Chronic Disease and Public Health

Margo Honeyman and Leonard Harrison

Summary

The rising incidence of allergic and autoimmune diseases imposes an ever-increasing burden on individuals, populations and economies. Possible mechanisms for this phenomenon, related to changed environmental conditions that impact on immune response genes are discussed. In this chapter, we consider the role of reduced and delayed exposure of infants to infections, as well as additional factors that could promote chronic immuno-inflammatory disease. These include changes in the quantity and quality of food consumed, lower energy expenditure due to reduced exercise and thermoneutrality of the built environment, and reduction in sleep. Any or all of these may result in obesity, in which a state of low-grade inflammation contributes to associated complications such as diabetes, cardiovascular disease and cancer. Increased air pollution and psychological stress and, finally, insufficiency of vitamin D, are discussed, as these may also promote inflammation and immune responsiveness.

What chronic diseases? The scope of the problem

Chronic diseases, defined as lasting 6 months or more, are by far the leading cause of mortality in the world, being responsible for 60% of all deaths (World Health Organization[1]). In 2005, 35 million people died prematurely of chronic diseases,

of whom half were under 70 and half were women. In all countries, the major chronic diseases are diabetes, vascular diseases such as heart disease and stroke, respiratory diseases such as tuberculosis and lung cancers, and other cancers such as breast, prostate and colon cancers. In higher income countries, neurological disorders such as Parkinson's disease and Alzheimer's disease, and osteoarthritis, are prominent. Eighty per cent of the deaths due to chronic diseases occur in low- and middle-income countries, in which the burden of these diseases is not only expressed in individual suffering but in the exacerbation of poverty. Even in higher income countries, such as the United States and Australia, increased survival times of those affected but treated impose economic stress on health care systems. While the incidence (number of new cases per year) of many chronic diseases is increasing when adjusted for age, the increase in the ageing population in many higher income countries is also contributory.

The prevalence (number of cases in the population with the disease) of coronary heart disease increases with age. However, the age-adjusted incidence has actually decreased over the last 10 years in the white population of Australia, falling by one-quarter between 1993–1994 and 2001–2002. In 2001–2002 there were 48,700 coronary events in Australia, of which half were fatal, leaving little room for complacency. The incidence of stroke (a vascular event affecting neurological function) is increasing: in 2003 the estimated number of strokes in Australia was 40,000–48,000; by 2010, the number is estimated to be 60,000, averaging one every 10 minutes — an increase of approximately 3000 per year.

The major cancer of males is prostate cancer and of females is breast cancer. The next four most common cancers for both sexes are colorectal cancer, melanoma of the skin, lung cancer and lymphoma. The incidence of lung cancer is decreasing in males and increasing in females, due to changes in the frequency of smoking since the 1970s, when marketers began to capitalise on the gender equality issue. Screening programs

for breast, cervical and colorectal cancer have resulted in earlier diagnosis, with the desired consequent diminution in mortality. Nevertheless, greater survival also means that the prevalence is increased, with attendant costs to the health care system and taxpayer. The incidence of these cancers will inevitably increase as the average age of the population increases.

Diabetes (high level of glucose in the blood) is Australia's fastest-growing chronic disease. Not only is the incidence of both type 2 diabetes (T2D, formerly known as maturity-onset or adult-onset diabetes) and type 1 diabetes (T1D, insulin-dependent, juvenile-onset diabetes) increasing, but the age of onset is falling. When diagnosed in adolescence, T2D can confound the diagnosis of T1D. The incidence of T2D increases with age. At present, 275 people in Australia are diagnosed with diabetes every day, T2D accounting for 90% of these cases. Diabetes is reported to affect 7.6% of Australians, but the exact number is unknown as up to 50% of cases may remain undiagnosed and asymptomatic in the early stages. In 2010, the number of Australians with T2D was 1 million, with the prevalence more than doubled over the past 25 years (data from Diabetes Australia). Indigenous Australians are at far greater risk of T2D, with a prevalence of up to 30%, the fourth highest in the world and fourfold higher than non-indigenous Australians. The ageing of our total population will continue to result in both increased incidence and prevalence. Professor Yan Lijing (The George Institute) estimates that one in ten Chinese now have T2D, and studies in Vietnam, Thailand and China together suggest that currently there could be 89 million cases in Asia, with two-thirds undiagnosed. The World Health Organization (WHO) estimates that more than 300 million people will have T2D by 2025 and more than 60% of them will be in Asia. The complications of both T2D and T1D include cardiovascular disease with heart attack, stroke, blindness, kidney failure and nerve damage, which increase with time from diagnosis. Diabetes will thus become a very significant cause of suffering and economic stress in the in many countries, particularly those with rising standards of living.

