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# Are we too clean?

Report of the RIPH Symposium September 2002:
*'Are we too clean?- a question of immunity balance'*

Dr Rosalind Stanwell-Smith

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## Introduction

*"These are strange times, when we are healthier than ever but more anxious about our health."* *Porter, 1997*[1]

The 20th century was a period of unprecedented improvement in both public and individual health. In developed countries this has been associated with increasing longevity: but chronic illness, inevitably, has also increased. Allergic disorders, in particular, have risen sharply during the last four decades. These disorders, also known as 'atopic', include atopic asthma, hay fever, eczema and food allergies. Autoimmune diseases, such as rheumatoid arthritis and Crohn's disease, have also become more common. The rise in asthma caused particular concern, both in its size and in its impact on child health, for example in manifesting as persistent disease at earlier ages than ever before.[2] Atopic disease appears to have been rare before the 19th century[3] and the rapid increase in allergic asthma and other atopic disorders started between 1960 and 1970, with a progressive rise during the 1980s and 90s. Asthma increased by about 1% a year from around 1980[4] and it now affects 20-40% of 13-14 years in industrialised countries and 2-3% of the population of developing countries[5]. Among children 5-18 years of age, the increase has predominantly been among allergic individuals[6] and recent studies in the UK indicate that atopic, rather than non-atopic, asthma is responsible for much of the rise[7,8]. Seeking an explanation, some have looked to the evidence of social and demographic trends, others to the side effects of an industrialised and urbanised society. Of the various hypotheses, David Strachan's hygiene hypothesis[9] **(Box 1)** has received the most attention, both in the field of immunology and in the media.

**Box 1: Statement of the hygiene hypothesis***

The apparent rise [in the prevalence of allergic diseases]…. could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally…. Over the past century declining family size, improved household amenities and higher standards of personal cleanliness have reduced opportunities for cross-infection in young families. This may have resulted in more widespread clinical expression of atopic disease.

*(Strachan, 1989)*

* At the symposium, Professor Strachan explained that the hypothesis had been dubbed later as the 'hygiene hypothesis', due possibly to the inclusion of 'hygiene' in the title to his paper – but the reason for choosing this word was related mainly to his being employed as a lecturer at the London School of **Hygiene** and Tropical medicine at the time…

The hygiene hypothesis focused primarily on the observed trend to smaller families, and epidemiological studies of a predominantly inverse relationship between atopy and family size: but the suggestion, that 'unhygienic contact' between young children may be needed for strong and healthy immune systems, sparked enormous interest. It seemed to explain some of the emerging information about how the immune system develops and functions. The hygiene hypothesis also appeared to be in accord with concerns about modern lifestyles. Hence the questioning about whether we have become 'too clean' and what, if this is true, can be done about it. Given the evidence of continuing high levels of many types of infectious disease, and the need to maintain measures that prevent, treat and control infection, the hygiene hypothesis has also raised questions for infection control specialists.

The Royal Institute of Public Health symposium in September 2002 examined the debate about postulated links between allergies and cleanliness and sought to find a balance between addressing concerns about allergies, lifestyle and the continuing need to control infection threats. The following summary of the symposium is based on the presentations given on the day.

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## The hygiene hypothesis:
*key concepts and current perspectives*

**Professor David P Strachan,**
**Professor of Epidemiology,**
**St George's Hospital Medical School, London**

Professor Strachan's hygiene hypothesis **(Box 1)** was based on a number of observations and epidemiological research: to understand its emergence, it is helpful to consider the history of 'atopy' and the attempts to understand its cause. Britain was the first of the developed countries to industrialise: this was associated with a move from rural to urban living and rapid expansion of towns and cities. Hay fever **(Box 2)** emerged as a 'post-industrial revolution' epidemic in the early 19th century: In 1828, a London physician, John Bostock, described 27 new cases of what he termed "catarrhus aestivus" ('summer catarrh') and this was soon known as hay fever, in the assumption that it was caused by pollen, since pollen exposure appeared to provoke attacks. In 1862, a German physician, Phoebus, launched an international appeal to identify cases of hay fever, an indication that it was still rare: he found 300 cases, all wealthy. By 1873 hay fever had become common enough to be identified as a disease of the urban, educated classes by Charles Blackley, a physician – and a sufferer himself from the disorder. Blackley noted that hay fever was rare in farmers, but the main difference in the epidemiology appeared, at first, to be between urban and rural lifestyles and exposure to pollen. Swiss studies between 1926 and 1958 showed an increase in urban levels of hay fever from 1.2% (ten fold higher than rural dwellers) to 4.8%. A Swiss study in 1985 reported that while the urban level of hay fever was now 8%, hay fever was also common in the country, affecting 10.5% of those studied[10]. Clearly, a simple 'urban-rural' difference was not a sufficient explanation for the hay fever trends.

A 'pollution hypothesis' was proposed by Ronald Finn in 1992[11], suggesting that air pollution damages the mucous membranes of the nose. Referring to allergies as "diseases of civilisation", Finn proposed that they could be reduced by control of chemical pollution. Yet, pollution differences did not explain the rural/urban/farming differences in epidemiology, nor why atopic disorders should have risen rapidly in the late 20th century era during which air pollution was increasingly controlled. The reunification of Germany in 1989 provided an opportunity to collect important evidence on atopy differences between the former West and East Germany: the post World War II 'iron curtain' had created a natural experiment in markedly different development in these two parts of a formerly united population. The West German population was more affluent, with smaller families: it had a lower level of industrial pollution (but more traffic pollution) and also a lower proportion of people in farming communities. While there was an inverse association between atopy (as measured by skin prick tests) and family size in both East and West Germany (i.e. levels of positive skin tests fell with increasing numbers of siblings), the trend was more marked in the West German population[12]. In another study, comparing West and East Germany, atopy had risen in males progressively since the 1950s, with higher levels in each decade in West Germany, although the pattern for females was less consistent[13]. Following unification, convergence of atopy rates has been more rapid than expected, prompting theories about the influence of 'Western lifestyle' on allergies. Strachan characterised the dilemma about cause as 'affluence or effluents'. His own research and review of the literature had identified a number of phenomena relating to the atopy rise: neither older nor modern forms of pollution appeared to offer consistent explanations, while the hygiene hypothesis looked more promising[14] **(Table 1)**. The link with infection exposure was suggested by the trends in social class and allergy appearing to be, to some extent, a 'mirror image' of the observed social class trends in infection. A 'community diagnosis' approach has proved useful in analysing the other potential factors involved and their possible contribution to the rise in allergies.

