals who have acquired atopy in the city. Protection (and possibly immunity) develops with early exposure to child care or to affected older siblings. T helper (Th) type 2 clones driving specific allergies remain active even without further allergen exposure. Other IgE responses remain normal. Once boosted to completeness, the patterns of skin test results remain quite stable, possibly by the localization of abnormality maintained by immunity. An example of a virus causing the immortality of Th2 cells is herpes simplex virus type 1. It infects mouse or human Th2 cells and, although it does not multiply, causes immortality by increasing FAS-mediated apoptosis of T cells directed against the infected cells. Human T-cell leukemia virus 1 and probably others use similar ploys. Abnormal levels of FAS receptors and resistance to FAS apoptosis in nasal polyp lymphocytes and abnormal Th2 clones of atopy are interesting in this regard. The localizing role of a staphylococcal superantigen in atopic dermatitis, and possibly in autoimmunity in nonatopic eczema and intrinsic asthma, encourage the consideration of roles for microorganisms in localization and etiology. The epidemiology and characteristics of atopic disease support the plausibility of a viral hypothesis. (CHEST 2003; 124:1968–1974)

Key words: asthma; atopy; epidemiology; etiology; viral infections

Abbreviations: HSV = herpes simplex virus; Th = T helper

There have been numerous efforts to prevent atopic disease without very substantial success. If we are really to succeed, we must know the cause of the atopic abnormality. Genetic factors fail to explain the increasing prevalence of atopy in Western countries¹ or their appearance in some undeveloped countries.^{2,3}

Atopy is more than a genetically determined tendency for excessive IgE responses. The abnormality includes self-perpetuating active production of high levels of specific IgE without requiring continued allergen exposure. T helper (Th) type 2 clones driving specific allergies are resistant to apoptosis, persist for years, and remain active, while most other

IgE responses are normal.⁴ In 1916, Cook and Vander Veer coined the term *atopy*. They recognized that the “spontaneously occurring” long-continued production of skin-sensitizing antibodies was abnormal and different from the temporary production of skin-sensitizing antibodies after giving antiserum. New understanding of the mechanisms used by viruses to immortalize their host cells makes it possible to theorize that a viral agent could immortalize the Th2 clones driving specific atopies.

Like atopy, herpes simplex virus (HSV) type 1 is a good example of a disease passed mainly by an affected parent in infancy and carried with recurrences for years while the majority of adults are resistant or have immunity without having had a recognizable primary infection or recurrences. It is interesting that mouse (or human) Th2 memory cells can be infected by HSV1. The virus does not multiply in Th2 cells, but the infected cells become FAS-resistant while causing FAS-mediated “fratricide” of the T cells directed against them.⁵ The infected Th2 cells become immortal instead of undergoing normal apoptosis. Both the Th2 clones

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driving atopic inflammation in asthma and the majority of lymphocytes found in nasal polyps show abnormalities in apoptosis.⁶⁻⁸ Th2 clones responsible for specific atopies have been followed for at least 6 years and maintain their characteristics.

Any relationship between atopy and HSV1 would have been noticed, and, since infants with eczema are susceptible to secondary infection with HSV1 they are not immune. Another virus defending infected T cells by fratricide is human T-cell leukemia virus type 1.⁹ It also depends on genes on the long arm of chromosome 5, which are reminiscent of genes with a role in atopy.¹⁰ Human T-cell leukemia virus type 1 also would have been recognized if there were a relationship to atopy, but these are probably not the only viruses using similar ploys, and these are not the only ploys that viruses use to avoid host immunity.

EPIDEMIOLOGIC FINDINGS SUGGESTING TRANSMISSIBILITY

The family pattern of atopy has led to the assumption that atopy is primarily a genetic predisposition. Infectious diseases to which the very young are most susceptible also have a family pattern. As in atopy, some sporadic cases develop outside the family situation. That genes play a part in susceptibility is not incompatible with the kinds of viruses that could be responsible for atopy. The presence of atopy rates as high as 40% among individuals of various races in places like Australia suggests that if a virus is involved, genetic permissiveness must be common.