Autoimmune diseases (in which the body's immune system attacks other 'self' tissues) such as T1D, rheumatoid arthritis, Graves' and Hashimoto's thyroid diseases, urticaria and multiple sclerosis, as well as many others, result in chronic disability that is not yet preventable. T1D has an onset early in life and can now be diagnosed before the onset of symptoms, being the paradigm for cost-effective prevention, including Australian initiatives.[2]

Allergic diseases (in which the body's immune system reacts in a specific way to a different environmental agents) are also on the rise. These include asthma, eczema, hayfever and skin and more life-threatening (anaphylaxis) reactions to unknown or known allergens (e.g., bee venom, house dust mite, foods such as eggs, milk and nuts). Asthma affects at least 30% of schoolchildren in Australia and other economically developed countries. Its incidence has increased 160% globally since 1964, but remains relatively low in low-income regions.[3]

The WHO has calculated that elimination of risk factors for chronic diseases would prevent 80% of heart disease, stroke and T2D and 40% of cancers. Defining risk factors is therefore of paramount importance to the future of the human race, for us to survive and live healthy and productive lives.

Why do we have a rising tide of chronic diseases?

Genes

Throughout human evolution, our genome has been moulded by our interactions with infectious agents. Examples are viruses causing measles, polio or influenza pandemics, bacteria causing diphtheria, whooping cough or tetanus, parasites causing malaria and, more rarely, fungi. Survival from acute disease due to these pathogens, especially in childhood, has selected for genes for strong immune responses. Such evolutionary processes operated in the Western world until quite recently, up to World War II, as a glance at the ages of death on gravestones in almost any cemetery will readily demonstrate. In addition, famine, which occurred more commonly in the in the past,

would suppress the efficacy of immune responses so that individuals who survived famine would also be expected to be better adapted genetically for strong immune responses.

However, more chronic, indolent infections also existed in the past, caused by pathogens that had become capable of evading strong immune responses elicited by acute infections. These included infections with the multiple herpes viruses that result in the oral and genital infections by herpes type I and type II, chickenpox and infectious mononucleosis/ glandular fever, bacterial infections with tuberculosis, leprosy and *Helicobacter pylori* in the stomach, and chronic parasitic infections such as those from various worms in the intestine. Death, if it occurred at all, would be more likely to occur post-reproductively. Thus, these types of infections would be less likely to result in rapid elimination from the evolutionary pool of genes for suboptimal immune responses. Instead, they would select for genes for immune responses struggling to keep such infections under control in the longer term.

We have been left with a genetic legacy for strong immune responses to pathogens that result in acute disease, but less effective responses to pathogens unlikely to kill but more likely to persist and result in chronic disease.