In the decade since the hygiene hypothesis, new clues had emerged to either add to or explain the 'old clues' of the atopy differences between East and West Europe, the association of hay fever and eczema (but not asthma) with higher social class groups, the family size effect and birth order (higher risk with first child, decreasing risk for younger siblings). The effect of all these factors was strongest for hay fever and not evident for 'wheezing'. The new clues included the studies of farming and non-farming families in East and West Europe, indicating that the main difference in atopy appeared to relate to a protective effect of living on a farm in early childhood. Clues to a 'lifestyle' explanation for the social class trends were found in studies of Rudolf Steiner schools and the choice to live an anthroposophic lifestyle, with an emphasis on differences in diet and other factors, rather than affluence.

**Box 2: Hay fever**

Hay fever, also called allergic rhinitis, is associated with a hypersensitive upper respiratory tract that reacts to grass and other pollens and also to moulds. The result is an acute reaction on inhalation including sneezing, watery nasal discharge, irritation and inflammation of the eyes (conjunctivitis) and nasal irritation/ blockage. Most cases start in childhood, with 90% cases developing by the age of 30. Hay fever symptoms tend to improve and lessen with age. The symptoms are seasonal and occur particularly during hot, humid, windy days. Hay fever may be associated with chest wheezing in about a third of cases. About a third also have asthma; 25% have eczema and 5% urticaria; about a fifth have a family history. Another form of hay fever, vasomotor rhinitis, is not seasonal.

**Table 1: Affluence or effluents as the cause of rising post war atopy: towards a 'community diagnosis'**

| Phenomenon to be explained | Hygiene hypothesis | Old fashioned pollution | Modern pollution |
|---|---|---|---|
| Emergence with industrialisation | Yes | Yes | No |
| Continuing rise in 20th century | Yes | No | Yes |
| More common in W Europe | Yes | No | Yes |
| More common in affluent countries | Yes | Unlikely | Yes |
| More common in smaller families | Yes | No | Unlikely |
| More common in firstborns | Yes | No | Unlikely |

Investigators looked at the influence of early antibiotic therapy as an alternative explanation to the family size effect. Studies of the infant bowel flora provided intriguing evidence: the bowel is colonised shortly after birth by commensal bacteria, but with differences in flora between the populations of different countries and levels of industrial/non-farming development.

## Infection and allergy: *review of epidemiological evidence*

Several infections have been implicated as protective against later development of allergy, including measles, pertussis (whooping cough), tuberculosis (or BCG immunisation) and hepatitis A. Examination of the postulated protective effects has involved assessment of the effect of natural infection and the immunity provided by vaccines.

The main evidence for measles came from a study of the survivors of a wild measles epidemic in Guinea-Bissau[15]. Those who had survived measles were approximately half as likely to have atopy, in comparison with children who had been vaccinated against measles after the epidemic. However, other investigations of a 'measles effect' reported conflicting results, with no evidence of this in the British Birth Cohort surveys of 1958 and 1970, and a small increase (4%) of allergic disease in Finnish children with a history of measles. **Pertussis** was implicated as protective when, in 1994, it was observed that in one British general practice, the children immunised against pertussis had 75% more allergic disease. Examination of the large ALSPAC cohort [Avon longitudinal study of pregnancy and childhood – over 11,000 children followed since pregnancy] showed no association between pertussis immunisation and asthma. The evidence was less clear-cut for another strong contender for protection against atopy: **tuberculosis and BCG immunisation**. A Japanese study[16] reported an inverse association between specific IgE (a serological 'marker' of atopy) and tuberculin reactivity: ie, those who had received routine neonatal BCG vaccine and had a positive tuberculin skin test were less likely to develop allergic disorders. Results of other studies, particularly in Norway, Sweden and Finland, suggest that any protective effect is very small and independent of clinical TB. **Hepatitis A virus (HAV)** is of particular interest because of its known association with poor sanitation and low socio-economic status. It is no longer acquired at an early age in many developed countries, particularly in more affluent groups. A study of Italian Air Force recruits[17] found that those with serological evidence of previous HAV had a 50% reduction in risk of allergic disorder: no such protective effect was found for serological evidence of other infections (including measles). A study of a sample of the general population in Italy, and a case control study in Scotland, produced similar results. It is not known whether HAV is a marker for differences in lifestyle or exposure to other infections, such as intestinal infections and others spread by the faecal-oral route, although this has been suggested as an explanation of the apparent effect; and the finding in the Italian recruits was independent of age, sibship size, birth order and area of residence[17].

The most promising 'new clues' as to the relationship between microbial exposure and protection against allergy relate to the studies on bowel flora. In addition to the reduced risk of allergy in children attending Steiner schools, marked differences in bowel flora were reported for allergic children in Sweden and Estonia, including fewer lactobacilli, more bifidobacteria and higher levels of *Staphylococcus aureus* in the Swedish infants. Such studies have renewed interest in the 'farming effect': the possible influence of a farm environment on the early microbial colonisation of the bowel. The explanations of this effect have included early contact with animals, exposure to endotoxins [from animal excreta: present in the cell wall of Gram-negative bacteria, many of which are associated with gastrointestinal infection], mycobacteria in the environment and consumption of unprocessed or unpasteurised food.