The greatest risk for atopy in infancy and young childhood is asthma or atopic disease in first-degree relatives, especially in an asthmatic mother. At least 80% of childhood asthma and all allergic rhinitis is atopic, so atopy can be assumed for most cases of asthma in the Tucson Children's Respiratory Study.¹¹ In that study, the risk stemming from maternal asthma was 44.2% compared with the risk from paternal asthma (31.4%; $p > 0.05$). Allergic rhinitis in either parent was a risk factor for asthma in the child, but when analysis was confined to children without asthmatic parents, only allergic rhinitis in the mother remained a significant risk factor for asthma in the child. If the disease were transmissible, the more prominent role of the mother could be related to the relatively few cases developing *in utero* and to her role in child care. These authors also found an increased risk with prolonged breast-feeding. For unknown reasons, there is a tendency for the form taken by atopic diseases, such as atopic eczema, allergic rhinitis, asthma, and nasal polyps, to be more common in

some families than in others.^{12,13} The family risk continues until early adulthood, but for new cases developing after age 25 years the presence of parental atopy loses most of its significance.¹⁴ This suggests that by then most children of an affected family have developed symptoms, have become immune, or lacked genetic susceptibility.

Most strong and multiple atopies begin in young children and somewhat fewer begin in later childhood. Scandinavian studies of birch pollen sensitivity suggest that around 6 weeks of age is a particularly susceptible period.¹⁵ Only about one quarter of all cases develop in adulthood, and many of these have a negative family history.¹⁴ In patients developing atopy in adulthood, the number of allergies is usually just one or two. Typical are military personnel developing their first and only allergy to mountain cedar while training in the southwestern United States.¹⁶ This and the susceptibility to multiple sensitivities in early childhood suggest that a clone or clones actively responding to the specific allergies were required for susceptibility. This is a requirement for some viruses. In old age, there are no scientifically collected data, but all allergists occasionally see hay fever with positive skin test results develop for the first time in patients > 70 years of age. The usual explanation is that they have met new allergens or have reached the personal threshold required. However, in the eastern United States this often can be ragweed hay fever in patients who have lived in high ragweed pollen areas all of their lives. It is also possible that a causative agent has entered the picture.

Another epidemiologic finding is that older children in large families are most at risk.^{17,18} Also, the risk is decreased for children who are placed in group child care as young infants.¹⁹ Children in more affluent and less crowded housing are also at greater risk for atopy.²⁰ Similar epidemiology in individuals with paralytic poliomyelitis is ascribed to early immunity resulting from small doses of virus immunizing children in group situations. In patients with type 1 diabetes and childhood leukemia, such findings have been considered supportive of infection theories. In patients with atopy, it has prompted the idea that modern children experience fewer infections than those of past generations and fail to fully develop the immune system. Many studies find a lower incidence of atopy in rural areas than in urban areas. Endotoxins or the bacteria of pets, farm animals, raw milk, or lactobacillus have been suggested as causes of "maturation of the immune system," but the data are conflicting.²¹ Although the bacterial flora can be different, the existence of more children in preschool and many more vaccinations make it doubtful that the immune systems of con-

temporary children have much less exposure than those of children in previous generations. Social factors like rural isolation and sexual conservatism also could reduce the transmission of an agent that, like some herpes viruses, require very close contact, for example with saliva or semen, to produce illness rather than only immunity.

One situation in which the number of cases of atopic disease increases, in both children and adults, is when people from less affected populations move to places where the disease is very common. Within a generation, the higher rates of disease of persons in the host country develop in the newcomers. This was seen in England after World War II when workers from British colonies came to work in the factories of Birmingham,²² in foreign students at the University of Michigan,²³ and most recently in Chinese immigrants in Australia²⁴ and Ethiopian Jews moving to Israel. About 80% of the new cases were people without the disease in their families. This observation is usually ascribed to meeting new allergens or reaching a personal threshold of exposure to common allergens like grass pollen. However, at least in childhood, there is good evidence that susceptibility depends more on whatever causes the Th2 abnormality than on any particular allergen exposures.²⁵ Other possible explanations for the experience of individuals moving to a new geographic area have been that they leave behind protective parasites and move to more sanitary conditions. However, the protective effect of parasites can be doubted because there are populations, such as the children of the Maldive Islands, where parasites and increasing atopic asthma existed.²⁶ Interestingly, in this case the increasing commonness of asthma followed some years after a British air base was established on the island. Increased sanitation also has been blamed for increased atopy, but the susceptibility of adults who move seems not to fit the hygiene hypothesis explanation.