Immune responses to diseases are controlled by genes that cooperate to work in two broad systems. The first is the innate immune system, inherited from the original multicellular organisms. It evolved as an extension of the earliest mecha- nisms to dispose of (i.e., engulf and break down) cells that die normally in the process of organ differentiation. As some organisms evolved to attack others, the need was created for the removal of greater numbers of cells in the victim. Receptors on cells that recognised danger signals from the dying cells and the specific molecular signatures (pattern- associated molecular patterns or PAMPs) of the different invading organisms then evolved. Stimulation of such evolu- tionarily conserved receptors triggers a rapid and vicious response to eliminate the pathogen as rapidly as possible, by

engulfing it with white blood cells of the innate immune system called macrophages ('big eaters') equipped with the ability to release toxic chemicals and call for reinforcements (predominantly other macrophages and natural killer cells) if necessary. If the pathogen is not removed fully, or if the body fails to cope adequately with the number of dying cells, the process continues. This is the basis of chronic inflammation, which underlies many of the chronic diseases.

The second or adaptive immune system is not only based on individual genes but on recombinations between bits of these genes to provide a vast number of receptors on immune T and B lymphocyte cells. Some of the many antibodies made by B cells and the receptors on T cells will specifically recognise pathogens. Selective expansion of the T and B cells that recognise pathogens is the reason for the term adaptive immune system. This is a slower but highly specific immune response system. In addition to antibodies produced by B cells, which are good at attacking pathogens like bacteria that live outside cells, T cells are able to directly kill cells that harbour pathogens inside cells such as viruses and some parasites. Vaccination in infants is designed to produce antibodies that prevent common childhood infections. At the time of re-infection by the pathogen, the pre-formed antibodies will be boosted and the clinical infection rendered less harmful.

Despite the evolution of 'hair-trigger' immune responses to things the body perceives as pathogens, the rapid contemporary rise in chronic diseases cannot be due to the selection of particular genes as this requires many generations. A comparison of the genes conferring risk for T1D in children over several decades is instructive.[4] The rapid increase in incidence is not due to an increase in the numbers of children at very high genetic risk but rather to the addition of children who have genes that several decades ago would have conferred only moderate risk. This clearly indicates that the increase in the incidence of T1D and the increased 'penetrance' of risk genes must be due to the environment. There is, however, cause for

hope. While we cannot readily change genes, identification of contributory environmental factors can guide us towards their reversal or modification. A telling example is smoking, the danger of which was recognised by Sir Richard Doll, a true hero of our times, whose fight to educate the community eventually paid dividends in some countries. The challenge therefore is placed squarely at the door of public health and our political masters.

Environmental risks

How could the modern environment increased penetrance of lower risk genes for chronic inflammatory diseases like T1D? It could promote inflammation and/or diminish regulation of innate and adaptive immune responses. Is the modern environment 'pro-inflammatory'? Does it activate innate immune inflammatory pathways that promote metabolic maladaptation, such as the insulin resistance seen in T2D and T1D, in arteriosclerosis, Parkinson's and Alzheimer's diseases? Or does it promote unbalanced or dysregulated adaptive immunity and promote autoimmune and allergic diseases? With these questions in mind, let us consider a number of candidate factors in the modern environment: hygiene and the age at which first exposure to infection occurs in infants, the quantity and quality of food, pollution, hours of sleep, amount of exercise, psychological stress and sunlight exposure — vitamin D sufficiency. We will then consider how these factors could interact.

Hygiene

The hygiene hypothesis was first proposed in 1989 to explain the greater incidence of asthma and allergies in children in the high-income, developed, clean, low-childbirth countries, compared to children in lower-income, less hygienic, high-childbirth countries. It posits that a lack of exposure in infancy to infectious agents, symbiotic organisms such as probiotic gut flora and parasites does not permit the normal development of

a balanced adaptive immune system. Lack of antigenic stimulation by infectious agents was suggested to result in increased susceptibility to not only allergic disorders such as asthma but to autoautoimmune diseases such as T1D and multiple sclerosis. The current concept is that an optimally functional immune system would be balanced in the capacity to mount effective responses that are appropriate and self-limiting but not disease-causing. This concept implies regulatory mechanisms for immune homeostasis. A substantial body of evidence demonstrates that the development of such regulatory mechanisms is intimately related to bacterial colonisation of the gut as well as exposure to systemic infection in the young infant.

