

Review Series: The “Long and Winding Road” to Our Goal of Primary Prevention of Allergic Diseases

Disease Prevention in the Age of Convergence - the Need for a Wider, Long Ranging and Collaborative Vision

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ABSTRACT

It is time to bring our imagination, creativity and passion to the fore in solving the global challenges of our age. Our global health crisis and the pandemic of noncommunicable diseases (NCDs) is clearly rooted in complex modern societal and environmental changes, many of which have effects on developing immune and metabolic responses. It is intimately related to wider environmental challenges. And it is unsurprising that many NCDs share similar risk factors and that many are associated with a rising predisposition for inflammation. Allergy is one of the earliest signs of environmental impact on these biological pathways, and may also offer an early barometer to assess the effects of early interventions. There is dawning awareness of how changing microbial diversity, nutritional patterns, sedentary indoor behaviours and modern pollutants adversely affect early metabolic and immune development, but still much to understand the complexity of these interactions. Even when we do harness the science and technology, these will not provide solutions unless we also address the wider social, cultural and economic determinants of health - addressing the interconnections between human health and the health of our environment. Now more than ever, we need a wider vision and a greater sense of collective responsibility. We need long-range approaches that aim for life long benefits of a ‘healthier start to life’, and stronger cross-sectoral collaborations to prevent disease. We need to give both our hearts and our minds to solving these global issues.

KEY WORDS

allergic disease, developmental origins of health and disease (DOHaD), diet and nutrition, microbiome, non-communicable diseases (NCDs)

ABBREVIATIONS

NCDs, non-communicable diseases; DOHaD, Developmental Origins of Health and Disease; RCT, randomized controlled trial; CVD, cardiovascular disease; UN, United Nations.

This is not a comprehensive review. Nor is it an up-to-date review. It is not even a balanced perspective of the topic. In fact, to my great delight, I have been instructed to completely ignore that conventional approach, and to focus on my personal experiences, my

struggles and even my failed efforts in developing primary prevention strategies for allergic disease.

First though, I will take the liberty of redefining the scope of this agenda, as I believe it is critically important to consider the ‘allergy epidemic’ in the context

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Conflict of interest: SP has received travel reimbursement and honoraria from Danone and Nestle Nutrition Institute.

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Received 14 November 2013.
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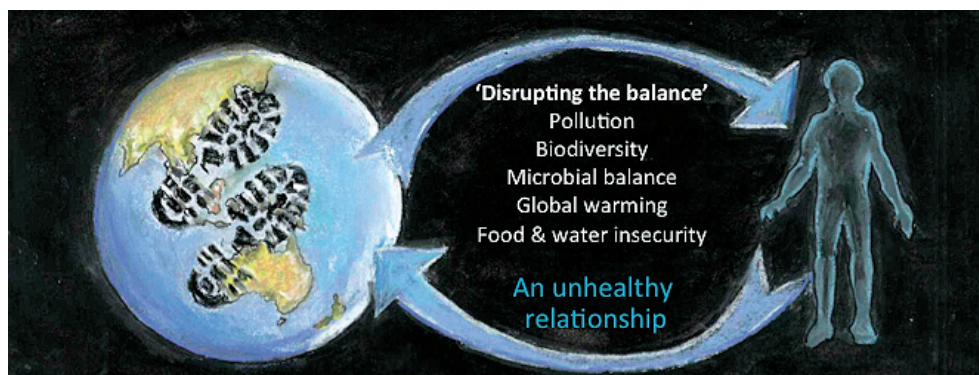


Fig. 1 The interconnections between human health and environmental health. Humans are affecting the 'health' of the planet with adverse effects on our own health.

of the much wider pandemic of noncommunicable diseases (NCDs).¹ It would be shortsighted to consider these as separate or unrelated, and quite against my personal philosophies. Many of modern diseases share the same lifestyle and environmental risk factors, and I strongly believe that we should be taking a more interdisciplinary, cross-sectoral approach if we ever hope to overcome these major global health issues.¹ We also need to see that the human health crisis is intimately linked with the declining health of our environment (Fig. 1).

For over 20 years I have been keenly interested in the 'developmental origins of health and disease' known as 'DOHaD', which was initially grounded in cardiovascular medicine. And although I might be better known for my research in allergy, my work has been inherently interdisciplinary for many years.