## The hygiene hypothesis now and current research needs

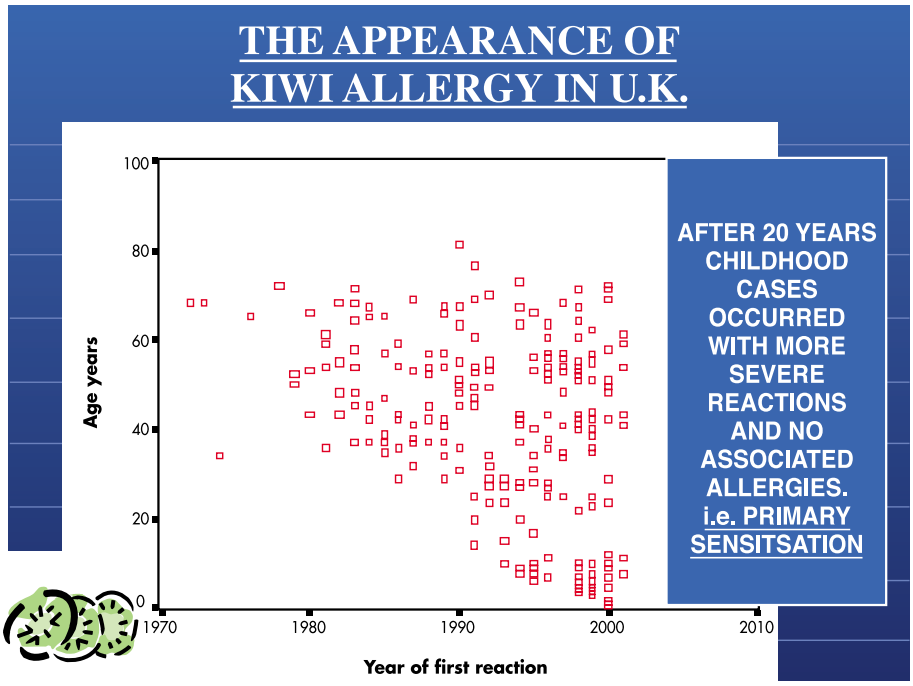
After a decade since his hypothesis, Strachan concludes that no specific organism has been identified, with no conclusive evidence as to whether respiratory or gastrointestinal infections are involved – or whether specific agents or a general 'burden of infection' is involved. Similarly, the timing of the postulated protective effects remains undefined: sometimes described as a 'window of opportunity' for the correct early development of a balanced immune system, this was initially thought to be in early infancy or childhood, but other evidence points also to the possibility of timing related to the first allergen exposure or even throughout childhood. The family size effect is consistent for total sibship size for atopy, hay fever and eczema – but much less so for asthma; and the association of hay fever and eczema with family size, although strongest for birth order (younger siblings protected), is not evident in all studies. Intriguingly, studies of adult atopy have shown that younger siblings have more protection against atopy from brothers than sisters. Of the factors known to differ with birth order (such as birth weight, head circumference, onset of early infections, stool colour), only gestational age at birth appears to relate to atopy. The family size effect must be an indicator of a third risk factor, as yet not confirmed and which may not be covered by the hygiene hypothesis: although this factor must vary in prevalence with family size and also be strongly associated with allergic sensitisation. This explanatory risk factor may have changed over time independently of family size. Strachan suggests that research must focus on biologically plausible factors that are strongly associated with socio-economic status, family size and birth order – and whether indirect markers of early infection indicate large differences in microbial exposure: meanwhile, a study is currently under way on exposures in Shropshire farms which may help to clarify the apparent protection afforded by the farming environment.

**Box 3: Hypotheses re: why are allergic diseases so common and increasing in prevalence***

- Increased allergen exposure?
  Increased pollutant exposure?
- Dietary changes?
- Hygiene hypothesis?
- Change in infectious triggers?
- Increased maternal and family stress?[21]
- Reduced use of aspirin/Increased use of paracetamol?[22, 23]
- Genetic diversity?[24]

*n.b. prevalence = new plus old cases, important in chronic disorders such as allergies; incidence = new cases

**Figure 1:** Appearance of Kiwi allergy in the UK




## Trends in atopy and allergy:
*the wider perspective*

**Professor John Warner, Professor of Child Health, School of Medicine, University of Southampton**

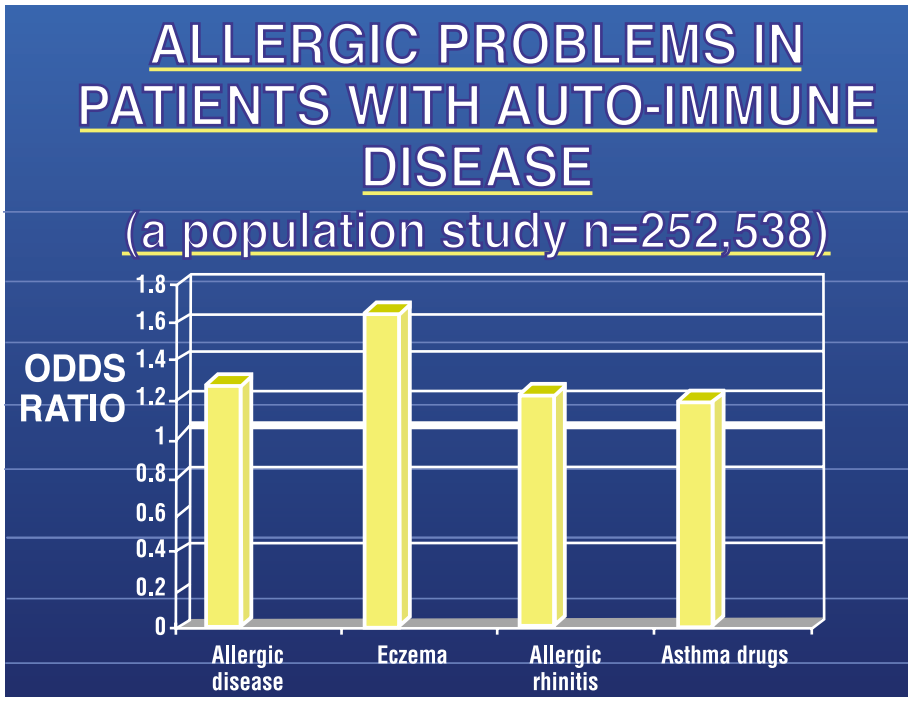
The context for the allergic diseases, and the reason for their continuing concern, includes the fact that they are very common, increasing in prevalence, with associated morbidity, socio-economic and therapy costs – and that there is no cure. A wide range of hypotheses has been put forward to explain the rise in these disorders **(Box 3)**.

Research on the role of allergen exposure has shown that allergic children were significantly more likely to have experienced high exposure to dust-mites and cat allergens[25]. Early exposure to house dust mites (HDM) has been particularly implicated in the aetiology of allergy, for example in research in Australia[26]. Children who had been exposed to high levels of birch pollen from the age of 1-3 months (a period considered important for immune system development) had significantly higher levels of seasonal asthma and birch allergy by the age of 4-5 years[27]. A controlled trial of egg avoidance found that this significantly reduced active allergy, compared with egg eating controls: but the issue of whether, in causal terms, the susceptibility to allergy or the response to allergen comes first, remains unresolved. Avoiding HDM in infancy, for example, reduces wheezing but not asthma[28] ; and while cat and dog ownership in early childhood has been claimed to reduce asthma[29], the explanation is not clear: it could be related to high dose tolerance or to confounding due to parents with allergies avoiding pets. Another dimension to be considered is that of the more diverse environment. Our ancestors had a very restricted diet and exposure to a limited range of aero and contact allergens. In our modern environment we have an enormously diverse exposure to many ingestant, inhalant and contactant allergens. Our genetic programming has evolved to be more in tune with our ancestors' limited environment rather than with the modern lifestyle. As an example, kiwi fruit allergy appeared very shortly after its first widespread introduction in the UK in 1970: the first affected were adults with pre-existing mild oral allergy syndrome, by cross reactivity. Twenty years on, severe childhood cases of kiwi fruit allergy now occur, in children with no other allergies – i.e. primary sensitisation is now occurring **(Figure 1)**. The role of 'modern pollutants' such as gas appliances[31], formaldehyde vapour[32], ozone and diesel particles has also been shown to be possibly causative, i.e. not just triggering existing allergic disease. The conclusion from the evidence appears to be that primary exposure in early life to some pollutants, at the same time as allergens, could increase the risk of sensitisation and disease. There is evidence from Japan that exposure to allergens of cedar trees is more likely to lead to allergic sensitisation and disease if it occurs in association with diesel particulates, as occurs in individuals living along cedar-lined roads. These individuals have a higher prevalence of sensitisation than those who live in the middle of cedar forests.

