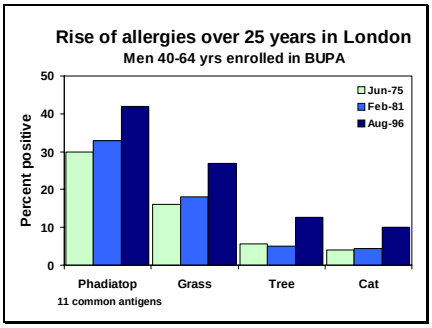
Slide 1

{Note: this lecture is based on many sources, some of which are quoted directly alongside the slides. Ask for specific sources if you need them: dyec@who.int.} In 1519, the year that Thomas Gresham was born, Martin Luther was drafting his 41 proposition for reform of the Roman Catholic Church, completed in June 1520. In 1521, Holy Roman Emperor Charles V summoned Luther to the Diet of Worms to ask if he would retract, following the condemnation from Pope Leo X. He refused. Luther was thus formally declared an outlaw in the Edict of Worms, and the battle lines of the Reformation were duly hardened. But this is really a physic lecture, and nothing to do with Imperial assemblies (diets) in the Rhineland city of Worms, home of the (in)famous Liebfraumilch. My "diet of worms" is actually about eating worms. The central idea of this lecture is that while too many worms are bad for your health, too few can be harmful as well. For human immune systems that have evolved to fight infection and other contaminants, too little infection in today's super-clean environment could be the cause of allergic and autoimmune diseases. Cleanliness may be next to godliness, but it might also leave you with hay fever (painting Anton von Werner).

Slide 2

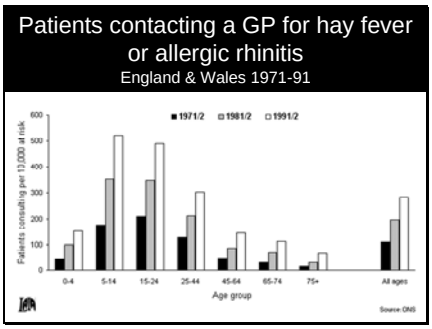
I'll start with the group of allergic conditions called atopy, or atopic disorders. Atopy is allergic hypersensitivity going beyond parts of the body in direct contact with the allergen. These are more or less severe diseases of skin, membranes and airways, including asthma, hay fever, conjuncitivitis and eczema. Allergic conjunctivitis is inflammation of the conjunctiva, the membrane covering the white part of the eye. Although allergens differ between patients, the most common cause/condition is hay fever. Symptoms consist of eye redness, excess fluid around the conjunctiva, itching and increased production of tears. If this is combined with rhinitis (irritation and itching of the nose), the condition is called allergic rhinoconjunctivitis.

Slide 3



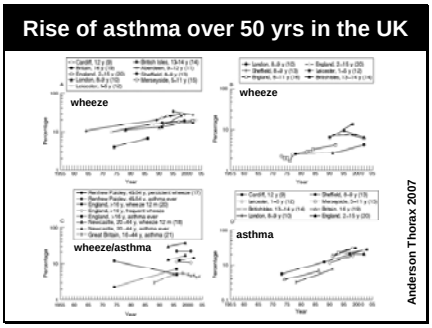
The worrying observation is that these allergies are on the increase worldwide. Starting with London (and working outwards to the rest of the world) this picture shows the increase in allergic responses of men aged 40-64 years positive to Phadiatop (a cocktail of 11 common antigens used as a marker of atopy) and with specific antibody responses (IgE) to three inhaled allergens (grass, tree, cat), over 3 time periods covering more than 20 years (BMJ 330, 1187, 2005).

Slide 4



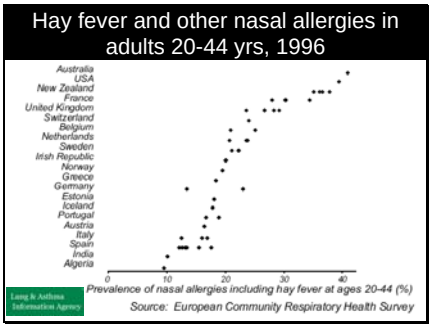
More widely, across the whole of England and Wales, this is the increase in numbers of patients contacting their GPs complaining of hay fever or allergic rhinitis. There were pronounced increases in all age groups over the period 1971, 1981 and 1991.

Slide 5



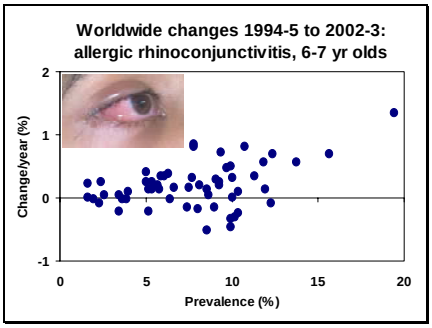
And these are trends in indicators of asthma from many population surveys and routine health statistics in the UK, reviewed from 1955 to 2004. (A) Trends in the period prevalence of any recent wheeze in children. (B) Trends in the prevalence of frequent or persistent recent wheeze in children. (C) Trends in the period prevalence of wheeze and of a diagnosis of asthma ever in adults. (D) Trends in the prevalence of a diagnosis of asthma ever in children. The prevalence of a life-time diagnosis of asthma increased in all age groups, and by as much as 2-3 fold in children. But the trend has flattened or even fallen since the mid 1990s. The earlier increase in asthma matches other evidence for increases in atopic eczema, allergic rhinoconjunctivitis and atopic sensitivity.

