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Learn to love those allergies

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HIGHLIGHT: From pollen to peanuts, we humans are an allergic lot. So could it be that allergies serve an evolutionary purpose? And why do we always think they are such a bad thing? Time for some better answers, say Noah Palm and Ruslan Medzhitov

"Someone allergic to flowers may show a reaction to a mere picture of a flower"

MOST of us seem to be allergic to something these days. For many, the itching, sneezing, coughing, dry eyes and runny nose triggered by allergies are a predictable seasonal event, and for some these symptoms are a near-constant annoyance. About 1 in 50 people globally are seriously affected, with allergies to such things as bee stings, peanuts or penicillin triggering a potentially lethal "whole body" allergic reaction called anaphylaxis.

Despite the prevalence and dramatic effects of allergy, the allergic response remains one of the most enigmatic features of our immune system. We still do not have good answers to such questions as: what determines which substances are potentially allergenic and which are not? What makes some people allergic to a particular substance while others remain unaffected? And the big one –; why does the allergic response exist at all? What possible evolutionary purpose could it serve?

The study of allergy is a relatively young field, with the term "allergy" coined early in the 20th century by paediatricians Clemens von Pirquet and Bela Schick. "Anaphylaxis" was put on the map around the same time by physiologist Charles Richet. The work won him the 1913 Nobel prize for physiology or medicine. For many years thereafter, studies of the allergic response focused on allergy as a sickness or disorder. Partly because of this, very few scientists asked why this severe and potentially dangerous type of immune response would exist in the first place, let alone why the immune system would respond in this way to the seemingly harmless substances that often act as allergens.

The answer appeared to come from studies of immune responses to multicellular eukaryotic parasites in the 1960s. Researchers found that many of the critical players in the allergic response also help to defend the body against parasitic worms called helminths. Helminth infections lead to the production of high levels of immunoglobulin E (IgE), the antibody responsible for allergic responses. Since then, the prevailing wisdom has been that allergies result from a mistargeting of immune responses that evolved to defend against parasitic worms. In other words, allergies are the price we pay for

effective defence against multicellular parasites.

Now, though, a few scientists have started to question whether this hypothesis is sufficient to explain even the most basic features of the allergic response. For example, while helminth infections do induce IgE antibodies, IgE itself is not critical for getting rid of most of these infections –; that is down to the type 2 cytokines IL-4, 5 and 13. So the cardinal feature and molecular mediator of the allergic response appears to be a bit player in defending us against helminths.

One alternative theory to account for the allergic response was proposed in 1991 by Margie Profet at the University of California, Berkeley. She speculated that the allergic response evolved to enable the immune system to protect us against environmental toxins, such as the noxious phytochemicals found in plants, and venoms. Indeed, while allergens are considered by most to be harmless, a closer look reveals that many are in fact toxins, an obvious example being venom. So, rather than viewing allergic response as a mistargeted response to helminths, it can be seen as an intentional and generally beneficial response that protects against noxious substances in the environment.

But the toxin hypothesis remains largely ignored by the biomedical community. We think this is wrong-headed for four reasons. First, allergic symptoms, including runny nose, tears, sneezing, vomiting and diarrhoea, can be understood as an attempt by the body to get rid of an allergen. Toxic substances found in the food and air elicit similar expulsive reactions in everyone.

Second, allergic responses are immediate, occurring within seconds or minutes of exposure. This rapid response is more consistent with defence against toxins, which can cause immediate damage, compared with helminth infection, which takes some time to develop. Moreover, affected people often become hypersensitive to allergens, reacting to minute amounts in the environment. Given that even immune responses to bacterial and viral pathogens fail to reach this level of sensitivity, it doesn't make much sense to have this level of sensitivity to helminths.

Our final objection concerns one of the most puzzling features of the allergic response –; the diversity of substances that act as allergens. This can be anything from small molecules found in penicillin and the urushiol chemical in poison ivy, to the complex mixtures of proteins in animal venoms, or components of common foods such as peanuts. While the helminth hypothesis fails to explain what these substances share that makes them allergenic, the toxin hypothesis predicts that what these allergens may share is their ability to cause harm.

But even if we accept that allergic processes evolved to protect their host from noxious substances in the environment, this doesn't immediately explain why the body would sometimes mount such a severe, potentially lethal anaphylactic response to even trace amounts of an allergen in the environment. Here again, though, we think we can show that this unique feature of the allergic response might also have a very useful purpose, particularly for our ancestors.

As anyone who suffers from allergies knows, the best way to treat an allergy is to leave the environment in which it flares up and avoid that environment in future. So if many allergens are toxic, then the allergic response could be interpreted as conditioning people to avoid environments that contain potentially harmful toxins.

But in rare cases, allergies themselves can also become "conditioned" via the nervous system. For example, someone allergic to flowers may reach a point where they show an allergic reaction to a mere picture of a flower. This makes sense of a sort because, unlike the sources of microbial pathogens, the sources of allergens are often readily identifiable by sight, which may make avoidance the key strategy for minimising exposure.

Most people who suffer from allergies will find it hard to believe the allergic response can be beneficial. But the benefit of the reaction may be akin to the benefit of pain: pain is

unpleasant, but its unpleasantness helps us avoid environmental agents that damage our bodies and, therefore, makes us more likely to survive. Likewise, allergies may have evolved to feel unpleasant to encourage us to avoid environments, animals, or foods that contain substances that may harm us. n

Don't let pollen ruin your croquet: in the 1980s, Hincherton helmets came to the rescue

Profile

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