Another hypothesis for the rise in allergies draws on the observation that the birth head circumference correlates with later asthma: 'big heads' (>37cm) have a greater risk[33, 34]. There has been a demographic trend to increasing head circumference in developed countries, probably as a consequence of better maternal nutrition. Good maternal nutrition programmes the fetus to grow more rapidly, but, paradoxically in the latter stages of pregnancy, nutrient delivery cannot keep pace with the demands of the quickly growing fetus. As a consequence, brain sparing results in continued head growth but at the expense of rapidly dividing tissues, such as those in the immune system. This has the potential to upset the balance between two competing pathways, Th-1 and Th-2, which regulate immunising and allergic responses respectively. Allergic sensitisation has been shown to correlate with dietary intake of monounsaturated fatty acids[35], while it appears to decrease with increasing fruit consumption, anti-oxidants and fish oils.

Regarding the association with family size and birth order, a study on the Isle of Wight produced interesting data: allergy as measured by skin prick test decreased with birth order, while asthma increased between the first born and fourth or subsequent sibling. Is this an example of T.H. Huxley's observation that the great tragedy of science is "the slaying of a beautiful hypothesis by an ugly fact"? While the Strachan hygiene hypothesis relates only to hay fever and eczema, not to asthma, the theory promoted by immunologists in support of this hypothesis rests strongly on the idea that allergic disease is associated with a bias towards the 'Th-2' pathway. This has been recently challenged by the observation that diseases related both to the Th-1 pathway (e.g. diabetes), and to the Th-2 pathway, have increased in the same population at the same time; and that they are therefore significantly associated[36]. This is further supported by a population study showing raised odds

**Figure 2:** Allergies and autoimmune disease




ratios for four types of allergic disease, including asthma, in patients with autoimmune disease **(Figure 2)**. The response to infection involves primarily the Th-1 pathway: studies on the influence of early infection and later allergy have also produced conflicting results, for example the risks of asthma and hay fever were increased by early infection in a large birth cohort study (n=29,238)[37]. While early antibiotic therapy was previously implicated as a possible cause of later asthma or other allergy, this now appears to be unsupported by consistent evidence: the only prospective study in a high risk birth cohort showed no association with either asthma or allergy[38]. Hospital admissions for bronchiolitis (viral lung infection) have increased over the last decade[39], with evidence also that respiratory syncytial virus (RSV), a major cause of severe bronchiolitis, increases the risk of both atopic and non-atopic asthma[40].

Probiotics (cultures of potentially beneficial bacteria of healthy gut microflora, such as Lactobacilli) have recently been shown to reduce the risk of eczema in a controlled trial[41]. This casts doubt on the hygiene hypothesis, though it does suggest that there may be a role for probiotics in, at the very least, modulating the expression of allergy in the skin. Overall, the balance of evidence suggests that there are still many facts to be considered other than the hygiene hypothesis.

## Trends in infection and microbial exposure

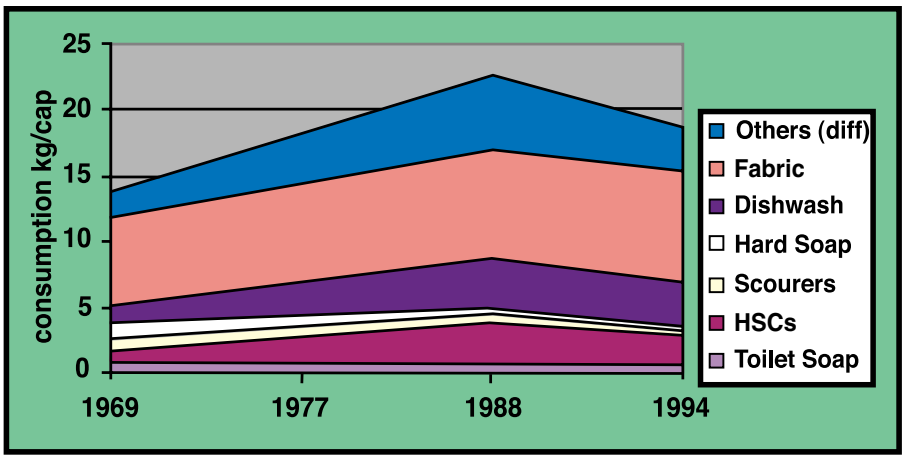
**Professor Hugh Pennington, Head of Medical Microbiology Department, University of Aberdeen**

In the 1960s a US Surgeon General, impressed with the rapid progress of antibiotics and vaccines, announced that "The time has come to close the books on infectious disease". As with so many optimistic predictions of the future, that view was premature – infectious diseases are still very much with us, including new, emerging and re-emerging infections. Nevertheless, there were considerable advances – and conquests - in the field of infection during the late 19th and 20th centuries: typhus fever, for example, declined from 1865 and was almost eliminated by 1905. This infection traditionally spread (and is still a risk) "in colder areas where people may live under unhygienic conditions"[19]. Caused by a rickettsial micro-organism carried by lice, typhus fever was a common problem in any crowded environment, including army barracks and it has been said to have destroyed more lives than the toll of all wars. The identification of the organism and its mode of transmission allowed control measures, including a vaccine in the 1940s that, along with laundry and DDT sprays, prevented typhus epidemics in the allied forces. Louse infestation is of relevance to a discussion of allergies, since the infestation suppresses allergies to other agents, although there is no evidence that it is beneficial in terms of immune system development and the infestation itself promotes a strong allergic response, hence the severe itching experienced by sufferers.

The control of bacterial dysentery is another hygiene success story: while dysentery still occurs, epidemics are rare. It was a different matter in the lunatic asylums of the past, the 'last bastion' for this micro-organism that thrives in wet and dirty conditions. Syphilis was also greatly reduced by the discovery of appropriate therapy, although as with other sexually transmitted infections, eradication is a distant and possibly unattainable prospect. Hygiene behaviours are still an important factor in preventing outbreaks: attack rates, in an *Escherichia coli* outbreak in campers celebrating the Millennium, were found to vary with hand washing frequency. Those who did not wash their hands after defaecation or before eating were nine times more likely to be ill than those who reported hand washing. The ease with which organisms can spread is demonstrated by a study of sixteen men in Antarctica living in total isolation for 32 weeks: there was much sharing of gut E.coli amongst the men, even in this pristine, regimented environment.