Slide 6



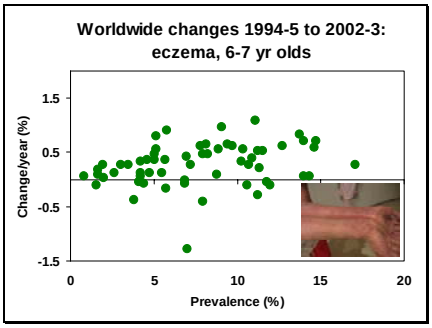
Putting the UK in the European context: hay fever is a common complaint in all age groups in all countries, but more so in adolescents and young adults, and more so English-speaking countries. The countries least affected are in eastern Europe and central Asia.

Slide 7



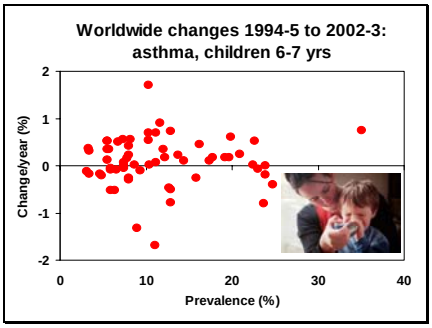
Bigger and broader surveys show the increase in allergies worldwide. About 200,000 children aged 6–7 years were studied at 66 centres in 37 countries. Most centres showed an increase (change >1 on vertical axis) in at least one disorder, here conjunctivitis, with increases being twice as common as decreases, and especially common among 6-7 year-olds (Asher Lancet 2006).

Slide 8



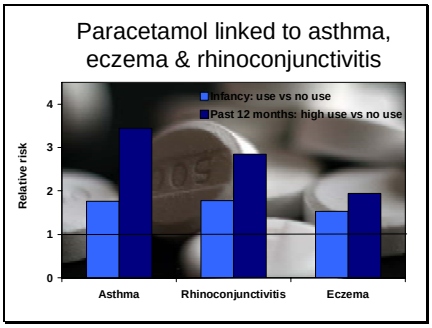
And eczema…

Slide 9



And asthma, though the increase in asthma is less marked. Asthma is declining in some areas, and behaves somewhat differently from the other atopic allergies.

Slide 10



Asthma (especially) and other allergic diseases do not have a single cause, and they are far from being fully understood. For example, use of paracetamol in the first year of life and in later childhood, is associated with risk of asthma, rhinoconjunctivitis, and eczema at age 6 to 7 years. So exposure to paracetamol might be a risk factor for the development of asthma in childhood (Beasley Lancet 2008). Air pollution is another factor in the development of asthma. But even though air pollution can worsen the clinical status of patients with asthma, it does not appear to affect the number of new asthma cases. No correlation has been established between pollution and asthma cases. Remarkably, experts attending a conference earlier this month in Berlin were still asking what is asthma, who gets it, and how should it be treated? These are rather fundamental questions (Editorial Lancet 2008).

Slide 11

Nevertheless, there appears to be a strong link between (the lack of) infection and allergy. David Strachan is credited with the proposition that allergic diseases have been prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally from the mother (Strachan BMJ 1989). This is known as the hygiene hypothesis.

Slide 12

Is infection a plausible explanation?

Is infection a plausible explanation? I'll discuss two lines of evidence: from population studies (i.e. epidemiology) and from studies of immune systems.

Slide 13

It's worth reflecting on our preoccupation that bacteria and other parasites are bad company. Handwashing is promoted as one of the most important ways of controlling the spread of infections, especially those that cause diarrhoea, vomiting and respiratory disease. We're told to wash hands after using the toilet, before eating or handling food, and after handling animals. To aid the process there was IZAL toilet paper which used to have printed on it "Now wash your hands" (why did we have to suffer IZAL?)

Slide 14

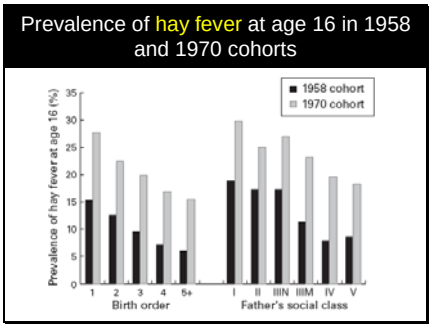
People are mostly bacteria

Humans + bacteria = "super-organisms"

Humans	
Functional cells (other than blood, neurons)	10^{12}
Bacteria (*Bacterioides*, *Clostridium*, *Escherichia*…)	
On skin	10^{12}
In mouth	10^{10}
In gut	10^{14}
	>1kg
	>1000 species
	>100 × as many genes