Strong immune responses at mucosal surfaces, such as in the lung, gut or skin originally evolved to fight chronic but low-level pathogenic agents such as parasites. In the absence of such parasites, such as pinworm, the immune system fails to develop effective regulation, with the result that allergic responses in the mucosa or skin, such as asthma and atopy, are rapidly rising in incidence.

The hygiene hypothesis has gained acceptance with ever-increasing evidence from epidemiological studies. One study compared the incidence of enteroviral infections, thought to promote T1D, in Finland and neighbouring Estonia. The expectation was that enterovirus infection would be more prevalent in Finland (an ultra-clean, high-income society with small families and the highest incidence of T1D in the world) than in Estonia where children have more intestinal worms, more breast-feeding, are from large, low-income families and where the incidence of T1D is among the lowest in the world. Unexpectedly, the reverse was found. Enterovirus infection was more prevalent and occurred at a younger age in Estonia than Finland. Back to the drawing board for enteroviruses and T1D: infection appears to be protective against T1D! Similarly, infection of the diabetes-prone non-obese diabetic mouse, the standard animal model for human T1D, with rotavirus shortly after birth significantly delays and reduces the incidence of

diabetes, whereas infection at weaning does not. In Australia, the incidence of T1D is higher in educated, higher income-earning and smaller families, and in first-born children.

Age at exposure to infections

Since World War II (WWII), opportunities for exposure to infection during infancy have diminished due to social changes. For example, previously the practice of placing neonates in hospital nurseries ensured swift transfer of rotavirus infection, with diarrhoea occurring in the neonates before they had received their mother's colostrum. However, with 'rooming-in' of mothers and their neonates, severe gastroenteric infection due to rotavirus has now been delayed, peaking at 18 months of age. Once home, infants were frequently infected with viruses by elder siblings in the first few months of life, but smaller family sizes result in less opportunities for such infections. During the first 9 months of life, transplacentally transmitted antibodies from the mother, and then antibodies in breast milk, coupled with antiviral molecules such as lactadherin in the milk, lead to diminished viral load and clinical symptoms but don't prevent actual infection — nature's vaccination. A decrease in the frequency and duration of breast feeding has impacted on this protective period for the infant, while compromising the development of a well-regulated mucosal immune response. Delay of infection to beyond this early period of antibody cover could conceivably lead to poor development of T-cell regulation of Th2 responses, or inadequate development of immune regulation.

Food, obesity and energy utilisation

Total energy intake in the developed world has increased since WWII, with the body mass index (BMI) increasing in children of different ethnicities. However, while asthma and other allergies increased along with BMI this was predominantly in Caucasoid not Asian children in the United States. This suggests an effect of genetic background or some other undefined, ethnic-associated difference in environment, such as obesity.

Acquisition of obesity is associated with the development of insulin resistance, which could account not only for the rising incidence of T2D but also T1D. Insulin resistance per se has been shown to accelerate progression to clinical T1D in children with pancreatic islet autoimmunity.

Although obesity is now recognised to be a state of chronic low-grade inflammation and adipose tissue in obesity a seat of inflammation, many factors in the obesogenic environment are themselves pro-inflammatory.[4]

The effects of dietary composition on mitochondrial free radical generation, activation of the NFkB pathway for pro-inflammatory immune factors (cytokines and chemokines) and endoplasmic reticulum (ER) stress are of considerable current interest. Accumulation of lipid in adipocytes increases ER stress, leading to the production of chemoattractants that recruit and differentiate blood monocytes to become pro-inflammatory adipose tissue macrophages implicated in insulin resistance. Specific dietary components such as advanced glycation end products (AGEs), saturated fats including trans fatty acids and fructose are associated with elevated circulating pro-inflammatory factors and insulin resistance. AGEs are proteins, lipids and nucleic acids that have formed non-enzymatic linkages with sugars such as glucose, especially in conditions of oxidant stress including hyperglycaemia in diabetes. Binding of AGEs to their receptors (RAGEs) — for example, on macrophages — activates the NF-kB pathway and generation of pro-inflammatory factors. AGEs are formed in foods following cooking of sugars with fats or proteins, and are particularly conspicuous in 'fast food', much beloved by children.