So why has a paediatrician and an immunologist with a focus on allergic disease been so intrigued by these ideas about the 'early origins' of adult heart disease? Why had I even been following this literature in the 1980s, in an era before the true dawn of interdisciplinary research?

PREVENTION IS IMPERATIVE IN THE FACE OF OUR GLOBAL HEALTH CRISIS

Before I get to my own philosophies and the journey of my work in disease prevention, I want to emphasize the enormous scale of the NCD pandemic and the need for a global response to the a global health crisis. 'Modern lifestyle' diseases are now recognized as the leading cause of death worldwide, in *both* developed and developing countries. This global health crisis has been building, slowly, silently, and deadly—yet largely unheeded for decades. NCDs are a major cause of poverty and must be viewed as a major global economic threat. In 2011, in response to this global health crisis, the United Nations (UN) General Assembly held its first high-level summit specifically to address the rising worldwide burden of NCDs. This has bought the issue squarely into the global po-

litical agenda, with participation of Heads of State and Governments from around the world. Based on the sobering figures presented in the UN Political Declaration on the 'Prevention and Control of NCDs', there are more than 36 million deaths each year from NCDs.² These chronic diseases account for more than 60 per cent of all global deaths. Tragically, at least 9 million of all preventable NCD deaths are in younger people, in their 'prime' years of life. An astounding 80% of all NCD related deaths occur in the developing, underprivileged regions of the globe.² Without urgent action it has been projected that NCDs will claim the lives of 52 million annually by 2030. Even in Africa, NCDs are also projected to well surpass infectious diseases as the most common cause of death by 2030. No region, no population is unaffected.

There is no doubt that this epidemic is hitting the developing world and lower income populations hardest. While poverty and lack of education are major risk factors for NCDs, NCDs also drive both individuals and economies further into poverty, creating a vicious cycle. It is clear that this cycle can only be broken by addressing the social and economic determinants of health. This underscores the compelling need for a multilateral 'whole-of-Government' approach.

Prevention is clearly the name of this game. It is stamped all over the global strategic plan. But, amazingly, the dominant focus has largely been on 'adult' interventions for NCDs, which are still seen largely as 'problems of adulthood'. Given what we know now, this still limited, shorter-term approach is neither sustainable, nor as likely to succeed as a more comprehensive 'life course' strategy that addresses *all* stages of life and specifically targets 'early life' the most logical period for true preventive intervention. If prevention is to be more effective, it is obvious that strategies need to be implemented *before* disease processes are initiated and *before* risk factors come into play. With clear evidence that the pathways and risk fac-

tors that lead to many NCDs begin to have effects very early in development, this should be a core element in the agenda and strategic plan. But it has not been.

By its very nature, such an approach immediately throws a spotlight on the central importance of education and health literacy in children, adolescents and parents, and in particular the need to educate and empower women of childbearing age in all regions of the world. I was privileged to play a very small part in an effort to address this need, through the World Universities Network (WUN), which met in *Shanghai in 2011*, with the task of developing a simple clear and unequivocal declaration to be delivered to the United Nations, ahead of the General Assembly. The resulting *Shanghai Declaration*³ was an opportunity to stress the social and economic benefits of low cost interventions applied *early* in the 'life course', and all the wider benefits of strengthening the basic human right to a healthy start to life, education and gender equity. It also endorsed a multi-agency approach synergistically linked to current programmes on maternal and child health, infectious disease and to the Millennium Development Goals. Small fragments of this were adopted into the UN Political Declaration on the 'Prevention and Control of NCDs'² but many believe that the importance of early intervention was not emphasized nearly enough.