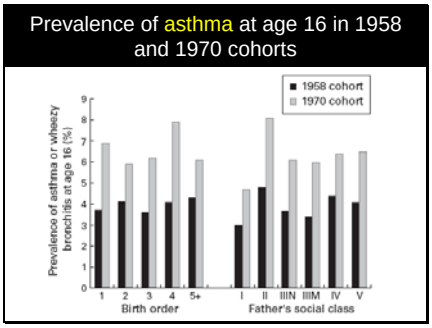
While we think of worms, bacteria and viruses as the enemy, we've been living with them and co-evolving for millions of years. In fact people are super-organisms consisting mostly of bacteria. We have about a trillion functional cells in our bodies. That's about the same as the number of bacteria on our skin. In our guts, there may be as many as 100 trillion bacteria, of 1000 species, with maybe 1000 times as many genes. The biology of our guts is bound up with the biology of these bacteria. They could make their living as parasites or as mutualists (symbionts) – they could be beneficial or they could be harmful, depending on where the opportunities and advantages lie. Most of the time we have a mutualistic relationship with species like *Bacteroides* – they help to break down food products and supply some vitamins and other nutrients that we cannot make ourselves. Occasionally *Bacteroides* get out of the intestine and into other parts of our bodies. A common outcome is an abscess, a ball of puss consisting mostly of bacteria. If the ball breaks then billions of bacteria spread throughout the body often resulting in death. Because it is clear that we have co-evolved with bacteria and other microorganisms, an obvious question is: what happens if they are removed?

Slide 15



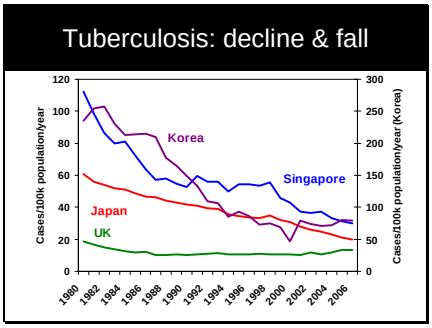
I now turn to the evidence that more directly links infection with allergy. The graphs show the effect of birth order and father's social class on hay fever prevalence in two national British birth cohorts. Within each cohort firstborn children (left) and those from more affluent families (right) were at highest risk of hay fever, but the prevalence was higher in 1986 than in 1974 irrespective of social-economic status or position within the family. Are single children in richer families are less exposed to infections?

Slide 16



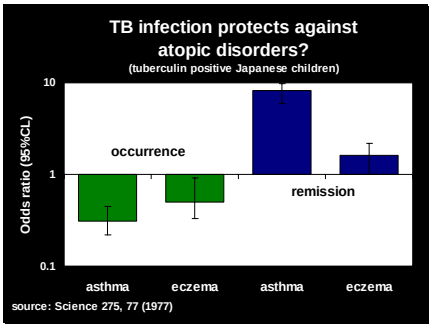
But the effects of birth order and social class effects do not apply to asthma. Once again, asthma is somewhat different from the other allergies.

Slide 17



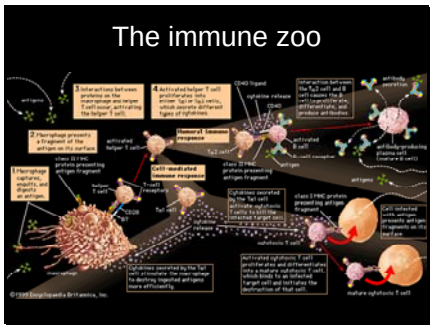
One important infection that has declined markedly in the rich world is TB. In the UK, case rates were already low 50 years ago; the same decline happened more recently in several Asian countries.

Slide 18



Japanese children who have been exposed to TB infection have lower rates of asthma and eczema compared with uninfected children, and infected children that do suffer from allergies have higher rates of remission.

Slide 19

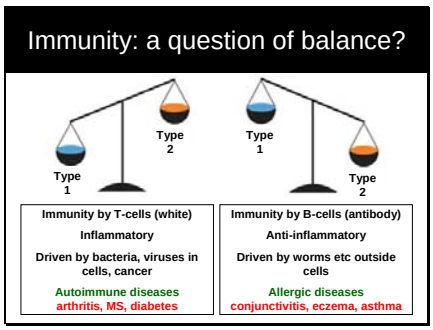


Those are some of the links based on population or epidemiological data. What about the mechanistic evidence – from immunology? Plunging into immunology is not for the feint-hearted. We try to deal with the complexity by looking for fundamental and general processes within all the detail. The risk is that simplification becomes over-simplification.

Slide 20

Here is one simple idea that could explain allergies, and it that has generated much research and discussion. It is that the immune system consists of two competing parts, like a see-saw. When pushed down on one side, it is pushed up on another; when one arm of the immune system is stimulated, the other is compromised.