An exception to the high incidence of atopic disease in children was seen in the Fore people of New Guinea, where atopic asthma first appeared in 7.3% of adults but only 0.6% of children. The earliest cases were in adults who had returned to the villages after developing asthma while in the European-influenced city. Still, the few affected children belonged to affected adults.² There were two households with an affected child in which both parents had developed symptoms within a year of one another. The development of cases first among adults, with eventual spread mainly from affected parents to their offspring, suggests transmission by adult activities at the beginning of this community's asthma experience. A later survey of the regional administrative town of Goroka,²⁷ adjacent to the Fore area

that originally had been affected, found that, except for asthma in the child of an affected family, the other 10 cases were in adults who had previously worked or lived in the Fore area. Dust mites were blamed and were found in higher numbers in the dwellings of asthmatic patients. It seems unlikely that this would account for the almost total sparing of children in the early stages of the community's asthma experience. Infants must surely have shared the maternal environment. The disease seems to have come to the villages with the affected adults.

A similar experience has been reported in Africa. In 1971, a Xerosa village group had no asthma, but Xerosa students being educated in Cape Town had developed asthma.³ This village has seen an "explosive" increase in cases of asthma.²⁸ It seems probable that asthma has been brought from the city to the village area.

The prevalence of asthma has increased in inner city black and Hispanic populations in cities in both the eastern and western United States. In the 1960s, studies in Baltimore and a study in the southwestern United States, black and Hispanic children had lower rates of asthma than did whites. Exposure to cockroaches, more moist and airtight apartments, and more time spent indoors have been suggested as possible causes. Cockroaches are an old plague in inner city apartments, and children who live in apartments always have spent a lot of time inside at ages at which they are most susceptible to atopy and asthma. Social changes, like the drug culture and the increase in sexual contacts, in these communities since the 1960s also could have increased the transmission of a disease.

Studies conducted in East Germany and West Germany before reunification found less atopy in East Germany despite the presence of more industrial pollution.^{29,30} With reunification, atopic diseases are equalizing. Similar comparisons have been made of Poland and Sweden, with less atopic disease existing in Poland despite the presence of heavy pollution,³¹ and of Finland and Russia, with less atopy found in Russia. Lacking another explanation, "westernization" is blamed. A whole population that was observed for years by the Mayo clinic in Minnesota showed an increase in the number of subjects with asthma or hay fever only in those persons born after 1958.³² Here too, the disease could be influenced by social changes in the West, such as increased numbers of sexual partners. Atopic diseases are more common in subjects with HIV. Whether this is a matter of one disease increasing susceptibility to the other or a matter of common factors favoring transmission is worth questioning.³³

In epidemiologic studies in the late 1950s and early 1960s,¹⁴ we found a small, but significantly

increased, risk for nonallergic, family history-negative adults who married partners with hay fever or asthma (Table 1). To our knowledge, this situation never has been explored further. Because the proposition met with so much skepticism, further work was dropped. However, we had an opportunity to perform a pilot study³⁴ by joining psychiatrist colleagues in adding our detailed questionnaire when they interviewed numbers of 367 adoptive families. Adoptive parents with asthma or allergic rhinitis, especially an adoptive mother with asthma, posed a high risk for hay fever or asthma in the adoptee (mother asthma/adoptee asthma, 31%; rhinitis, 24%), which was comparable to that posed by asthma in a natural mother. Other prospective studies should be performed.

Two studies of pulmonary therapists³⁵ compared with physiotherapists and radiology technicians found that 7.1% of the pulmonary therapists with a negative personal and family history had developed asthma since beginning their profession, compared with 2.4% of those in a control group. The low, but very significantly increased, risk for pulmonary therapists and marital partners seemed to indicate substantial immunity in the adult population. Well-planned prospective studies are needed.

To sum up, there is enough circumstantial evidence to warrant performing studies that would be carried out if the idea of an infectious cause were not considered to be impossible.

THE NATURAL COURSE OF ATOPY AND THE POSSIBILITY OF IMMUNITY

In childhood, the pattern of positive skin test results often develops over a period of a few years, as though boosting may be necessary for the abnormal immortal clones to reach a clinically manifested level. The age of onset of symptoms and sometimes the localization of symptoms depend on heavy allergen exposure. For example, in an Israeli study³⁶ of pediatric patients, 72% of rural children had developed hay fever between 2 and 4 years of age compared with only 24% of urban children with hay fever.