Neither hygiene, nor medical treatment and vaccination, can take all the credit for the decline in some of the major infections over the last century: McKeown famously proposed that steady improvements in nutrition from the 18th century onwards, and improved living and sanitation standards following the industrial revolution, made a dramatic impact on infectious disease well before effective medical measures were available[20]. An important issue for the hygiene hypothesis is whether infectious disease declined rapidly before the rapid rise in allergic disorders and how to interpret current surveillance data. Key factors in assessing whether particular infections have declined, increased or altered in pathogenicity (for example the emergence of 'flesh-eating' strains of streptococci in the 1980s) include understanding the pyramid of prevalence and incidence: those identified take up only the tip of this pyramid. Thus any surveillance fig-

**Figure 3: Trends in per capita consumption of soap, detergent and cleaning products, Europe, 1994 (AISE data)**




ures are likely to be gross underestimates of the current burden of infectious disease. Another issue is the existence of appropriate tests and correct interpretation of results: an outbreak of swine 'flu in the USA led to an ill-judged mass vaccination campaign – partly due to political pressure; always an important influence in the management of epidemics. Commensal organisms are still ubiquitous. Discussing the issues for the hygiene hypothesis, Professor Pennington emphasised the need for an organism-specific angle in any implication that microbial exposure could be protective: the evidence of continuing infection risk makes caution essential in referring to general microbial burdens and their postulated benefit.

## Trends in home and consumer hygiene

**John Pickup, Consultant in Scientific Issues, John Pickup Associates.**

Despite the predominant focus of the hygiene hypothesis on the idea of protection by childhood illness against atopic disorders, public discussion led by the media often focuses on homes and talks simplistically in terms of 'the dangers of being too clean'. Typical quotes include "Our obsession with cleanliness… could be costing us our health"; "We fill our cupboards with cleaning products for every surface"; and "We are more hygiene conscious than ever before."

Undoubtedly, people and homes have become cleaner in developed countries, but it is necessary to closely examine trends in domestic hygiene to assess whether they fit with a perception that the progress in cleanliness is in some way harmful. Often, the scientific discussion of the hypothesis presupposes that there have been major reductions in both microbial exposure and infection rates, particularly in children, during the decades in which the sharp rise in the prevalence of atopic disease has occurred. Meanwhile the public may gain the impression that our homes have become dramatically cleaner during this period, or that many of us are living in near sterile conditions – and that 'germs' are becoming a thing of the past. Data conflicting with this impression, for example the estimated 9.4 million cases of infectious intestinal disease occurring annually in the UK[42] and the emergence of pathogens such as *Escherichia coli* O157, are rarely presented when discussing the idea that being a bit dirtier would be good for health.

Examination of timescales and trends in home hygiene indicates that the most dramatic improvement occurred about a century ago during the era of providing safe sanitation and clean public water supplies. Consumption figures for soap and other hygiene products in the USA correlate closely with the abrupt downward trend in infant diarrhoea and associated infant mortality in the years leading up to World War 1[43]. Increases in soap and detergent usage in the last 30-60 years have been more modest than the trend at that time. While other social and economic factors could produce a similar apparent correlation, it is relevant to the hygiene hypothesis debate to examine current data on soap and detergent use. The participating countries in the international study of asthma and allergies in childhood (ISAAC)[5] provides a suitable frame for investigating whether there is any correlation between reported rates of atopic disease and consumption of hygiene products (kg/capita). Broad international statistics show some notable differences from the ISAAC data, with relatively low consumption in Latin America while Peru, Costa Rica, Brazil, Paraguay and Uruguay have high levels of atopy[43]. Statistics to chart trends in soap and detergent usage are not easily handled, not least because product definitions have changed frequently, but analysis of data acquired from the European association for the detergent industry (AISE) serves to show overall patterns and trends. In Western Europe, per capita consumption across 11 countries rose by about 50% between 1969 and 1994. Figures peaked in the late 1980s (Figure 3), probably reflecting two trends: the rapid rise and subsequent settling back of fabric washing liquids (high water content). The introduction of 'compact' detergents in the early 1990s, which delivered more performance per kilogram. The overall trend appears to be a gradual levelling off to around 50-75% above 1969 consumption levels.

Over the last 50 years, use of soap and soap based products for cleaning has been replaced almost entirely by synthetic detergents: fabric washing products account for over 60% of per capita consumption, reflecting also a trend to more frequent washing of expanding wardrobes of clothing, for aesthetic rather than hygiene reasons. Surface cleaning products have grown as a category, seemingly tripling in volume between 1969 and 1994. However, these products are more dilute than the hard household soap previously used, and the true increase of active ingredients is less - probably comparable to that of fabric products. Crude plots of per capita consumption of soaps, detergents and cleaning products for 1994 show no apparent correlation with the average reported prevalence of asthma, hay fever or eczema in the ISAAC study **(Figures 4, 5 and 6)**. The scatter plots are apparently random, with an indication, if anything, only of an inverse relationship. This is the opposite of what one would expect from the hygiene hypothesis.

Western European countries such as the UK and Ireland head the 'atopy

**Figure 4:** Asthma prevalence (ISAAC data) vs soap and detergent use (AISE data)

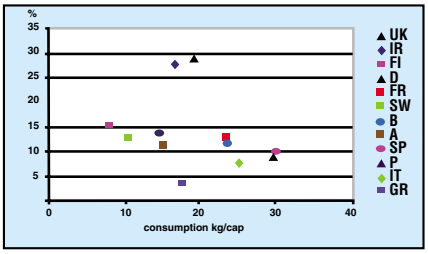



**Figure 5:** Atopic eczema (ISAAC data) vs toilet soap usage (AISE data)

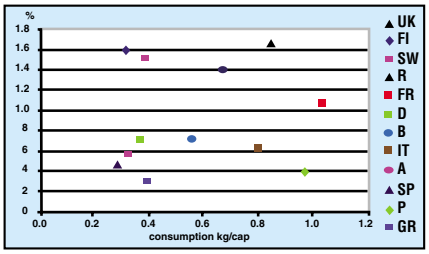
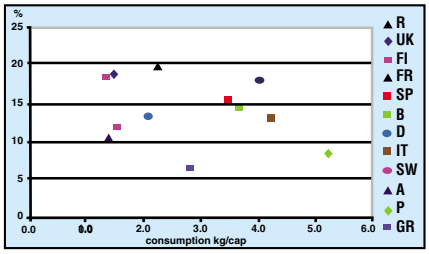