Slide 21



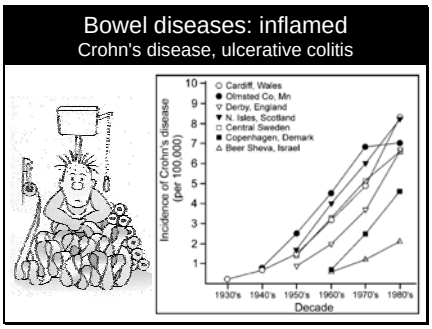
The idea (devleoped as recently as 1986) is that a balance is maintained in the body between two sets of T-cells, called Th1 and Th2 (I'll call them type 1 and type 2). Type 1 cells stimulate an inflammatory immune response that destroys intracellular viruses, bacteria and parasites (left). Type 2 cells stimulate an anti-inflammatory immune response, which is suited to destroying pathogens and toxins found in fluids outside of body cells, like worms (right). The type 1/type 2 balance shifts to favour the appropriate response against a particular invading pathogen. Allergy (right) is a type 2 imbalance, possibly caused by a lack of type 1 stimulation. The Type 1 pathway generates organ-specific autoimmune disease (such as arthritis, multiple sclerosis, type 1 diabetes).

Slide 22

Infections, parasites (worms) and autoimmune diseases

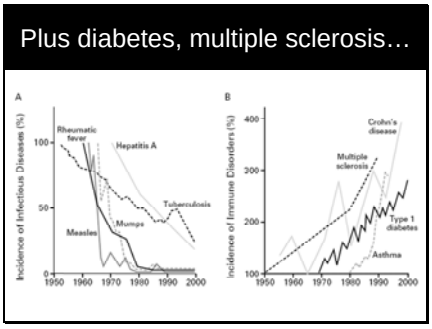
The theory is elegant but contradicted by at least two findings: (1) autoimmune diseases supposedly caused by type 1 stimulation are also increasing, and apparently where there is less infection; (2) worms that stimulate type 2 responses also protect against atopic (type 1) disorders.

Slide 23



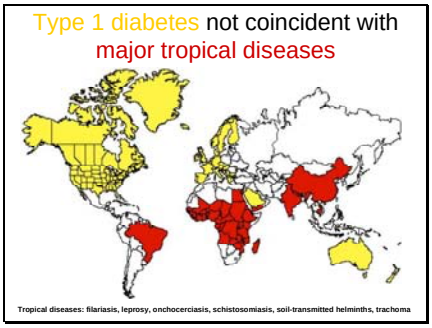
It's not just the allergic disease that are on the increase; a variety of type 1 autoimmune diseases are also becoming more prevalent (cartoon SACCA).

Slide 24



Once again, the inverse relation between infectious diseases (A) and immune disorders (B) from 1950 to 2000 (Bach NEJM 2002).

Slide 25

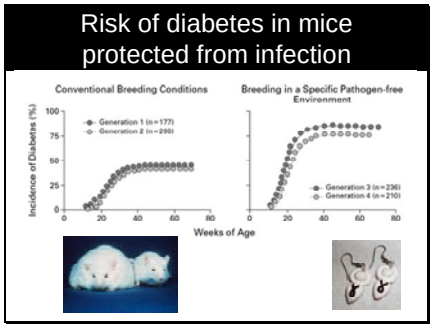


This is weak evidence, but there is an exclusive geographical association between diabetes (type 1, T1D, not to be confused with the Th1 immune response) and parasitic diseases. T1D is juvenile diabetes, an autoimmune disease destroying insulin-producing cells in the pancreas. Red marks areas inhabited by 6 or more of the low-mortality parasitic diseases (filariasis, leprosy, onchocerciasis, schistosomiasis, soil-transmitted helminths, and trachoma). Yellow marks areas where there are relatively high incidences of T1D (> 8 per 100 000/year). Non coloured areas delineate where T1D < 8 per 100 000/year and where the parasitic diseases are not endemic. The fact that these parasites cause chronic, rarely fatal infections is likely to be important in immune control and regulation, as we shall see shortly.

Slide 26

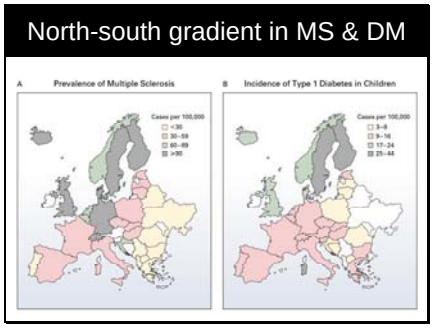
The effects of hygiene may extend to some forms of cancer. Acute lymphoblastic leukaemia (ALL) is a rare cancer of white blood cells, in which cells divide very quickly but do not mature. The permanently immature cells cannot do the work of normal white blood cells, which leads to an increased risk of infection. The bone marrow, overcrowded with immature white cells, cannot make enough healthy red cells and platelets. ALL occurs most frequently in children under 15 years of age. Nowadays about 85% of children with ALL live five years or more under treatment. Infections have long been implicated as possible etiologic factors for childhood leukaemias. The theory assumes that delayed exposure to common infections results in a deficient immune system and a consequent higher risk of common childhood leukaemias, particularly ALL. Where there are influxes of people to previously isolated communities, nonimmune children are exposed to infectious agents and consequently, it is proposed, at higher risk of ALL (Ribeiro Int J Cancer 2008).