Trans fatty acids (TFAs) are produced in deep fried foods by the transformation of polyunsaturated fatty acids from their natural cis form to the trans form. The process of partial hydrogenation also converts vegetable oils to semisolid fats like margarines and peanut butter that contain high concentrations of TFAs commonly found in bakery products. Ingestion of diets

high in fat, especially TFAs, but not isocaloric high fibre diets, provokes pro-inflammatory changes detectable in the blood within hours.

The intake of fructose in the United States rose >1000% from 1970 to 1990. Excessive intake of fructose (>50 g/d) has been proposed to be a major contributor to the development of obesity-associated complications, the 'metabolic syndrome', including type 2 diabetes. While the primary sources of fructose are sugar (sucrose) and high-fructose corn syrup, the recent trend to drink 'healthy' fruit juices can result in consumption at the one time of the equivalent of 10 fructose-containing oranges without the associated fibre. Unlike glucose, fructose does not stimulate secretion of insulin or leptin, key afferent signalling molecules in the regulation of food intake and body weight.

Obesity is encouraged not only by too much food of the wrong sort but by diminished total energy outlay due to changes to work and leisure practices, including less exercise, fewer natural play areas for children and increased TV viewing and use of computer games. It may also result from a reduction in hours of sleep. The average hours of sleep of adults in the United States has diminished from 9 to 7 over the last few decades. Sleep curtailment in young adults results in a constellation of metabolic and endocrine alterations, including insulin resistance, decreased glucose tolerance, increased evening concentrations of cortisol, increased and decreased levels, respectively, of the orexigenic hormones ghrelin and leptin, decreased satiety and increased appetite. These findings suggest that increasing the duration of sleep might be a curiously simple means of combating the relentless rise of obesity and its consequences. Reduced energy expenditure may also result from the deliberate control of humidity and temperature in our living and working environments. Air-conditioning and heating mean that energy required in the past for thermoregulation is now diminished, even when we are inactive.

Pollution

Recently, it was reported that differentiation of T cells into regulatory T cells is controlled by a receptor, the aryl hydrocarbon receptor (AHR), activated by polycyclic aromatic hydrocarbons. AHR activation leads to the production of certain inflammatory factors (IL-17, IL-22 and IL-21) implicated in range of inflammatory disorders. Numerous candidates for endogenous ligands of the AHR have been proposed, including prostaglandins, bilirubin at high concentrations, and modified low-density lipoprotein, but the evidence is strongest for ultra-violet photoproducts of tryptophan. The capacity of the AHR to recognise exogenously-derived polycyclic aromatic hydrocarbons, such as 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD), ubiquitously present in atmospheric pollution, potentially links immune dysregulation to environmental toxins. The less subtle effects of TCDD are clearly illustrated by the disasters at Seveso, Italy in 1976, and Bhopal, India in 1984, where victims were immunosuppressed and had chloracne.

Background levels of polycyclic aromatic hydrocarbons are 0.1-1ng/m3 rise to 0.5-3 ng/m3 in urban environments, and close to some industries involving coal or coke burning levels can reach 30 ng/m3. In urban environments, polycyclic aromatic hydrocarbons are derived domestically from tobacco smoke, cooking and heating (coke and wood burning), as well as industrial activity. In rural environments, stubble burning, open burning of moorland and bushfires also contribute polycyclic aromatic hydrocarbons to the atmosphere. Cars are estimated to contribute 24% to measurable atmospheric polycyclic aromatic hydrocarbons, industrial combustion 24%, domestic combustion 19% and natural fires 18% (European commission working paper on polycyclic aromatic hydrocarbons, 2001). Atmospheric levels of polycyclic aromatic hydrocarbons are higher in winter, due to meteorologic conditions, greater use of heating and reduced degradation by photo-oxidation. While environmental regulations in Europe since the late 1990s have begun to diminish levels of polycyclic aromatic

hydrocarbons, levels continue to rise in emerging industrial giants like China.