THE 'EARLY ORIGINS' OF MY RESEARCH

When I first came to the allergy field in the early 1990's I was already well schooled in concepts of prevention. As a paediatrician, this was second nature. But through my research earlier in the 1980's, I was also very familiar with the notions that nutrition, lifestyle and other environmental factors play a fundamental role in disease predisposition. Although I am now well known in the 'allergy world', few are aware that I actually started my research career in cardiovascular medicine, and that my first randomized controlled trial (RCT) was actually studying the effects of nutrition on blood pressure.^{4,5} In those days I was working in a group that were in the process of discovering the anti-inflammatory properties of diet nutrients.^{6,7} It was also at a time when there was dawning recognition that cardiovascular disease (CVD) was an 'inflammatory' disorder rather than simply a mechanical narrowing of vessels secondary to cholesterol deposition. Macrophages and their cytokines had begun to feature as likely mediators in pathogenesis of atherosclerosis. At almost the same time there was a similar paradigm shift in the field of asthma. As a medical student I had learned about asthma as a reversible, mechanical narrowing of airways, with the emphasis very much on aberrant smooth muscle responses and neural reflexes. However, in the 1980s we also began to 'inflammation' take a more central role in our understanding of the pathogenesis of

asthma. By extension, this also became the dominant focus of treatment, as inhaled corticosteroids became more widely used in the control of the disease through reducing airways inflammation.

In 1986, through the cardiovascular field, I began to learn more about the 'early life origins' of heart disease and other chronic inflammatory diseases.⁸ David Barker's group had just published a *Lancet* paper suggesting strong geographical variations in ischaemic heart disease in England and Wales might be linked to impaired fetal growth and nutrition in pregnancy.⁸ Much higher rates of coronary heart disease were seen in poorer rural or industrial areas where infant mortality had been also been highest. They proposed that the same 'in utero' risk factors for infant mortality were also risk factors for poor fetal growth the survivors, and that this poor early nutrition might be the contributing risk factor for later heart disease in the region. This was consistent with earlier reports in the 1970s by Norwegian researchers who had also noted higher rates of CVD in regions of high poverty.⁹ Both groups proposed that early nutritional deficits lead to permanent damage, and that later affluence was a prerequisite for disease. It seemed that the risk was greatest if there was significant 'mismatch' between the *anticipated* environment based on our 'in utero' experience and what *actually* happens after birth. For example, if we encounter an *overabundance* of food after birth when our metabolism has been programmed for scarcity, we are more prone to disease. Without detailed data on birth weights and infant growth this was largely conjecture at that point.

That same year, one of the postdocs from our group, Barrie Margetts, who had also been working on the RCT of dietary interventions on blood pressure, moved to Southampton in the UK to work with Barker on the Hertfordshire cohort in an attempt to confirm this association. It was this link that drew my attention when they went on to their next *Lancet* paper on the 'early life origins of disease' in 1989.¹⁰ In Hertfordshire they found the ideal opportunity to map long-term disease outcomes in relation to early growth and development. From 1911 onwards the midwives and health visitors had recorded birth weight and visited homes to measure infant weights. Follow-up of over 5,000 men born between 1911 and 1930 revealed that the risk of coronary heart disease was proportionally higher as birth weight decreased. This appeared to confirm Barker's earlier theory that in utero stress and poor nutrition increased the future risk of CVD. In the years that followed they also published evidence that adult lung function, chronic lung disease, obesity, diabetes risk and other noncommunicable diseases (NCDs) are similarly related to early nutrition, birth weight and other early life events.

The same is true of virtually all body systems. It is very obvious now that 'adverse conditions' in early life can have lasting effects on all aspects of growth

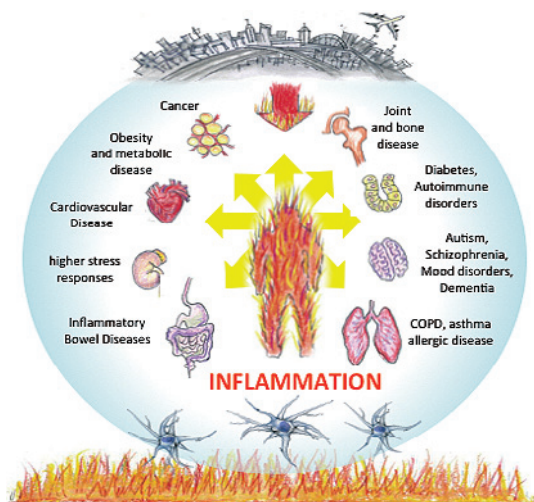


Fig. 2 A rising propensity for inflammation is implicated in the parallel rise of virtually all NCDs. This suggests a central role of the immune system, as one possible nexus for multi-system effects of modern environmental changes.

and development. These very early effects on both structure and function, shape our physiological (functional), immune, metabolic, and even psychological and behavioural response patterns to the environment and can have life-long effects. Most importantly, this can influence the susceptibility to diseases decades later. On the flip side, it is logical that promoting 'optimal conditions' in early life is the best hope we have of hardwiring 'healthy' physiological, structural, immune, metabolic, and behavioural response patterns in order to prevent so many avoidable diseases. One of the best-known examples of this is how fetal growth patterns can influence the risk of heart disease, obesity and type 2 diabetes in later life. And there are many more examples.