Slide 27



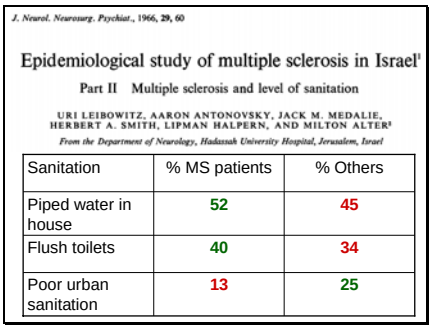
Infection is also linked to diabetes in mice. The incidence of diabetes, which is normally stable in successive generations of mice bred in a conventional environment (gen 1 and gen 2), increases immediately after breeding conditions are changed to a specific pathogen-free environment through the use of cesarean delivery and solitary confinement (gen 3 and gen 4, Bach NEJM 2002).

Slide 28



The North–South Gradient in the prevalence of multiple sclerosis (A) and the incidence of type 1 diabetes (B) in Europe. Allergic and autoimmune diseases are not evenly distributed among continents, countries, well-circumscribed regions within a given country, or ethnic groups. There is a north–south gradient: the incidence of disease decreases from north to south in the Northern Hemisphere (and reciprocally from south to north in the Southern Hemisphere). A comparison of Europe and Africa reveals a similar and even clearer trend, although the epidemiologic data are less well documented in Africa. There are similar geographic differences in Europe for allergy and Crohn's Disease; in North America for multiple sclerosis, type 1 diabetes, and Crohn's disease and in Australia for multiple sclerosis (Bach NEJM 2002).

Slide 29



J. Neurol. Neurosurg. Psychiat., 1966, **29**, 60

Epidemiological study of multiple sclerosis in Israel[1]

Part II Multiple sclerosis and level of sanitation

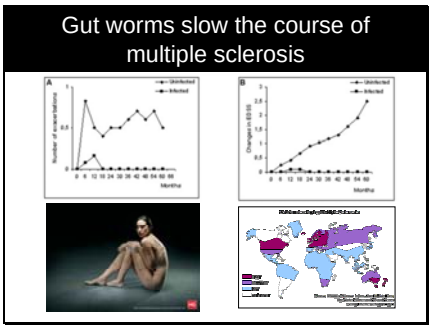
URI LEIBOWITZ, AARON ANTONOVSKY, JACK M. MEDALIE, HERBERT A. SMITH, LIPMAN HALPERN, AND MILTON ALTER[2]

From the Department of Neurology, Hadassah University Hospital, Jerusalem, Israel

Sanitation	% MS patients	% Others
Piped water in house	52	45
Flush toilets	40	34
Poor urban sanitation	13	25

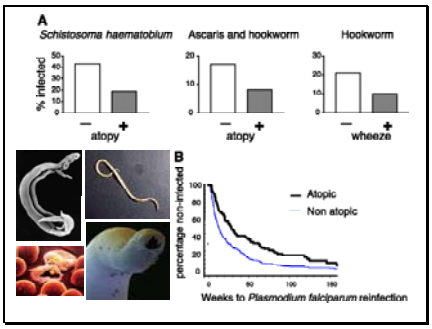
Infection and MS: If sanitary level had any relevance to aetiology, patients with multiple sclerosis would report a higher sanitary level before the onset of illness than controls from the same area. Measures of sanitary level included source of drinking water, toilet facilities, and degree of crowding, all pertaining to the childhood home. Childhood was emphasized because of evidence that a childhood experience or exposure may determine the risk of developing multiple sclerosis. On all three indices a higher percentage of patients than controls had higher sanitary levels (Leibowitz J Neurol Neurosurg Psychiat 1966).

Slide 30



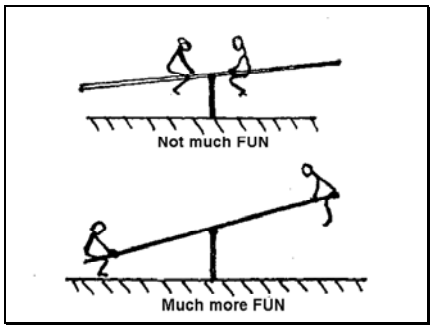
Worms (type 2) protect against autoimmune diseases. Number of exacerbations (A) and changes in extended disability status scale (EDSS; B) observed over time in parasite infected (squares) and uninfected (diamonds) multiple sclerosis (MS) patients. During the 2 years before study enrolment, the annual MS relapse rate in parasite-infected patients was 0.76/year, and 0.90/ year (median, 0.90) in uninfected MS patients(no significant differences between groups). Over the 56-month study period, 3 clinical relapses were observed in the infected MS group (9 patients remained clinically unchanged), and 56 relapses occurred in the uninfected MS group (A). Thus, median annualized relapse rate was 0 in infected MS patients compared with 1.09 in uninfected MS subjects. Furthermore, only two infected patients showed minimal EDSS changes lasting less than 3 months. EDSS scores did not change in the remaining 10 patients. Conversely, by the end of the follow-up period, 11 of 12 uninfected patients showed an overall increase in baseline EDSS (B). (Correale Ann Neurol 2007).

