‘Hygiene Hypothesis’ – a brief introduction to its various forms

Development of Hypotheses

1989

D.P Strachan suggested exposure to childhood diseases, small families giving less exposure – hypothesised that these diseases ‘trained’ the auto-immune system & reduced incidence thereof caused rise in asthma and hay fever.

Immunologists and epidemiologists investigated and broadened into a more general tool in which reduced microbial exposure lead to a range of chronic inflammatory disorders including Type 1 diabetes.

2003

Graham Rook propose the ‘old friends’ hypothesis version: here it is not the common childhood diseases, which on the whole are relatively recent phenomena resulting from overcrowding after the Neolithic revolution, but the microbes and intestinal worms etc., with which we have evolved with over millions of years. The former tend to kill or immunise and so do not persist at any significant level in small hunter-gatherer groups; but the latter co-habit with us in a parasitical or chronic manner and have done with most mammals. Later this was expanded to include symbiotic bacteria.

2010

Paulo Matricardi proposes the ‘microbial diversity’ hypothesis that assigns a key role to microbial diversity and turnover in the gut mucosa as a key factor in training the immune system.

Allergy Mechanism

The immune system operates via a large variety of white blood cells (leucocytes) and we shall be concerned, in the hygiene hypothesis, with a sub-set of these called T-helper (T\textsubscript{h}) cells. Basically we can look upon T\textsubscript{h} cells as mainly look-outs & signalers in the white-cell army that wages war against unwanted invasions; identifying invaders, signalling to - and priming - other attack cells. There are a number of different types of T\textsubscript{h} cells, but we need only be concerned with three of them:- type 1 (T\textsubscript{h1}), type 2 (T\textsubscript{h2}), and regulatory (T\textsubscript{h\textsubscript{reg}}).

Allergic responses are inappropriate immune responses to harmless antigens by the adaptive part of the immune system. An antigen is any substance that produces a response from our adaptive immune system (the name means it is capable of causing the antibody-generation). Antigens are commonly harmful and so
the response is desired, but when the antigen is harmless then the response is not desired and we call it an allergen, an allergic response generator.

The adaptive immune response is very complex, but a very simplified summary as far as allergies are concerned is as follows:-

The reception of the allergen is initially made by it landing on receptor sites in T_h2 cells. These cells then start off the response process by promoting lots more immature T_h cells to T_h2 cells and also triggering the production of specific antibodies that can bind to this antigen and effectively neutralise it. They cause the production by interacting with another type of immune system cell known as a B-cell. These antibodies are of a particular type known as immunoglobulin type E (IgE). The B-cells then secrete large amounts of this IgE which then circulate in the blood and are caught by IgE receptors on the surface of two types of cells – mast cells (the name just comes from them looking full of objects which their German discoverer thought were for fattening cells – mast is German for fattening) and basophils (they’re also full of similar looking objects but their name just means they take up a basic dye if you want to stain them). The packages within both these cells are actually chemical weaponry to be released when the IgE encounters that antigen again. These packages contain, among other things, chemicals to increase blood flow to the site, increase mucus secretion, contract smooth muscles - such as in the respiratory tract, and stimulate nerves – i.e. these are the chemicals responsible for the actual inflammatory symptoms. The mast cells and basophils are now primed to release their packages if they encounter these antigens {for reference the chemicals are histamines, cytokines, interleukins, leukotrienes, prostaglandins and serotonin}. The difference between the two types of cells containing all this weaponry is that mast cells sit in fixed sites (normally those that will be particularly exposed to harmful invasion – like the respiratory tract) whereas basophils roam around in the blood, like coppers on the beat.

{There are other types of immune system warrior cells with a variety of names – macrophages, eosinophils, natural killer cells - and other arms of the immune system, for example the ‘innate’ immune system which can be primed by ‘immunogens’, substances capable of generating an immune response rather than just antibodies.}

Possible Hygiene Hypothesis Mechanisms

The original Strachan version of the hygiene hypothesis was that the T_h1 arm of the system, which is triggered by many bacterial and viral invasions and which damps down T_h2 responses which kick the whole train off, needed to be sufficiently stimulated in infancy by the experience of many childhood diseases. If such T_h1 stimulation was inadequate then we got an over-stimulated T_h2 response to harmless antigens, thereby leading to allergies.

The ‘old friends’ hypothesis lay not so much in an under-stimulated T_h1 arm as an under-stimulated T_h2reg arm. Regulatory T-helper cells have, as their name implies, a more general regulation effect on the immune system and can moderate both T_h1 and T_h2 arms. They can be stimulated by both infectious invaders but also by the less harmful invaders we have, during our evolution, learnt to live with. These can vary from the fairly unwelcome, such as intestinal worms and other parasites; through the pretty harmless, such as the many bacteria that can live on un-washed skin; to the distinctly welcome ones from which we benefit, and in some cases come to depend upon, such as our friendly gut bacteria. In the absence of these ‘old friends’
we develop insufficient stimulation of the T_H(reg) arm and so become prone to both T_H1 and T_H2 over-activity.