Interestingly, resveratrol in red wine is an antagonist of AHR activation by polycyclic aromatic hydrocarbons, but we are not recommending that red wine is the solution. The role of polycyclic aromatic hydrocarbons in the genesis of immune disorders is complex but likely to be a fruitful area of research relevant to diseases of the modern society.

Psychological stress

While no studies clearly indicate that population stress overall has increased, psycho-neuroimmunologic studies show that acute mental stress not only elicits increases in blood pressure and heart rate but also in the circulating pro-inflammatory cytokine IL-6 (56% rise two hours after a stressful task). Stress has been related to both the development of asthma and atopy, as measured by IgE levels at 6 years of age. Parenting difficulties at three weeks of age correlated with six-year measures of maternal depression and child psychological risk score, and children with asthma were rated as being at greater psychological risk. Stress is important in the evolution of atopic dermatitis, aggravating a number of underlying disease mechanisms including infiltration of the skin by particular white blood cells called eosinophils. The stress neuropeptide substance P is released in the skin from cutaneous nerve fibres, with resultant 'neurogenic' inflammation. Such a stress-induced process may also be involved in the initiation of autoimmune skin diseases. In the early stages of alopecia areata (autoimmune hair loss), which has been associated with stress, the number of substance P-positive nerve fibres in the skin increases, resident mast cells in the skin degranulate to release their toxic chemicals and hair follicles regress.

The hypothesis that maltreatment in childhood results in low cortisol steroid release that facilitates chronic low-grade inflammation later in life was tested. Significantly raised C-reactive protein (CRP), a marker of stress, was observed in 32-year-old adults who were reported as experiencing episodes of

maltreatment 20 years previously. Elevated CRP was graded with maltreatment, being 1.8 times more likely in those who experienced multiple episodes, independent of co-occurring early life risks (low birthweight, low socio-economic status, low IQ), stress in adulthood and adult health and behaviour. Finally, two studies suggested that stress affects the development of T1D, in that life event — for example, actual or threatened losses within the family — were more severe in T1D cases. Serious life events, foreign origin of the mother, high parenting stress and low paternal education gave odds ratios of 2.3–1.6 for development of T1D-related autoantibodies at 1 year of age, independent of a family history of T1D.

Vitamin D

Vitamin D, a steroid hormone previously thought to be necessary only for healthy bone development, is made in the skin by the action of ultraviolet (UV) B light (290-315nm) on cholesterol in the skin. Humans evolved in the sunny tropics where they synthesized at least 5,000 international units (IU) of vitamin D per day. However, in contemporary populations of Northern Europe, southern regions of Australia and all of New Zealand, this has dropped to 200–500 IU/day, resulting in a high prevalence of vitamin D deficiency. Skin pigmentation slows the synthesis of vitamin D, promoting selection against dark skin in populations that prehistorically travelled northward, especially to beyond latitude 35° where vitamin D-producing wavelengths are absent in winter and the day lengths short. Diminished exposure to UVB is consistent with the (northern hemisphere) north–south gradient in diseases such as multiple sclerosis and T1D, which is reversed in the southern hemisphere, as well as with winter onset of T1D and winter relapses in multiple sclerosis.

In the last 15 years, many studies have demonstrated that vitamin D is also critical for immunological health.[5] Vitamin D facilitates killing of intracellular parasites by activating cathelicidin and other anti-bacterial peptides within the macrophage;

it promotes dendritic cells to generate IL-10-secreting regulatory T cells and enhances the capacity of defective regulatory T cells. Sun-avoidance behaviour, working indoors, lack of mobility of the elderly or very young, shift work, rapid migration of dark-skinned people to low UVB, high-latitude zones of the world, covering clothing, global dimming due to atmospheric pollution, and combinations of all these can reduce UVB exposure and lead to vitamin D deficiency. This occurs particularly in dark-skinned (and/or covering) populations that have migrated to live in high-latitude environments; for example, Asian immigrants to the United Kingdom or African refugees in southern Australia in whom tuberculosis re-emerges, Latinos in the United States who have a high incidence of asthma, and the Maori of New Zealand, who have a very high prevalence of T2D and higher mortality due to breast cancer.