Slide 31



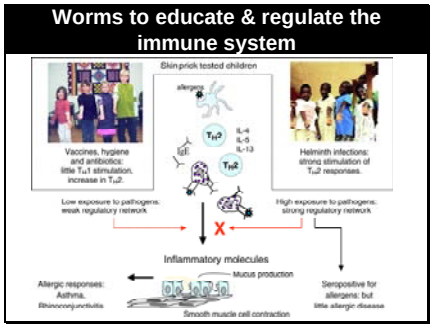
But worms also protect against allergy. (A) The prevalence of schistosomes (left), roundworm/hookworm (middle), and hookworm (right) infections was higher in individuals who were free from allergy (atopy or wheeze) compared to those who were allergic. (B) The malaria (Plasmodium falciparum) reinfection scores in young Gabonese children who were either positive or negative in skin testing to HDM. Non-atopic children (blue line) had significantly shorter periods to reinfection and therefore higher incidences of infection than did atopic children (black line) (Yazdanbaksh Science 2002).

Slide 32



Therefore (1) type 1 infections seems to protect against autoimmune disease as well as allergies, and (2) type 2 worm infections protect against both allergies and autoimmune diseases. We therefore need to modify the simple see-saw. Current thinking is that infection leads to dampens down the entire immune system, thus preventing any kind of damaging hyper-immunity. The picture takes the metaphor a step further: nervous children may have less fun, but they are safer. The key idea is that type 1 and type 2 are regulated.

Slide 33



We now know that worms (helminths) of many types restrict both allergic and autoimmune diseases. While each helminth tested has been strongly type 2, their suppressive effects are found on both type 1 (autoimmune) and type 2 (allergic) diseases. A high prevalence of chronic infections in developing countries results in persistent immune challenge, with cycles of infection and inflammation, which is followed by the triggering of anti-inflammatory molecules to restrict immune pathology. This dynamic interaction educates the immune system to establish a robust regulatory network, possibly the key to controlling allergic diseases, and to the survival of worms in their hosts. Such a network would be weakly developed in industrialized countries with a low pathogen load, allowing inappropriate immunopathological reactions to develop more readily (Yazdanbakhsh Science 2002, Maizels Curr Opin Immunol 2008).

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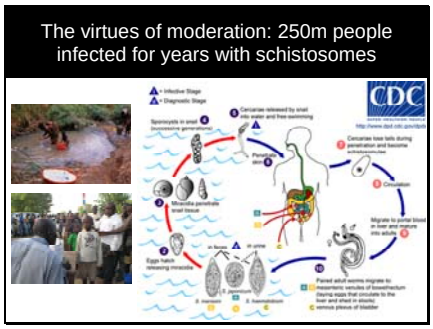


It is easy to imagine why worms like schistosomes, which live for years in their human hosts, have evolved mechanisms for down-regulating the immune response. Schistosomes (trematodes) infect ~200 million people throughout the world, primarily in developing countries in the tropics. They are adapted to have a balanced relationship with their human hosts, with <10% of infected people developing severe disease. Nevertheless, schistosomiasis is the main parasitic worm infection that affects humans in terms of morbidity and mortality. The pathology of schistosomiasis is primarily attributed to the T-cell-dependent granulomatous infiltrates evoked around parasite eggs that become trapped in the tissues in various organs, in particular the liver and intestines. In *S. mansoni* infections granulomatous inflammation must facilitate the passage of eggs through the intestinal wall so that they can be excreted from the infected host. This process of passing eggs through the intestinal wall has to be tightly regulated — if not adequately controlled, the resulting exacerbated intestinal inflammation and endotoxin leakage can cause sepsis and death of the host.

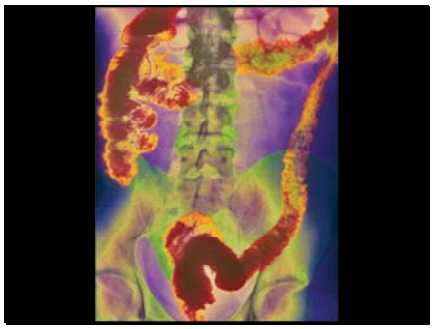
Regulatory cytokines have an important role in managing the balance between type 1 or type 2 immune responses that can lead to severe disease (Fallon Nat Rev Immunol 2007).

Slide 35

Rebalancing immunity
Amnesty for parasites?

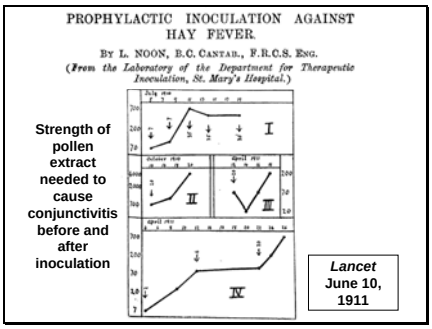
If the complete absence of infection is harmful, can restoring infection be beneficial? Having spent centuries trying to rid ourselves of infections and parasites, there is a certain irony in trying to rehabilitate them. What we're trying to do is the antithesis of vaccination. Vaccines stimulate a protective immune response; now we are trying downgrade excessive and damaging immune responses that are presumed to be due to the absence of infection especially in childhood. But we have some problems because of the nature of the evidence: we often do not know which infections are responsible, and we don't fully understand the immune responses.