This would help explain why some autoimmune diseases, such as Crohn’s disease, Type-1 Diabetes, Multiple Sclerosis, Ulcerative Colitis, which are seen as the result of T_H1 mediated attacks, have shown the same increasing trajectory in modern times to the growth of allergies. The growth of these diseases presents a distinct problem for the original form of the hypothesis, since we might expect an under-stimulated T_H1 arm would suggest these diseases should be less likely rather than more.

Supporters of the hypothesis have imagined our immune system as starting out like a bunch of computer programs with little actual data to work upon. Exposure to a diverse range of organisms allows the system to build up a large database upon which to work and hone the immune system response. It is proposed that evolution selected systems which made best use of this data and produced responses that benefitted us. Since for much of our evolutionary history we have been exposed to muck and decay, the inevitable presence therein of bacteria and parasites was made into a beneficial necessity.

**Evidence**

Much epidemiological fits with the hypothesis: asthma and other chronic inflammatory disorders, as well as autoimmune diseases such as Type-1 diabetes and MS are much more common in the ‘cleaner’ industrial world than in the developing world. However prior to the 19th century ‘clean up’ of the western world, through efficient sewerage systems etc, infectious diseases were much more common and allergies much less so. When people move from the developing world to the industrials world, their pattern of acquiring these disorders moves slowly from that of the low incidence of the developing world, to the high incidence of the industrial world. Repeating studies ten-years apart in Ghana, as it becomes wealthier and supposedly more ‘hygienic’, has shown a growing incidence of asthmatic responses.

There appears to be a reduced incidence of allergies in children raised in farm environments, where allergens themselves are certainly not absent, than in those raised in more urban areas. In the USA the incidence was seen to have a curious double peak, one in wealthy sub-urban areas and another in poor inner-city areas; this could be that hygiene level was very high in the former and that exposure to friendly microbe-rich soil was absent in the latter. Of course it could be that the culprit is not lack of microbes in the urban environment but the presence of high levels of pollutants, and the rich suburban areas may produce the other peak from the much greater use of chlorinated water in pools. In indoor pools the presence of relatively high concentrations of chlorine gas above the pool has been shown to damage asthmatic lungs. However this latter counter argument to the hygiene theory has less force in outdoor pools – the gas concentration is kept much lower but the chlorine in the water would still cleanse the skin of mycobacterial ‘old friends’.

Experiments on animals have shown reduced incidence of certain autoimmune diseases in animals which have been infected with various viral conditions in infancy. Mice specifically bred to spontaneously develop type-1 diabetes showed reduced incidence when infected with parasitic worms. Germ free mice showed greater incidence of asthma than those exposed to their normal range of microbes and parasites. {Indeed well before the first hygiene hypothesis was proposed there was evidence that lab animals raised in sterile environments had impaired immune systems.}
Asthma incidence is greater among infants that have received antibiotic treatment (antibiotics significantly reduce the population and diversity of gut bacteria). It is also greater in those that were delivered by Caesarean section than naturally (i.e. via a more sterile delivery method than the natural one).

A double blind study of 2500 pregnant women in Uganda showed that the infants of those mothers who were treated with anti-worm drugs were significantly more likely to develop infantile eczema, than those who had no such infections.

A recent study of Finnish teenagers found that those who lived in the countryside had a greater diversity of bacteria on their skin and lower allergen sensitivity than those who lived in less bacterially diverse environments (the latter included those living near large bodies of water as well as in more urban environments).

Suggested ‘treatments’.

As can be seen from the above, the establishment of the scientific validity and extent to which the hygiene hypothesis applies is still a ‘work-in-progress’. So far there are no standard treatments based on the general premise, other than in research trials.

There are a number of trials on the use, in particular, of parasitic worms for many ailments – e.g. asthma, Crohn’s disease, ulcerative colitis, and multiple sclerosis. It may well be that they are also therapeutic in arteriosclerosis and heart disease and this is also subject to research. The results so far are said to be ‘encouraging’.

As yet there is no clear evidence that ingesting probiotic drinks and foods directly actually does improve gut microbe populations.

Research is underway to see if appropriate lifestyle changes – e.g. natural childbirth, prolonged breast feeding, encouraging play in naturally microbe-rich environments - has any effect at reducing the incidence of allergies and autoimmune disorders in Western society. If successful, this may lead to recommended lifestyle changes and the greater introduction of ‘green’ spaces in urban environments and encouragement of exposure of infants to agricultural environments.

A problem is that hygiene is responsible for a huge reduction in infectious disease. One cannot simply propose a return to a less hygienic state, whilst still living unnaturally in huge conurbations, without massively increasing a clear and present risk. This risk is much better scientifically established than the benefits that might accrue from adopting the hygiene hypothesis wholesale.

An approach to hygiene in the home that is gaining some approval is one which identifies the key routes to infection within the home and tackles those with full anti-bacterial/viral measures (for example on hands, hand utensils, and food preparation surfaces), whilst being more tolerant general visible cleanliness.