

## Brave new allergic world

The prevalence of allergic diseases seems to be increasing unabated with no end in sight. The dramatic rise, as seen by the doubling of children diagnosed with atopy in the past two to three decades, suggests environmental factors are the main driver of the epidemic. With objective measurements clearly showing that allergic diseases escalate fastest in developed countries, this malady seems to be a price we are paying for our modern lifestyle. But which environmental concerns or man-made interventions induce or exacerbate allergies and how do they operate? Starting with this issue and spanning 2005, *Nature Immunology* will explore some of the factors that affect asthma and allergies in a series of commentaries by experts in the field. These commentaries aim to stimulate discussion on a disease for which the etiology remains vague and the cure continues to be a distant promise.

The 'hygiene hypothesis' was first proposed in the late 1980s to explain the increase in asthma in developed countries. This hypothesis asserts that the cleaner environment from modernization decreases the exposure of the immune system to infectious agents, resulting in an increased incidence of allergy. The mechanism underlying this hypothesis originally suggested that infectious agents induce a 'type 1' T helper cell response that dampens the 'type 2' response commonly associated with allergies. Thus, decreases in infectious diseases promote 'type 2' responses and, with them, allergic diseases. Mounting data, however, indicate that this hypothesis may be an oversimplification and that allergic diseases such as asthma also involve an inflammatory component inducible by a myriad of pathogenic agents. Current theory invokes additional participants including regulatory T cells, which are activated by pathogens in less hygienic conditions and may thus provide a broader control mechanism such as suppression of asthma-causing inflammatory mediators. Along with genetically determined responses, these environment-induced reactions provide an explanation for the triggers of allergic diseases, most commonly manifested as asthma and food allergies.

The increase in allergic diseases is unquestionably a small trade-off for the decrease in morbidity and mortality due to improved sanitation. While we continue to dissect the interplay between improved hygiene and increased incidence of allergy, there is also considerable momentum for understanding potential triggers of allergy for which control may be more tangible and immediate. Pollution, obesity and genetically modified food are some of the factors that will be explored in this series of commentaries. Our understanding of the environment-immune system interface may be assisted by insights gleaned from studying the more 'traditional' inhalant allergens such as pollens, dust mites and cat dander, a topic that will also be discussed later this year.

Saxon and Diaz-Sanchez launch this discussion series by examining the relationship between pollution and asthma. Although epidemiological studies may not support the idea of pollution as the sole cause of the asthma epidemic, there is ample evidence that corroborates involve-

ment of pollution in triggering and exacerbating asthma. As discussed in this article, pollution such as diesel exhaust particles induces oxidative stress, which aggravates the immune response initiated by other allergens. People might also be genetically susceptible to the effects of these pollutants because of their innate inability to cope with reactive oxidants induced by diesel particulates. Thus, in addition to providing support and pressure for legislation to decrease pollution, this understanding provides hope for the rational design of therapies to treat asthmatics living in areas with unacceptable amounts of pollution.

Another dangerous health trend that has reached epidemic proportions in developed nations, especially the US, is obesity. Obesity results in considerable morbidity, and research is now attempting to determine whether and how asthma and obesity may be linked. Epidemiological studies indicate the two diseases are linked, paving the way for further research into plausible mechanical, immune and genetic mechanisms. Although allergy is not commonly associated with obesity-related morbidity, probably because other, more life-threatening diseases such as heart failure and type 2 diabetes assume priority, the suffering, health-care cost and decreased productivity related to asthma in these people may be substantial.

A chief concern of human interventions that may influence our health is the effect of genetically modified food. Can food that contains altered genetic components cause allergy? Such concerns are topics of ongoing debates by scientists and various interest groups. Possible scenarios include the incorporation of allergens such as those from peanuts into crops or the introduction of new allergens because of the genetic modifications. Knowing these risks will allow us to institute appropriate precautions and risk assessments. In contrast, ongoing studies are attempting to 'engineer' allergens, such as those from peanuts, out of plants to circumvent their allergic effects. Strict and careful testing of genetically modified crops is warranted, but the discussion on their use must be approached with an open mind.

Much of our understanding of how the immune system responds to environmental allergens comes from studies of inhalant antigens, including those derived from pollens, house dust mites and cats. Although these allergens have a common nasal route of entry and interact with the mucosal surface of the lungs, the responses they induce are not identical. These discrepancies may reflect unique characteristics of our exposure to these allergens as evidently represented by these perennial, seasonal and incidental antigens. Such nuances in allergic responses highlight the complexities in understanding this multifactorial and multidimensional disease.

Allergic diseases are a major public health concern. To successfully manage this broad range of medical conditions ranging from asthma and eczema to food allergy, it is important to identify all the potential instigating factors. Deciphering how the immune system responds to these individual factors will build collective knowledge to help fight this new world epidemic.