Slide 36



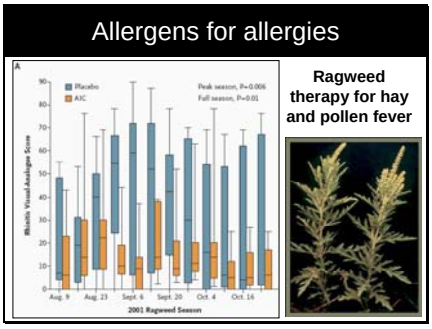
One of the problems is that we do not know what causes some autoimmune and allergic diseases. I've mentioned asthma. What are the causes of Crohn's disease? They could include environmental stimuli, genetic susceptibility, and overactive inflammatory and immune responses triggered by an unknown event. Several bacteria are currently under consideration as possible infectious triggers, including the bacteria *E faecalis, E coli* and *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the latter being the strongest contender. However, the body of evidence linking Crohn's disease with MAP infection remains weak and circumstantial. If we don't know the cause, it will be harder to devleop specific treatments (coloured radiograph of the colon of a patient with Crohn's disease, CNRI/Science Photo Library). Nevertheless…

Slide 37



Among the earliest studies of inoculation against hay fever was done by Noon in 1911 (Lancet June 1911). He tested whether subcutaneous injections of pollen extract could protect hay fever sufferers from conjunctivitis. The numbers at the sides of the graph denote the resistance of the patient, given in terms of the strength of pollen extract, one drop of which was sufficient to excite a conjunctival reaction. The arrows mark subcutaneous inoculations of pollen extract. Figures I and II refer to one patient at different periods of treatment; Figure III shows the response obtained after about a month's treatment in another case; and Fig. IV the early stages of treatment. These experiments showed that the sensitivity of hay fever patients can be decreased, by properly directed dosage, at least a hundredfold, while excessive or too frequent inoculations actually increase the sensitivity. These experiments were therefore partially successful, but they also predicted the clinical difficulties of managing complex immune responses, which still broadly apply.

Slide 38



Immunotherapy with a ragweed vaccine for allergic rhinitis. Standard allergen immunotherapy has been a cornerstone of the allergist's therapeutic options since its introduction in 1911. But this approach is limited by the potential for systemic allergic reactions, including anaphylaxis, caused by the relatively large doses of allergen required for efficacy. Furthermore, standard allergen immunotherapy is logistically difficult to administer because it requires regular, frequent dosing, typically over a period of 3-5 years, and frequently results in noncompliance. We therefore need new immunotherapeutic agents that have decreased risks of serious adverse events and involve shorter regimens that are more easily followed. One possibility is a novel immunotherapeutic compound made of ragweed-pollen antigen, containing DNA. The study shown gives preliminary evidence that a 6-injection regimen reduces allergic rhinitis symptoms during the ragweed season. And the clinical effects seem to be associated with the induction of long-lasting immune modulation. This ragweed vaccine has properties that make it qualitatively superior to standard allergen immunotherapy (Creticos N Engl J Med 355,1445, 2006).

Slide 39

Immune therapy for asthma too?

20 trials of allergens given to reduce asthma symptoms

Net effect: **7%** improvement

Allergen immunotherapy is a **treatment option in highly selected patients** with allergic asthma

Ragweed therapy shows **first year benefit not sustained**

But this approach does not (yet) work so well against asthma, even though asthma is a type 2 inflammatory condition. Immunotherapy in the form of whole-allergen injections has been used in the treatment of asthma for more than a century (Freeman Lancet 1914). A recent overview of 20 trials found only a 7% improvement on average. The clinical effects were that were limited and many were not sustained for two years (Creticos NEJM 1996). So allergen immunotherapy is a treatment option in highly selected patients with extrinsic ("allergic") asthma (Abramson Am J Respir Crit Care Med 1995).

Slide 40

Vaccines for multiple sclerosis?

BCG 57% reduction in brain lesions activity in 12 patients (Ristori 1999)

DNA favourable trends in brain lesion activity, and in immunity (Bar-Or 2007)

"If successful in MS, DNA vaccines can be developed related diseases… type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis and myasthenia gravis" (Bar-Or 2007)

Ristori studied the effect of BCG vaccine as an immunomodulator in MS. BCG is a live attenuated vaccine used to protect against TB, but it is made from the bacterium that causes TB in cattle. So BCG is effectively a controlled dose of TB. A MRI-monitored trial (magnetic resonance imaging) was performed in 14 patients with relapsing-remitting MS. After treatment, MRI activity was significantly reduced without major adverse effects were reported (Ristori Neurology 1999).