**Figure 6:** Hay fever (ISAAC data) vs surface cleaner usage (AISE data)




league' but are only average users of soaps and detergents: the heaviest users (for example, Spain, Portugal and Italy) have below average levels of atopy. Consumption figures are distorted by product preference (more dilute, bulky products in Southern Europe, with higher consumption in kg/capita), but more detailed analysis by product type, or analysis of earlier time periods, still produces no sign of a pattern that would be statistically significant. Consumption of bleach in France, (figures standardised to 3.6% active chlorine) increased between 1950 (200 million litres) and 1980 (360 mill litres) with a decline after 1990 to 300 million litres in 2000. The trend has included increasing use of more dilute products. On the international scale, France is a relatively heavy bleach consumer (about twice the UK level, while the bleach averse Scandinavians use only 0.3 kg/capita – both areas of high atopy). There is no apparent correlation between this 'germ killing' product and atopy. The introduction of anti-bacterial cleaning products, based often on quaternary ammonium compounds, is too recent to have had an impact on atopy. Thus, although rates of atopy have varied, this is not reflected in the broad trend of domestic hygiene product use. The analysis is necessarily crude. Nevertheless, it provides no support for the notion that increased use of cleaning products leads to higher levels of atopy.

Microbiological surveys of pathogens and other microbes in the home environment show that, in contrast to popular perception, homes are far from sterile: *E.coli* is easy to isolate from a variety of sites (64.5% of 201 British homes in one survey[44]), while damp places and cloths provide reservoirs for high numbers of micro-organisms. More exhaustive sampling studies in the USA reflect a similar picture, including contamination of dry sites such as handles and worktops[45,46]. These surveys have also shown the relatively transient and often insignificant impact of disinfectants on randomly sampled microbial counts: Rusin et al[45] found that introduction of hypochlorite containing products, without clear instructions on when or where to use them, resulted in only a small reduction in the geometric mean bacterial count of weekly samples from surfaces in the home. Use of hypochlorite with a directed cleaning regime produced a substantial reduction, particularly for dry sites, which tend to be the most hygiene critical. Microbial recontamination of cleaned surfaces is a rapid phenomenon[47].

Bacterial and viral pathogens inevitably and routinely enter homes on hands, pets and food. Surveys have shown how easily primary pathogens such as Salmonella spp or Campylobacter spp spread from contaminated poultry and other food[48,49]. Viral contamination, although harder to measure, also appears to be widespread in the home[50].

Such evidence points to the importance of process rather than amount of cleaning or disinfectant products used. Observational studies suggest that, left to their own devices, few people use appropriate food safety measures and hygiene (such as hand washing)[51]. Appropriately applied hygiene procedures can reduce organism counts and protect against infection when used in high risk sites, such as food preparation areas, but there is no evidence that this dramatically reduces the general microbial exposure.

Overall, there is evidence of increased detergent and cleaner usage, replacing the earlier trends in soap use, but increasingly for aesthetic rather than hygiene use. Since patterns of the use of these products shows no correlation with the prevalence of atopy, it must be concluded that if reduced microbial exposure is driving the rise in atopy, it is not an exposure that is directly limited by hygiene in the home. Gastrointestinal and respiratory infections remain common, and the proportion of susceptible people in the population, through age or chronic disease, is rising. Given the rising challenge for infection control, the challenge for the hygiene hypothesis is to confirm whether micro-organisms are required to protect against atopy, and to define what types these are, as well as whether exposure or invasive infection is involved, the route of transmission, when this exposure may be beneficial – and for whom. Otherwise, there is a risk that the public will randomly reduce hygiene standards and compromise a century of improved hygiene.

## Trends in public hygiene

**Dr Martin Schweiger, Consultant in Communicable Disease Control, Leeds NHS Health Protection Unit.**

The medical dictionary definition of hygiene is 'the science that treats the laws of health and the methods of their observation.' The term derives from the Greek goddess Hygeia, whose remit was wider, perhaps closer to the definition of health as positive well-being. Top of the list for public concerns about hygiene, if complaints to local authorities are a guide, is the problem of dog faeces on pavements. Many people live in grimy, uninspiring environments and the 'public space', while cleaner than it was, is still a rich source of microbial exchange through contact, breathing, coughing and the like. Catering, from a public health perspective, involves an ever longer and more complicated food chain, with associated opportunities for microbial contamination – and it is worth bearing in mind that the set-up costs for small commercial catering is

**Box 4: Diogenes' syndrome**

A syndrome of marked self neglect in the elderly, characterised by little interest in cleanliness or social activity, in the absence of marked psychiatric illness to account for the behaviours noted.

cheaper than for most other businesses, and hard to monitor and control. However, most cases of food poisoning, like most murders, are domestic incidents: an examination of the contents of the average 'fridge is often instructive. Hospitals are now larger and more complex, with accompanying challenges for cleaning, particularly now that cleaners are no longer part of the ward team and reduced in number. The cleaning is all too often cosmetic, rather than targeted at risk areas: sometimes no-one is available to give permission or instruction to clean complex equipment. Hospital acquired infection is now a major challenge and significant cause of morbidity. Cleaning is also a problem in schools, where cleanliness of toilets is often a low priority and out of hours use increases the risk of infection: surveys have shown that the highest counts of faecal organisms are on the 'story time carpet', thanks to rubbing by tiny unwashed hands. There is a strong public health case for hand washing to be in the national school curriculum. There are some good initiatives countering the hygiene problems, such as 'The Clean Gang' health promotion work in Leeds (including characters with child appeal such as Flossie Flannel, Sammy Soapflake and Tessie Toothbrush). Public toilets are fewer and further between, with consequent fouling of doorways and other public areas. Why, in this era, do hand basins in public toilets still usually have separate hot and cold taps, and no plug – making effective hand washing difficult? Also, such toilets rarely have lids – when they are flushed the fine spray from the bowl has an excellent opportunity to contaminate the environment. As for insanitary conditions, these are hard to assess in the absence of an official definition, although odour and the 'tac o mat' test is invaluable to public health practitioners (prompting the thought on some domiciliary visits: - "Should I have brought my Wellington boots?"). There is a need to recognise the 'senile squalor syndrome' (also known as Diogenes' syndrome **(Box 4)** after the old founder of the cynic sect, who lived in a paltry narrow tub), and for whom the deplorable conditions prompt calls for the use of Section 47 of the National Assistance Act – to compulsorily remove them for health care and a clean up, although alternative routes rather than this legislation are now preferred.

