Parasites and the hygiene hypothesis

Author: Dr. Kristen Kerksiek
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In the 20th century, quality of life in developed countries was dramatically improved by reducing bacterial, viral and parasitic infections, the result of combined efforts of improved sanitation, hygiene, vaccines and antimicrobials. However, the last 50 years have seen startling increases in the frequencies of allergy and other atopies. At the same time, the frequency of autoimmune diseases seems to be on the rise. Is there a connection? Does modern and seemingly healthy living in itself represent a public – and, of course, for many individuals a very personal – health problem?

Wash hands! But not too often?

Naturally a great deal has changed. Automobiles have made us more mobile (and yet more sedentary), and fast food has changed the way we eat, contributing to a huge increase in obesity. New materials have made life easier but may expose us to potentially poisonous chemicals: flame retardants, dioxins, pesticides - environmental toxins that some scientists believe can wreak havoc with our immune systems. Another theory is that our increasing attention to – and sometimes obsession with – cleanliness has backfired, robbing our immune system of the practice to function properly.

Practice makes perfect or The devil finds work for idle hands

In 1989, David Strachan published the observation that first-born children and those born into small families are more likely to be affected by hay fever (BMJ 299: 1259–1260). He suggested that the exposure of young children to infectious agents – those, for example, brought into the home by older children – can help to prevent allergic rhinitis. It was the beginning of the hygiene hypothesis, the idea that an immune system that hasn't had the chance to learn the difference between what is dangerous and innocuous (or that is just plain bored because it has nothing to do) may go haywire and attack innocuous foreign substances (allergy) or even the body's own tissues (autoimmunity)

The hygiene hypothesis: Decreased exposure to infectious agents early in life increases susceptibility to allergy (and perhaps autoimmune diseases) by limiting immune system development.

In the nearly 20 years that have passed, the hygiene theory has been tested and tweaked, expanded and extended. Besides our friendly neighborhood viruses and bacteria, gut flora and parasites are believed to play a role in training the immune system. And in addition to allergic disorders, autoimmune diseases have been encompassed by some researchers into the hygiene

hypothesis; in fact, some 20 years before Strachan, it had been suggested by Leibowitz *et al.* that the risk of multiple sclerosis is increased among persons who live under highly sanitary conditions as a child (J. Neurol. Neurosurg. Psychiatry 1966 29: 60–68).

Epidemiology supports the hygiene hypothesis. For example,

- Many allergic and autoimmune diseases are more common in the industrialized world, and an increase in immunological disorders is seen in developing countries as they become more prosperous (and, presumably, cleaner).
- Studies following the German reunification showed that although East German cities were more polluted, their residents suffered less from allergy and hay fever.
- Children who grow up on German, Swiss and Austrian farms, exposed to animals, stalls and unpasteurized milk from a young age, develop fewer allergies than non-farm children from the same region.

Nevertheless the hygiene hypothesis remains just that - a hypothesis – and the mechanism by which infections modulate the immune system is still controversial.

Immunology of the hygiene hypothesis: The importance of being balanced

The key players, $CD4^+$ T helper (Th) cells:

Th1:
Effector cytokines: IFN- γ, TNF-β
Effector function: stimulation of cellular immunity (macrophage killing, $CD8^+$ T cell proliferation in response to intracellular bacteria and viruses)
Pathological effects: autoimmunity (multiple sclerosis, insulin-dependent diabetes mellitus, Crohn's disease) and cell-mediated allergy (contact dermatitis)

Th2:
Effector cytokines: IL-4, IL-5, IL-13
Effector function: stimulation of humoral immunity (B cell proliferation, antibody production, class switching in response to extracellular pathogens)
Pathological effects: type 1 hypersensitivity (IgE-mediated allergy, asthma) and autoimmunity (lupus, atopic dermatitis, ulcerative colitis)

The two subsets regulate each other: expansion of Th1 cells suppresses Th2 cells and vice versa. For many years it was believed that the overzealous Th2 responses that cause allergy result from a failure to activate Th1 (via viral and bacterial infections) and "redirect" the immune system. However, this fits poorly with the rise in Th1-driven autoimmunity.

Recent studies suggest that immune regulatory mechanisms induced by our microbial environment control and fine-tune antigen-driven Th1 and Th2 responses. Regulatory T cells (Treg) are thought to be responsible for this "immune management".

Treg:
Effector cytokines: IL-10, TGF-β
Effector function: immunosuppression (shutting down immune responses after pathogen clearance, controlling immune responses that might lead to unnecessary inflammation)
Pathological effects: none known

Another T helper subset has recently been implicated in autoimmune diseases:

Th17:
Effector cytokines: IL-17, IL-21, IL-22
Effector function: defense against bacteria at external/internal interfaces (skin, gut mucosa) by secreting defensins, recruiting neutrophils (inflammation)
Pathological effects: autoimmunity (Crohn's disease, ulcerative colitis, psoriasis, multiple sclerosis)

The good, the bad and the ugly: The hygiene hypothesis and helminths

Adult male of *Enterobiasis vermicularis* (pinworm) © CDC

Colonization of humans with worms was nearly universal until the early 20th century. While helminth infection remains a common and very serious problem in many tropical developing countries (see Perspective October 2008), even minor parasites such as *Enterobius vermicularis* (pinworms) have lost their foothold in developed countries over the past decades.

By definition, parasites are harmful to their hosts, but the relationship between humans and their uninvited guests varies widely, from deadly to benign. Over thousands of years, parasites have generally evolved to cause low-level chronic infections, as they benefit from a long-living host. Humans have co-evolved, selected on the basis of their ability to survive infections. This evolutionary battle has been compared to tug-of-war. So what happens when one team lets go of the rope? What happens when the parasites are suddenly gone?