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We're told in Genesis that Abraham owed his longevity to sour milk. It's taken a while for the probiotic industry to take off, but it does now seem to have momentum. In 1996, the first probiotic food appeared in the UK: a fermented milk drink (Yakult). This was developed over 70 years ago in Japan. Probiotics are mainly lactic acid bacteria (Lactobacillus, Bifidobacterium) that can survive transiently in human intestines when taken by mouth. As these probiotics make contact with the gut mucosa they can stimulate systemic, type 1 immunity. So probiotics can down-regulate conditions linked to type 2 overactivation: children born to families who consume traditional Lactobacillus-rich fermented foods experience fewer allergies than those from families who consume more sterile foods. There is growing evidence of the benefits of probiotics on symptoms of atopic dermatitis (products.mercola.com/probiotics/), and for treating dysfunctions of the gut mucosal barrier, including acute gastroenteritis, food allergy, and inflammatory bowel disease (Isolauri Am J Clin Nut 2001).

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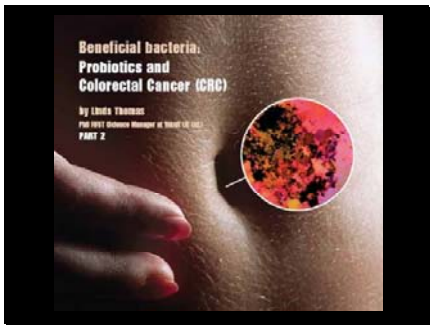

In the UK, colorectal cancer (CRC or bowel cancer) is the third most common cancer for men and the second most common cancer for women. Do probiotics help by e.g. preventing damage to the chromosomes of the gut cells? This is still surmise.

Slide 43

And what about the dirt of worms? One of the factors leading to the emergence of IBD may be lack of exposure to worms. Exposure normally begins early in childhood, setting up immune response patterns that continue for the life of the individual. Exposure to schistosomes can protect animals from developing insulin-dependent diabetes or experimental autoimmune encephalitis (a model of multiple sclerosis). Exposure to helminths may also protect from allergy and asthma, and autoimmune conditions like ulcerative colitis.

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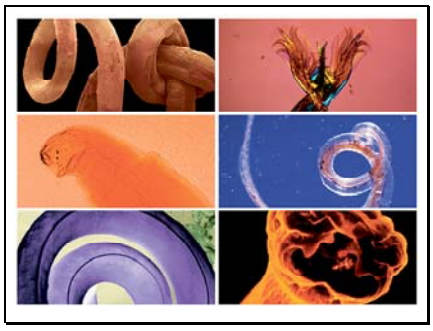
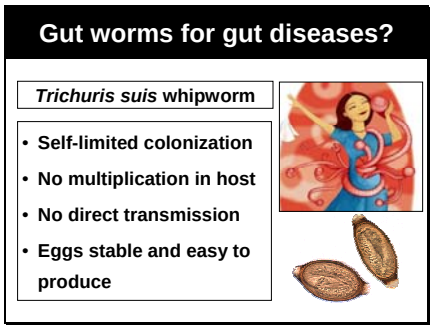


Portraits of the pig whipworm, Trichuris suis, which…

Slide 45

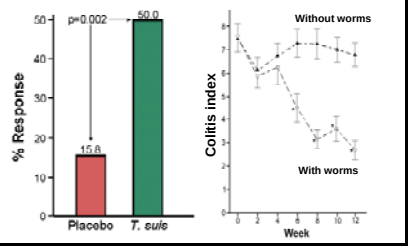


…is safe for people (being a a parasite of pigs). T suis cannot be transmitted to other people, and no human diseases have ever been attributed to T suis. It is possible to isolate clean T suis eggs (Zaccone Parasite Immunol 2006; slide derived from Goldblatt & Chintz).

Slide 46

But does it work…?

50% patients given worms improved, some greatly within 12w



Controlled trial of T suis in patients with ulcerative colitis. 54 patients received either placebo or 2500 T suis eggs every 2 weeks for 12 weeks. Patients given placebo showed no improvement, whereas patients who received T suis had a significant decrease in scores. The scores for patients who improved markedly are on the right. 50% of patients given T suis improved compared with 16% on placebo (left). This study shows that helminth colonization can effectively reduce symptoms and inflammation caused by ulcerative colitis (left, Elliott Curr Opin Gastroenterol 2004). Further experiments have shown effective treatment for Crohn's disease. After ingesting 2500 microscopic T suis eggs at 3-week intervals for 24 weeks, 23 of 29 Crohn's patients responded positively, and 21 went into complete remission.

Slide 47

For a diet of worms:
too much hygiene is bad for your health

- Allergic and autoimmune diseases increasing worldwide
- Hygiene hypothesis conforms with evidence from studies of populations and immunity, though neither give full understanding
- Immune rebalancing has a long history and a promising future, but so far with less success than vaccines/drugs

The hygiene hypothesis emerged because we needed to explain the worldwide rise in allergies. The epidemic of allergies was obviously coincident with the decline in bacterial and other infections – in a more hygienic environment -- that stimulate type 1 immunity. However, the decline in infections was also coincident with the rise in type 2 autoimmune diseases. Moreover parasitic worms that stimulate type 2 responses also seem to be protective against type 1 diseases. So the picture is more complex that the type 1/type 2 see-saw, in which parasites probably have a regulatory role. We don't fully understand the immunity, but there is clearly potential for immune therapies. Some of these work now, but they have so far been much less successful than conventional vaccination.