A clean environment can be defeated by the efforts of a single individual: historical examples include the widow of Hampstead, Mrs Eley who was the only victim of cholera in Hampstead in the famous outbreak investigated by Dr John Snow in Broad Street, Soho, 1854 (she had the contaminated water brought up to her for its taste); and Mary Mallon -'Typhoid Mary' – who, ignorant of hygiene precautions such as hand washing, caused several clusters of typhoid fever in the homes in which she worked. So a clean environment can give a false sense of security. If you think the environment is microbe free, look at what a beam of sunlight highlights in a darkened room, or what grows in surface swabs. Modern society is a dynamic balance between risk reduction (cleaner surfaces, better cleaning agents, more understanding of risks and affluence, and better air quality) and the risk development associated with a more urbanised society, with far flung travel opportunities, new diseases finding new niches and, importantly, a loss of 'cultural' memory of how to prevent the risks familiar in the past. In relation to the hygiene hypothesis, there may also be a need to examine the procedures and methods used to control micro-organisms, in case this in some way modifies them to our detriment. Meanwhile, infection risks, despite the success of eradicating smallpox and the slow progress in eradicating polio, remain a public health priority, recognised by the Chief Medical Officer's report 'Getting Ahead of the Curve' and in the plans for the new Health Protection Agency.

**Box 5: Obesity as an international problem[52-54]**

**An increasingly obese world**

- **300 million obese adults worldwide**
  - Increase of 100 million since 1995 (WHO 2001)
  - Increasing body mass index correlates with increasing risk of adult asthma (Camargo et al 1999)
  - Triceps skinfold thickness increased by -8% in English boys and girls between 1972 and 1994 (Hughes et al 1997)
- **Time scale of rise in USA & Europe similar to rapid rise in atopy**
  - ?'allergic' combination of fast food diet, lack of exercise and obesity

## Other possible factors involved in the hygiene and allergy debate

**Dr R Stanwell-Smith, Public Health Consultant and Scientific Adviser, RIPH.**

Some commentators have described the rise in atopic disorders as the 'price' for modern lifestyles, an exchange in health terms for the infection pandemics of the past. But the contemporary lifestyle in developed regions also involves marked changes in diet, obesity, exercise, environment, exposure to animals and different types of pollution, including natural as well as controllable sources – and even in our patterns of sleep, with evidence of increasing problems related to sleep deprivation in children and in adults. The rapidity of change has also prompted an understandable yearning to return to traditional, less complicated lifestyles. In the 18th Century, Queen Marie Antoinette and her court tried to capture a similar yearning by milking cows in a 'pretend' dairy at Versailles, so it is tempting to coin a 'Marie Antoinette hypothesis' to cover the idea that a suitably sanitised set of rural exposures would be beneficial for health. The reality is that the traditional rural lifestyle of the past was far from idyllic, particularly in terms of infection risk. On the other hand, few people were obese, while in our time, obesity is an increasing problem in children as well as adults **(Box 5)**.

There is no doubt that most of us have less exposure to farm animals than in earlier traditional communities. If microbial exposure, for example in the form of endotoxins, is proved to be essential for our immune systems, a possible remedy is the administration of environmental bacteria, for example in probiotics, in vaccines, in 'controlled exposure', if this is feasible, to dirty environments (when and if the extent and nature of beneficial 'dirt' is defined by research). Probiotics are currently strongly favoured as helping to create favourable gut flora that may assist in resistance against infection, as well as possibly helping to ensure healthy gut

**Box 6: Box 6: What do we mean by home hygiene?**

Home hygiene is the sum total of measures used to prevent transfer of infection, including:

- General home hygiene
- Food hygiene
- Home health care: for people who are infected; and for people at increased risk of infection

The home is an environment where all human activities occur.

immunity. They have been shown to enhance gut specific immunoglobulin (IgA)[55], to reduce eczema[41] and to prevent diabetes in mice[56], with possible therapeutic relevance to human diabetes. The popularly termed 'dirt vaccines' are in fact cultures of saprophytic mycobacteria: strains that used to be common in water, milk and mud. Trials suggest a beneficial effect on some types of autoimmune disease, such as multiple sclerosis. The scientific basis for these effects is still uncertain as regards whether it relates to a microbial lack in the early stages of development – particularly as the studies on the effect of BCG or exposure to tuberculosis have reported conflicting results. Further research and therapeutic trials may assist in reducing the effects of severe immune disorders, while the search for their cause continues.

## What could this mean for hygiene: do we need to adjust our approach?

**Dr Martin Jones, Hygiene Research manager, Unilever Research and Development, Port Sunlight.**

The investigation of the hygiene hypothesis has contributed to a previously ongoing debate on the best advice for the prevention of infection. If further research validates the hypothesis, there will be a need for hygiene professionals and the hygiene industry to respond appropriately, especially given the evidence of continuing exposure to potentially dangerous infections – and to the largely invisible risks of microbes. The challenge is to find ways of improving infection control whilst minimising environmental impact and any impediment to 'training' the immune system. The debate has led to a re-thinking of hygiene policy in terms of how to protect the most vulnerable groups in domestic and other settings: infants, sick people and the elderly. This seminar has pointed to the need to avoid encouraging obsessive behaviours or irrational fears of dirt and germs, while promoting a sensible approach to hygiene and awareness of situations with potentially high infection risk. The responsibility for this is, ideally, shared between industry, consumers and health professionals. This involves agreeing on critical areas for hygiene practice and on messages to give to consumers, as well as recognising the anarchy of the home: a rational educative approach has little effect on behaviour, partly because of the distractions present in the home.

The risk assessment needs to be tailored to the needs and circumstances in the home. HACCP (Hazard Analysis and Critical Control Point), a process that has successfully controlled microbial hazards in food and other manufacturing environments, provides a useful model, but it cannot be directly applied to the wide scope of home hygiene **(Box 6)**. A risk-based approach to home hygiene has become known as 'targeted hygiene' to emphasise the link to minimal, but effective, application of control measures.

Effectiveness of a home-based risk assessment approach includes hazard identification, dose response assessment, considering the probability of contamination with harmful microbes and their infective dose. The scientific basis for this approach derives from recent research specifically focused on the domestic environment. This has provided information on how, and to what extent, enteric pathogens can be spread in this environment and how, in turn, their transmission can be prevented by hygiene practice. The research has allowed hygiene policy to be formulated by reference to data specific to the home, rather than by extrapolation from other environments – much of the previous research was based in hospitals and other large institutions.