These concepts provided a strong grounding for my research as I specialized in paediatric immunology and allergy, and as I became increasingly interested in inflammation as a common linking theme underpinning many of these NCDs. For me it also raised the likelihood that many of the environmental risk factors shared by NCDs may exert at least some of their effects through effects on the developing immune system.

EARLY IMMUNE PROGRAMMING - A COMMON PATHWAY TO NCDs?

From 1995 I worked with renowned cell biologist Patrick Holt, mapping early immune development in humans. By 1999 we had published our own *Lancet* paper,¹¹ which turned the spotlight onto the 'early origins' of allergy and immune diseases. This was the first to map very early immune responses over the first years of life and to find early differences in children with allergic inflammation. Some of these differ-

ences were already apparent at birth, providing evidence of 'fetal programming' of allergic disease and fueling interest in much earlier events.¹² Differences in the very early postnatal maturation of immune responses also indicated the importance of events in the first months of life. As with the 'Barker story', this contributed to a significant shift in thinking towards the 'early origins' of allergic disease. In some ways this was an easier case to sell than the 'early origins' of heart disease. Because eczema, food allergy and asthma appear so much earlier in life it is more obvious that early events *must* be important.

The allergy epidemic is the clearest evidence we have that the early immune system is exquisitely sensitive to modern environmental changes. And I could not help wondering if the same environmental risk factors might be implicated in the rise in so many other inflammatory diseases. Given that diet, microbes, exercise and modern pollutants all affect the developing immune system, it can be no surprise that these are also linked with the rise in so many other NCDs.

And for this reason, when I set up my own independent research team in 1999, my primary focus was on trying to demonstrate that a number of specific early in the environmental factors, such as maternal diet, smoking and early microbial exposure have at least some of their effects on the developing immune system.¹³⁻¹⁷ It is certainly becoming clearer that the developing immune system is exquisitely vulnerable system to early environmental changes, and has a central role in the risk of so many different diseases.¹

In 2001, the International DOHaD Society officially was founded and the very first international congress was held in Mumbai. In true interdisciplinary spirit, this brought together experts from diverse fields of medicine and science, all with a common goal: promoting the importance of a 'healthy start to life', beginning from (and even before) conception, for the future health of all body systems and as the best hope for preventing diseases later in life. I was invited to 'represent' the immune system and allergy. At that time I was not really sure that many people understand the relevance of what I was doing. But attending that first DOHaD meeting made it even clearer to me that the immune system is a core part of the wider NCD story. My early research into heart disease taught me a lot about the role of the 'inflammation' in hypertension and cardiovascular disorders. In fact, it has become increasingly obvious that inflammation is a common element of most NCDs, including heart disease, lung disease, joint disease, bowel disease, diabetes and obesity related diseases (Fig. 2). There was little doubt in my mind that modern environmental changes promote inflammation and, as a paediatrician, I could already see the first hand effects of this in the first years of life in the epidemic al-

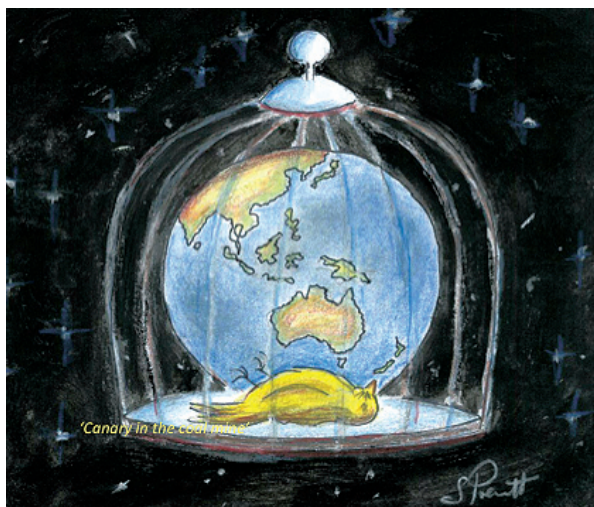


Fig. 3 The allergy epidemic as a canary in the coal mine. An early indicator of the impact of modern environmental change and specific vulnerability of the immune system. This early propensity for inflammation and immune dysregulation has implications for rising risk many other later onset inflammatory diseases (NCDs).