Table 1—The Incidence of Marital Partners Affected by Hay Fever*

Variables	Rural Study	Urban Study
Man with affected spouse	11	9.8
Man with normal spouse	4.5	2.4
Woman with affected spouse	7	10
Woman with normal spouse	2	2.7

*Values given as %.

The idea that common respiratory viral infections may increase the susceptibility of individuals to atopic sensitization has not been settled because of conflicting data. Martinez³⁷ has reviewed these studies.

Whether atopic sensitization occurs as an event or over some longer period is not known. The presence of spring and fall allergies suggests a longer time period, but there is enough of a relationship between spring and fall allergens to leave this uncertain.

Once the pattern of positive skin test results becomes complete, we only occasionally find new unrelated sensitivities in patients who have been observed for many years. Years ago, we followed up university students who had been seen in our clinic 15 to 25 years before to ask about their experience with new allergies after settling in various regions. Even in the geographic areas that were the most different from the Midwest, very few subjects described new allergies that were not already known from the results of our skin tests.³⁸ Most allergists only retest if there is a new story because the pattern usually remains the same for years. Even when there are new symptoms, they are more often allergies to things already identified by previous skin test results.

Experiences that look like exceptions to the uncommon presence of new allergies in people with established atopy are found in industry. Family history and previous allergies are predictive of difficulties with organic allergens but not for chemicals like toluene diisocyanates, usually not met in childhood. An example of experience with organic allergens is a study of sensitivity to laboratory animals that found that a previous allergy to cats and dogs was a risk factor for rat allergy, while pollen allergy alone was not. On the other hand, pollen allergy was a risk factor for baker's asthma.³⁹ These experiences support the concept that atopic sensitivities remain localized to certain abnormal Th2 clones with only very occasional spread to involve new clones. This suggests that immunity may prevent whatever causes the Th2 abnormality from moving to affect new clones.

THE LOCALIZATION OF ATOPIC DISEASES

Bone marrow transplantation transmits atopy to the recipient, but it takes about 9 months to reach a level at which skin test results are positive.⁴⁰ In a study of bone marrow donors⁴¹ and recipients between the ages of 14 and 47 years, two asthmatic donors gave marrow to asymptomatic sibling recipients. Both developed allergic rhinitis without asthma. Three donors with allergic rhinitis gave marrow to nonallergic recipients. One developed

asthma, and two developed mild allergic rhinitis. It is atopy that is transmitted, not the organ localization of symptoms. In one case, graft-vs-host disease may have reduced the transfer of atopy. A severe new allergy that had not been seen in the donor developed during the reconstitution of one recipient's marrow. This might suggest that susceptibility to whatever causes atopy requires the rapid expansion of responding cells (a requirement for some viruses). More studies of transplants are needed.

Common respiratory viruses cause exacerbations of asthma.⁴² Both in children and adult patients, we often obtain in the medical history an account of what the patient describes as a chest cold at the onset of asthma. Infections such as respiratory syncytial virus and parainfluenza may have a role in initiating localization in the chest, but conflicting data have caused some uncertainty.⁴³ No trace of these viruses can be found later despite continuing bronchial irritability. Holtzman and colleagues⁴⁴ have postulated a hit-and-run scenario for the long-term changes caused by these viruses.

In about 90% of eczema cases *Staphylococcus aureus* can be grown from the lesions. Staphylococcal superantigen up-regulates a cutaneous localizing antigen on Th2 cells.⁴⁵ High-affinity IgE receptors are up-regulated on antigen-presenting cells and mast cells. Specific antistaphylococcal IgE develops, and antibiotics cause improvement. No equivalent homing device has been recognized for the respiratory tract, but there is some evidence that staphylococci can have pulmonary effects.⁴⁶

Atopic respiratory symptoms may develop soon after positive skin test results occur or not for several years, as if some other event may be required for localization of the disease. A follow-up of university students tested and questioned as freshmen, and questioned again about symptoms 4 years later as seniors, gives a good example showing the variable latency period between the development of positive skin test results and the development of symptoms. Very occasionally, symptoms develop before positive skin test results occur, perhaps because of local IgE production. In the same university student population that was observed 23 years after their original testing as freshmen, both hay fever and strongly positive skin test results raised the rate of future asthma to about 10% compared with 3% in alumnae with neither previous hay fever nor positive skin test results.⁴⁷ Thus, beyond childhood the risk for new asthma was small even for the atopic population. Although the 10% occurrence of asthma in those with previous hay fever or positive skin tests seems a low risk, half of those who developed asthma had previous atopy or hay fever. Thus, atopy remained a substantial risk factor.