## Developing a risk assessment approach to the home

Data on dispersal, survival and transmission of enteric pathogens in the home environment suggest that the high risk surfaces are in the kitchen (hands, cloths, food contact surfaces and hand contact surfaces such as taps or door handles) and the bathroom and toilet (hands, cloths and the toilet seat, handles and taps). Foodborne or food related infection in the home occurs in a number of ways:

- consumption of contaminated food that has not been appropriately stored or cooked.
- Cross-contamination of raw to cooked food
- cross-contamination from surfaces or utensils
- food contaminated by an infected food handler in the home
- person to person transmission from an infected 'non-food' handler such as a child to a food handler

Preventing foodborne infections goes beyond the kitchen environment and relates to all the hygiene activities in the home – and not all gastrointestinal infections are foodborne: person to person spread by the faecal-oral route remains a well used route of infection. In a study of meal preparation using chicken contaminated with salmonellae and campylobacter, these bacteria were most likely to be isolated afterwards from chopping boards (60% of those sampled) but also from most sites in the kitchen, including 35% of hands, 25% of dishcloths and 30% of sinks – even on 5% of the salt and pepper pots[49]. Toys are another high risk site, as shown in studies of the transmission of bacterial dysentery *(Shigella sonnei)*. Pets pose an obvious, but often over-looked, source of enteric and other infections; insects are also an important risk factor, even in a cold climate.

Communicating these risks involves an understanding of how to motivate behavioural change and of the 'anarchic home': the domestic setting is fundamentally different from hospitals, manufacturing and other settings. The multi-functionality of the 'polycentric kitchen', meals in front of the TV, fewer family meals and a generally low priority to cleaning and hygiene are just a few of the issues to consider. In addition, the general public understanding

of hazards and risks is very low. For example, a study in the Wirral showed a low rate of hand washing after nappy changing, mostly due to distractions and other priorities. Since education seldom has a lasting effect, the messages must be simple, clear, empathetic and empowering. Guidelines on best practice are available from the International Scientific Forum on Home Hygiene (IFH) website[57], although a range of options can be helpful to avoid the impression of dictating one type of behaviour. Work on behavioural change by Dr Val Curtis in the London School of Hygiene and Tropical Medicine has identified the inertia involved in altering approaches to hygiene, an inertia fuelled by cultural barriers, laziness, force of habit and a lack of triggers to motivate change. Providing clearly attainable goals and aspirations (such as healthy pregnancy and childbirth, aesthetic aspects of a clean looking home, belonging to a group that places a high priority on hygiene, status) is one means of overcoming inertia to behavioural change. Disgust with obvious poor hygiene can be a motivator. Products that can communicate or facilitate sensible hygiene behaviours include smart toothbrushes with timers, elbow taps, hands free 'phones, end of use indicators (such as those on water filters), disposable wipes and diagnostic tests to show the contamination on hands, surfaces and in water.

Whether or not the many 'unknowns' in the hygiene hypothesis debate are resolved, and even if the hypothesis is rejected, the debate has provided the opportunity to re-affirm the continuing threat of infection, the need to target hygiene measures where they are most likely to reduce transmission risk and where they will reduce microbial contamination to safe levels: not the creation of 'super clean' homes or 'germ free' environments.

## Points raised in the panel discussion

The discussion ranged from TV cooks and their influence (for good or ill) on food hygiene, the British pre-occupation with toilet jokes, hygiene behaviours on the reality TV show 'Big Brother', the efforts to make hand washing campaigns interesting and effective - and whether the public would react kindly to being advised that exposure to animal faeces in the street could be potentially beneficial. In particular, the panel and audience debated the epidemiological and research challenge of the hygiene hypothesis, as well as its practical implications and whether allergy is the price that has to be paid for reduced levels of infection mortality.

The different perspective of the various specialists involved in both infection prevention and the investigation of atopy was suggested to be a barrier to resolving practical issues. One answer to the 'hygiene dilemma' was agreed to be achieving a balance between different desirable outcomes: reducing atopy while continuing to maintain over a century of progress in hygiene and sanitation. Clarifying some of the questions requires a reductionist approach, eliminating one factor at a time. Studies involving a multitude of factors tend to be large, unwieldy and have relatively non-specific results – with funding implications for the required size of intervention studies. While large samples are needed for analytical epidemiology, the value of natural experiments should not be ignored – even if this term really means, as Professor Strachan quoted, "an observational study viewed by an optimist". Examples of natural experiments include the studies on farming families and those with atypical lifestyles, or groups refusing vaccination. The conflicting data concerning BCG exposure could be investigated by the natural experiment of differing policies on neonatal BCG in, for example, adjacent areas – although the issue of interpreting tuberculin skin tests would need to be resolved. One difficulty in natural or uncontrolled observational research is that families with a strong history of allergy tend to alter their behaviour and lifestyle, for example in duration of breast feeding, and it can be hard to identify factors that preceded or followed the onset of the allergies under study – as well as to define selection criteria. Genetic profiling may help with such selection.

Microbiological studies are difficult to conduct in retrospect: long, prospective studies are required to determine the effects of infection or of absence of infection. While microbiologists and infection specialists remain sceptical about the beneficial effects of microbes, particularly pathogens, further research into probiotics appears to be justified. A limitation to research with microbes is our lack of knowledge about how to do such research safely and the technological issues of separating different strains and species. If bowel flora are important in immune system development, it may involve repeated challenge rather than one-off or narrow windows of exposure.

Encouraging people to keep diaries of exposures and symptoms has proved helpful in public health research of risk factors, but although the 'n=1' approach may provide the required detail, it might not be representative of the population at risk. How far back does the research need to go, given evidence that childhood obesity may be linked to the mother's weight in early childhood? One of the broad conceptual questions about increasing prevalence is whether the duration, rather than the incidence, of a disease is being affected. The target organs involved in different immunological disorders may be just as important as the underlying immunological factors. Given the high numbers of allergy reports in the population, it is possible that susceptibility is almost universal, and research into the factors that suppress inappropriate and damaging response to allergens may be more relevant. Overlapping cohorts (of different ages) may be one way of addressing the need for long-term cohorts.

When asked by the audience for a conclusive assessment of the hypothesis, the panel agreed on the need for more research, the need to find other alternative biological mechanisms; and the dilemma of finding causes for such a wide range of diseases. Faced with this complexity and the uncertainties or inconsistencies in the evidence, the best way of summing up the combined panel view would be that the hypothesis is 'not proven', but that there is a need to keep an open mind as further research unfolds. Meanwhile, there was, at least, consistent support for focused hygiene policy and, indeed, for hygiene itself - since there is no direct evidence linking atopy to hygiene per se. So Hygeia, Ancient Greek goddess of health, invoked in one of the presentations, was well served by this symposium.

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