lergic inflammation. I decided that I would keep trying to get that point across. As you might imagine, with so many parallel sessions, the allergy and immunity session was tucked away and did not compete well with the sessions on cardio-metabolic disease, so I did not get to sell my message to many people.

Since then, there has been mounting evidence that the immune system plays an important role in the developmental programming of many organ systems, and the predisposition to many diseases. It is also clear that the early environment heavily influences the 'dynamics of inflammation' in later life (below).¹⁸ Even in the brain, there is now good evidence that the immune system plays a critical role in the establishment of synaptic networks in the developing brain,^{19,20} and that the balance of cytokine levels in the hippocampus is important for learning and memory.²¹ Early life events can alter response patterns of microglial (the innate immune cells of the brain) to inflammatory challenges in later life will increase the risk of inflammation and a range of neuropsychiatric disorders, many of which have been linked to increased inflammatory cytokine production.²⁰⁻²⁴ This is really to illustrate the point that improving 'immune health' in early life may achieve a great deal more than just preventing allergy and immune disease, but is likely to have benefits for many other developing organ systems, and our future predisposition to many other diseases as well.

THE ALLERGY EPIDEMIC AS AN IMPORTANT SIGNPOST

There is every indication that allergic diseases are

rapidly rising in almost all developing regions, and it is estimated that already, around 30-40% of the world's population are affected by one or more of these allergic conditions with vast personal, social and economic costs.²⁵ But a key and important difference is that allergic diseases appear *much earlier* in life than other NCDs. Allergic diseases are arguably the *only* common NCDs to appear in the first year of life, with children bearing the brunt of the very dramatic recent rise in disease. This indicates that the developing immune system is particularly sensitive to environmental changes. Many will have heard me refer to allergy as 'the canary in the coal mine' (Fig. 3). By extension, this means that the immune system is a useful *early barometer* of environmental impact, and an early measure of effectiveness of any interventions that we might try to prevent disease—not just allergy but other NCDs. So why is allergy not on the global NCD agenda?

Those of us working in this field can very easily see that many environmental risk factors influence immune function, including maternal diet, maternal smoking, maternal stress and early microbial exposures. We can see how changes in diet can specifically alter immune function in the gut with implications not just for immune diseases, but also diabetes, heart disease, obesity and even neurological disorders. The immune system is *designed* to respond quickly to the environment. That is how we survive. This may also be the reason that modern environment changes lead to symptoms of immune disease so early in life. This can offer us vital clues about why we are also increasingly prone to other NCDs, which all generally feature inflammation and immune dysregulation.

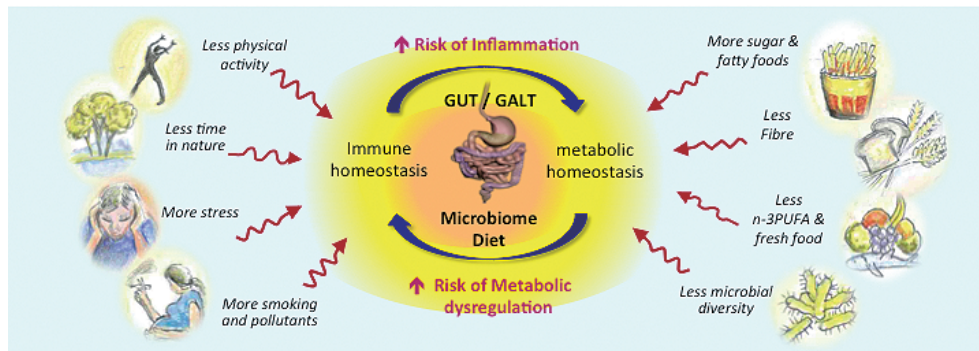
The dominant focus of the NCDs agenda is usually on 'the big four' - cardiovascular disease, metabolic disease (obesity and type 2 diabetes), cancer and chronic lung disease. While both asthma and smoking related disease are considered in the context of 'chronic lung disease', allergic diseases *per se* are typically overlooked in this agenda, despite now being the most common and the earliest onset NCDs in most regions. This multi-disciplinary alliance is at the very core of how we need to move forward with a more integrated interdisciplinary vision of human health. It is now important to broaden this agenda, and that other extremely common NCDs and their risk factors are progressively incorporated into the agenda—not as competing interests but a part of a bigger picture, which reveals the inter-relationships between these conditions and may help us understand the pathways to disease better.