The immunosuppressive qualities of helminths are well known. Worms subvert the immune system for their own benefit, but perhaps over the course of evolution, humans have also come to rely on the suppressive qualities of their nearly constant live-ins to help regulate their own immune systems.

Reports of an inverse correlation between helminth infection and allergy date back to the early 1970s (before the dawn of the hygiene hypothesis), and a host of epidemiological studies support a role for parasites in immune regulation:

- Chronic infection with either intestinal worms or schistosomes is associated with lower atopic reactivity in individuals living in parts of Africa and Central/South America where helminth infections are still prevalent.
- Antihelminthic therapy results in a rise in allergic reactivity.
- Increased levels of the immunosuppressive cytokine IL-10 correspond with decreased hypersensitivity in parasite-infected children.

Infection with helminths has also proven protective against autoimmunity in animal models of type 1 diabetes, multiple sclerosis, inflammatory bowel disease, Crohn's disease, colitis and collagen-induced arthritis.

In evolutionary terms, the disappearance of helminths (and the immunomodulating substances they produce) from populations living in the developing world is a sudden development. This "dropping of the rope" in the constant battle between host and parasite just may be a critical factor in the dramatic increases in allergy and autoimmunity observed over the last decades. Worms are very often "bad" and can certainly be described as "ugly"… but sometimes they may be good for their human hosts. Nevertheless, whether nematode, tapeworm or fluke, most of us would not willingly invite parasites back in to share our living space. For individuals with severe autoimmune diseases, however, the decision might be different.

Pass the worms, please

Helminthic therapy is not what you might think. Given the burden of morbidity and mortality caused by helminth infections, there is a great deal of scientific effort focused on development of drugs that can expel worms from the body. These are antihelminthics. In helminthic therapy (or worm therapy) individuals are deliberately infested with a worm or the ova of a worm.

Ready for a worm cocktail? *Trichuris-suis* Ova used in worm therapy

Why?!?! Well, the data indicate that helminths interact with both the innate and adaptive immune systems of the host to stimulate immune regulatory circuitry and to dampen effector pathways that drive rogue inflammatory responses. And many patients suffering from allergic or autoimmune disorders are desperate for therapy that works.

Take, for example, inflammatory bowel disease (IBD). IBD includes ulcerative colitis and Crohn's disease, which both cause diarrhea, abdominal pain and bleeding. An estimated 2 million people in the USA and Europe have Crohn's disease or ulcerative colitis, which usually begins during the second to third decade of life. There is no cure, and treatment usually involves a cocktail of medications to eliminate infection and reduce inflammation. However, both conventional drugs and biological alternatives (i.e. anti-TNF antibodies) can have nasty – and even fatal - side effects. And they don't always work.

Enter worms. For treatment of IBD, *Trichuris suis* (pig whipworm) has taken center stage. *T. suis* doesn't cause disease or reproduce in humans and can be eliminated rapidly with anti-

helminthics if needed. *T. suis* ova (TSO) must be administered every 1–3 weeks, as the worms have a short lifespan. No side effects have been reported, and the results are impressive.

TSO therapy has been used to effectively treat both Crohn's disease and ulcerative colitis:

Patients with active Crohn's disease (n=29) received 2500 *T. suis* ova every 3 weeks for 24 weeks. At the end of the study period, 79.3% of patients responded to the treatment, with 72.4% remission. (Summers, R.W. et al. *Trichuris suis* therapy in Crohn's disease. (2005) Gut 54: 87–90).

In a double blind placebo-controlled trial, 54 patients with active ulcerative colitis received either placebo or 2500 *T. suis* ova every 2 weeks for 12 weeks. Of the 30 patients that received ova treatment, 43% reported improved disease activity compared to 16.7% of patients that took the placebo. Improvement was seen after 6 weeks in patients with high disease activity, while those with mild disease were not as responsive to the treatment. (Summers, R.W. et al. *Trichuris suis* therapy for active ulcerative colitis a randomized controlled trial (2005) Gastroenterology 128: 825–832).

In treatment of more than 110 patients (some for >4 years), no side effects or complications have been reported, and in many patients remission has been successfully maintained. (reported in "Worms on Trial", see additional reading below).

The company Ovamed GmbH (Barsbüttel, Germany) produces *T. suis* ova for therapeutic use and is in the process of applying for drug approval.

The other star on the worm therapy scene is hookworm (*Necator americanus*). Like TSO, hookworm makes a suitable therapeutic agent because it doesn't cause disease at therapeutic doses, doesn't multiply (allowing dose control) and can be easily eliminated. Its advantage over TSO is its lifespan (estimated at 5 years), which eases the therapeutic schedule a bit, but side effects appear to be more common. Hookworm may be promising for therapy of IBD as well as asthma and inflammatory diseases, but the studies are not as advanced as for TSO.

The human ecosystem

We are not alone with our genetic material. We live in symbiosis with a complex community of bacteria in our gut, and we miss them when they're gone. Our intestine lets us know. And for thousands of years we have lived with parasites, many of which cause entirely benign – even asymptomatic – infections. Do we miss them when they're gone? Removing organisms that have become part of our human "ecosystem", that have co-evolved to contribute to our homeostatic welfare, could send the system into chaos. Research indicates that this may be a significant contributing factor in the dramatic rise in allergic and autoimmune disorders in our "clean" developed world.

This knowledge has spurred research teams to start developing worm-based therapies, to look for parasite-derived regulatory factors and even to study worm "vaccines" that might help bring a dysregulated immune system back into balance. And it tells us that a little dirt – and even a few worms – are really not such a bad thing.

Additional reading:

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