That asthma represents a persistent localized disease in the lung has been proven by experiences with lung transplantation. Corris and Dark⁴⁸ have reported transplanting two lungs from subjects with very mild asthma into patients with cystic fibrosis. Although the conditions of the patients improved, compared with their life-threatening cystic fibrosis, both developed more severe asthma than the donor. The same authors reported transplanting normal lungs into two patients with life-threatening asthma with no recurrence of the asthma. More recently (P.A. Corris, MD; personal communication; December 1997), they have transplanted a single normal lung into a severely asthmatic teenager who then continued to have typical asthma in one lung, while the transplanted lung remained free of asthma. This patient had positive skin test results. Apparently, whatever mechanism in the asthmatic lung selects the inflammatory cells that are responsible for asthma has failed to move to involve the transplanted lung.

SIMILAR DISEASES WITHOUT ATOPY

Whether the same disease causes infantile eczema without positive skin test results or intrinsic asthma with its nasal equivalent is not entirely certain. There are a great many similarities.

Where allergic asthma is common, intrinsic asthma is common and visa versa. An example is the high rate of asthma in the isolated community on the island of Tristan da Cunha where 74% of asthma cases were extrinsic and 26% were intrinsic.⁴⁹ The intrinsic asthma picture is clouded by a fairly large group of patients with earlier symptoms of atopy who become more chronically asthmatic, develop sinus disease, and behave more and more like persons in the intrinsic group. The onset of purely intrinsic asthma in adults can be quite sudden, and it is often chronic and severe from the start. Women in their childbearing years are particularly susceptible, and lung autoantibodies have been found. It joins the list of diseases involving autoantibodies that develop more commonly in women, with the immunologic changes of pregnancy and the postpartum period. Autoantibodies also have been found in persons with infantile eczema without atopy.

One curious finding in patients with aspirin-sensitive asthma, which is usually intrinsic, is that the herpes drug acyclovir, an inhibitor of DNA polymerase, reduces bronchial inflammation and protects against a reaction to aspirin.⁵⁰ Does the antiviral effect have anything to do with this or do other pharmacologic effects cause this phenomenon?

The chronic respiratory infection caused by vari-

ous organisms such as mycoplasma, Chlamydia, and latent viruses such as adenovirus probably contribute to the severity and chronic nature of asthma in some cases. The treatment of sinusitis sometimes is followed by sustained improvement of asthma.⁵¹ Before the use of antibiotics, surgical treatment of sinusitis was the only measure that sometimes caused a lasting improvement in persons with intrinsic asthma. Cooke⁵² recruited an otolaryngologist, and together they followed up a great number of asthmatic patients who had been treated for sinus disease. They concluded that for long-term improvement it was important to treat all the affected sinuses, not only the ones affected the most. Cooke also reported that in some cases the injection of bacterial vaccines, either autologous or a mixture (*ie*, staphylococci, *Streptococcus pneumoniae*, *Neisseria catarrhalis*, and streptococci), could cause a delayed asthmatic response a few hours later. In the 1960s, Hampton et al⁵³ also performed many experiments and skin testing, and administered inhaled bacterial extracts. He too described delayed positive skin test results and delayed asthma attacks in some subjects inhaling extracts of *N catarrhalis*.

The failure of bacterial vaccines in double-blind tests seemed to lay to rest the idea that bacteria had any significance as allergens in patients with asthma, and no other role has been imagined. Interest has been rekindled because of the role of staphylococcal superantigens in eczema and the function of DNA containing cytosine and guanosine motifs as an adjuvant. Determining the various roles for bacteria and viruses indicates the need for renewed study.

CONCLUSIONS

Much in the epidemiology of atopic diseases suggests a transmissible cause. Viruses can cause long-term changes in the survival of specific Th2 clones and could result in the abnormalities that are characteristic of atopy. This should be understandable enough to make it no longer impossible to gain support for studies in this vein. With good evidence that most adults have become immune, there is hope for more effective prevention if a cause can be found.

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