TARGETING INFLAMMATORY PATHWAYS TO PREVENT A RANGE OF DISEASES

Economic prosperity is associated with a rising propensity for chronic low-grade inflammation, and ris-

Many lifestyle risk factors for NCDs promote inflammation

Many have *direct* effects on immune function



Targets for prevention strategies: multisystem benefits

Fig. 4 Many life style risk factors for NCDs have both immune and metabolic effects. These are also the logical targets to prevention inflammation and metabolic dysregulation.

ing susceptibility the chronic inflammatory NCDs. The environmental conditions in utero and in early childhood also appear to contribute to the risk of subsequent inflammatory diseases.¹⁸ This includes both early onset NCDs such as allergy, asthma and some autoimmune diseases, as well as later onset NCDs including cardiovascular disease, metabolic disease and neurodegenerative disorders - which appear to share many common environmental risk factors.¹ While inflammation and the pathways to disease are clearly multifactorial, dietary changes, pollution and declining microbial diversity are central themes, and increasingly implicated in the immune and metabolic dysregulation seen in many NCDs²⁶ (Fig. 4).

The role of the early environmental and inflammation is obvious in allergy, but low-level chronic inflammation, even at levels previously thought to be inconsequential, appears to contribute to many NCDs and diseases of aging¹⁸ including cardiovascular disease²⁷ and type 2 diabetes.²⁸ Even in childhood, early arterial changes that predict atherosclerosis can be readily detected.^{29,30} The cardiovascular research team I still collaborate with have shown that a strikingly high proportion of Australian 14 year olds show inflammatory and metabolic changes that predict cardiovascular disease and other NCDs.³¹ There is also emerging literature in the allergy field, showing that IgE levels are linearly related to BMI (body mass index) and CRP in children.³²

These observations are also consistent with evidence that both baseline levels of CRP in adulthood and the 'dynamics of inflammation' are influenced by the early life environment.¹⁸ This includes a wide range of nutritional and microbial exposures, environmental toxins, and maternal health factors including obesity, gestational diabetes, preeclampsia (high blood pressure) in pregnancy and a range of other

factors and stressors that can influence both growth and inflammation. The interrelationships between metabolic health and immune health are recurring themes and major determinants of disease risk.

While the global NCD agenda has tended to focus on 'the big four risk factors' (poor nutrition, tobacco, alcohol and lack of exercise) this overlooks the vital role of the microbiome which is now known to play a critical role in both metabolic and immune programming.^{1,26} This has been of longstanding interest in the field of allergy where the hygiene hypothesis originally emerged,³³ but the role of the microbiome in metabolic health has only emerged relatively recently.³⁴⁻³⁷ The high fat, low fibre 'western' diet is now understood to adversely change the gut microbiome, with associated effects on gut barrier function, increasing systemic antigenic load and low-grade endotoxaemia - as a driving factor for insulin resistance, obesity, and diabetes.³⁸ This is associated with increased CRP and higher levels of circulating IL-1 β , TNF, IL-6 and adiponectin as evidenced by increased low-grade systemic inflammation.³⁹ Microbiota can also directly regulate host genes involved in lipid metabolism³⁴ with associated effects insulin resistance, food craving, altered lipid profiles and liver function, which collectively contribute to obesity and metabolic dysregulation.³⁴⁻³⁷ Notably, many of these physiological and metabolic adaptations can be reversed through restoring a more 'favourable' gut microbiome.³⁷

Using the brain as another example, because it is often overlooked in this discussion, we can see that as the main immune cells of the brain, microglia are very sensitive to any inflammatory triggers in the systemic circulation. They are able to detect the same broad range of 'danger signals' as other immune cells, including microbial signals and *non*-microbial

danger signals. These can be in the external environment or 'alarmins' that are released from damaged tissues and inflammation within the body.⁴⁰ This all means that the microglia may be potentially re-programmed by a range of other inflammatory events early in life, to modify developing brain function. In this context we also see new dimensions to the 'gut-brain'.⁴¹⁻⁴⁴ Most researchers in the field of allergy are very familiar with the highly quoted studies of Sudo and colleagues in germ free mice⁴⁵; which demonstrate the failure of immune development and the development of immune diseases when normal gut colonization is prevented or delayed. But they are generally less familiar with the effects that Sudo's team showed on the developing brain.⁴¹ Essentially, in germ-free animals showed reduced expression of the neuronal growth factor BDNF in the cortex and hippocampus, and heightened cortisol stress responses,⁴¹ consistent with patterns seen in depression and anxiety. This shows that without normal bacteria, 'germ free' animals develop not only immune and metabolic dysregulation, but also maladaptive changes in brain function and in regulation of the HPA axis. Critically, these effects can all be reverse by either giving probiotic bacteria, or by 'faecal transplant' from a normally colonized mouse.⁴¹ Critically, and just as for immune development, timing was critical—reversal was only possible at an *early* stage of development. Once the responses patterns become established with age, they cannot be readily changed. This is consistent with what we know about 'critical early periods' for both immune and neural development and the declining plasticity of neural networks with age. Even in mature animals, disrupting the established normal gut flora with antibiotics can result in changes in BDNF in the brain and altered behaviour.⁴³

In this light we need to address the many lifestyle factors promote chronic inflammation, and these appear to contribute to significantly higher baseline levels of inflammation. There is a very strong case for promoting 'immune health' as an integral part of NCD prevention. Now more than ever, these notions underscore the need for a more integrated, interdisciplinary approach in collectively addressing these problems, which have all arisen in response to modern environmental conditions. It seems to be so blatantly obvious that strategies that promote early immune and metabolic homeostasis, will reduce the risk of cardiovascular disease, diabetes, obesity, neuropsychiatric disorders, allergy and other immune diseases, and many other NCDs.

I could now launch into a discussion of all the usual culprits in the allergy epidemic, how we might address them, and what the evidence is at present. And there are many reviews that do just this every year, including ones I have written.¹ I even wrote a whole book about it.⁴⁶ So, I am not going to trawl through

all that here. We all know the main broad risk factors: changing microbial diversity, changing dietary patterns, changing lifestyles (more indoor, sedentary behavior and stress), more environmental toxins and pollutants (Fig. 4). Every discipline would probably list the same risk factors for its major NCDs focus. This covers quite a lot of potential risk factors and we also know it is hard to separate the relative effects of each of these. Animal models confirm metabolic and immunological effects of almost all of these potential factors and in many cases we can only extrapolate this to humans. In other cases the evidence is more compelling.

But how much evidence do we need to be able to see that smoking, unhealthy food, physical inactivity and environmental pollution are bad for our health? How much evidence do we need that declining biodiversity and declining environmental health is adversely affecting human health? And why, for allergy in particular, are we so slow to make recommendations and propose change?

SO WHY IS THIS SO HARD TO SOLVE?

Albert Einstein said '*The world is a dangerous place to live; not because of the people who are evil, but because of the people who don't do anything about it.*' Taking responsibility at both the individual and the societal level is essential for to address our global health challenges. Inertia is our greatest enemy in this. The first critical step in solving any problem of such magnitude is to recognise it, acknowledge it and *collectively* agree that action is needed. This needs a very broad-based collaborative effort, at every level of our communities. The 'health' sector needs to engage more widely, because most of the underlying 'causes' of the NCD pandemic do not lie within the traditional domains of 'health'. It is critical to address the much wider social, cultural and economic determinants of health (the 'causes of the causes').⁴⁷

At the highest levels, the 2011 United Nations *Declaration on the Control and Prevention of NCDs*² has been of pivotal importance in recognizing that 'the global burden and threat of NCDs constitutes one of the major challenges for development in the twenty-first century', and for taking a multilateral stand on this.

Even this initial step, before any solutions are posed, can take considerable time and effort. We experienced the decades of inertia before efforts to address global warming and the environmental crisis began in earnest. Lack of acknowledgement and lack of consensus were largely to blame, in no small part due to sabotage from self-interested parties. Now that we recognize the mistakes we have made with the delicate health of our planet, it is important that we don't make the same mistakes with our own health. There are frightening parallels. Again, we have to contend with sabotage from serious villains - Big To-



Fig. 5 A significant component of NCD risk is programmed early in life and early exposures have the greatest long term consequences. Our challenge is to overcome the effects of urbanization as the major culprit in the NCD pandemic, by targeting the early environment.



Fig. 6 Time is of the essence. Prevention must begin in early life but it is never too late to choose a brighter future.

bacco. There is absolutely no doubt that smoking kills, costs billions every year and drives economies further into poverty. Yet it continues. An industry built on addicting youth and promoting chronic ill health and disease still thrives. We face other threats; from the Food and Drink Industry, contributing to damaging levels of fat, sugar, salt and 'fast' food consumption. It was not that long ago that cigarettes and soda drinks were openly and blatantly advertised as healthy. Now tactics are slightly more subtle. But while we can ban tobacco, we can't ban food, and a more challenging, collaborative approach with industry will be needed to overcome those threats. As with global warming, before any action can be taken, a global consensus is needed.

The global NCD political agenda has also been fundamental for making real progress towards a unified vision for health, including firm measures towards addressing the major risk factors for NCDs. However, while it is recognised that a large proportion of NCDs are inherently preventable, the prevailing approaches focusing on adult interventions are far less effective than early life approaches. While the vision of promoting health in early life is more logical in the long-term, this still too commonly overlooked. It is now es-

sential that we make every effort to promote a greater awareness of the importance of a 'life-course' approach for disease prevention, beginning with strategies to promote maternal health, both before and after conception (Fig. 5).

Albert Einstein also said '*We cannot solve our problems with the same thinking we used when we created them*'. Like so many of our other global challenges, our NCD pandemic may be a crisis of our making, but we have the power to overcome it. But only if we stand together and be prepared to take a new approach. If we don't, it will surely be our undoing. This all needs to begin with a greater awareness and 'buy-in' through our communities, our health systems and our governments. Fortunately this is an idea that is coming of age, and there is gathering momentum around these concepts. We might be turning the corner, but we need to be realistic about how far and how long this will take, and not lose enthusiasm in the process. We need to be in this for the long haul.

GETTING TO THE HEART OF THE MATTER

This might not have been what *the Journal* had in mind when they extended me these liberties, but these kinds of discussions rarely find a home in scientific journals and I congratulate them for taking this vision. In the spirit of what they might have intended, I will return to the 'immune system' and some scientific questions that we need to consider in preventing NCDs, allergy included. Could the immune system be a common link between many of the NCDs? Are the effects of many of the environmental risk factors mediating their effects (at least in part) through immune effects? Are some of the differences in genetic (and racial) susceptibility to NCDs mediated through genetic polymorphisms in immune pathways and inflammatory responses? Regardless of the mechanisms, lifestyle and environmental interventions that reduce inflammation are likely to have benefits for the risk and progression of many NCDs.

There is a very strong case for promoting immune health as an integral part of NCD prevention. Now more than ever, these notions underscore the need for a more integrated, interdisciplinary, cross-sectoral approach in collectively addressing these problems, which have all arisen in response to modern environmental conditions.

In closing, I really hope to appeal to the heart and humanity in all of us, at every level and in every walk of life. Because in the end, it is the passion and conviction of our inspiration that brings about change. For too long we have allowed a hard, cold dispassionate view to dominate. Where 'issues' and 'problems' have been stripped of their true human dimension. We truly have to get to the 'heart' of the matter! There is absolutely nothing to loose and everything to gain. And we might feel even 'healthier' and happier just by thinking this way. We are at a fork in the road and it is not too late to choose a brighter future (Fig. 6). Our leaders are committed, and this is the time to express our commitment as individuals.

ACKNOWLEDGEMENTS

SP is supported by a Practitioner Fellowship from the National Health and Medical Research Council (NHMRC) of Australia.

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