The vitamin D receptor (VDR) binds to 2776 positions in genomic DNA and significantly affects expression of 229 genes. VDR binding is enriched at sites identified previously by genome-wide association studies as being associated with T1D (2.9-fold enrichment), Crohn's disease (3.5-fold), systemic lupus erythematosus (5.1-fold), colorectal cancer (4-fold), chronic lymphocytic leukaemia (8.3-fold), rheumatoid arthritis (2.8-fold) and multiple sclerosis (2.2-fold).[6] Further genetic evidence for the role of vitamin D comes from multiple studies involving other essential molecules in the pathway of vitamin D conversion or action, such as 1-alpha hydroxylase which converts circulating 25OH vitamin D3 to its active form 1,25 (OH)2 vitamin D3 predominantly in the kidney but also in macrophages and other immune cells. First, changes in the CYP27B1 gene encoding 1-alpha hydroxylase confer susceptibility to T1D, Graves' disease and Hashimoto's thyroiditis. Second, a highly conserved vitamin D response element (VDRE) has been discovered in the promoter DNA for HLA-DR15, a gene that confers susceptibility to multiple sclerosis. Diminishing levels of UVB exposure or deficiency of vitamin D have been linked to autoimmune diseases such as T1D,

multiple sclerosis and rheumatoid arthritis, and to diseases associated with low-grade inflammation such as T2D and atherosclerosis. Wheezing at age 5 has also been linked to vitamin D deficiency prenatally, as have autism and schizophrenia.[7]

It may also be relevant that while the incidence of T1D in Finland has increased to become the highest in the world, the recommended daily allowance of vitamin D in Finland has dropped from 2000 IU/day to 200 IU/day (the amount in a teaspoon of cod-liver oil sufficient to prevent rickets) over the last 40 years. Vitamin D deficiency during pregnancy has been demonstrated in Scandinavian studies of children developing T1D in the first year of life, and the offspring of pregnant women with the highest intake of dietary vitamin D had a one-fifth chance of developing T1D compared to offspring of mothers with the lowest intake of vitamin D. Deficiency of vitamin D during pregnancy could have effects on the developing foetus, including epigenetic effects (modification of DNA and its function by environmental factors operating on the fetus or infant). While our understanding of epigenetics is yet rudimentary, the genetic effects of starvation of the mother have been shown to last at least 60 years. In pregnant mice, a diet high in methyl donors (folate, vitamin B12, choline, methionine) led to offspring with more methylation of the Runx3 gene, which was heritable through several generations. Importantly, these offspring had transgenerational allergic airways disease, indicating that immune responses may be controlled epigenetically. Recent evidence suggests that many inflammatory genes, including those in the innate immune system, are regulated by vitamin D and epigenetic modifications. One could speculate from these studies that children of vitamin D-deficient mothers could potentially have upregulated immune responses for their and their children's lifetimes. Prospective, randomised controlled trials are required to demonstrate definitively a protective effect of vitamin D on the emergent immuno-inflammatory disorders.

Migration — synergism of environmental factors

Migration of people from low-income, low-latitude, low-food intake, high-family-size countries to high-income, high-latitude, high-food-intake, low-family-size countries started with the enforced recruitment of slaves from Africa to the colonies of Britain, continued with refugees from wars and now with voluntary migration. The reduced exposure to sunlight, greater concentration on hygiene and the changed exposure to infections, and the ready availability of food in the new environment all impact on immigrants who were genetically selected for an environment in which darker skin was protective against too much UV, parasites enhanced immune responses and obesity was unknown. Immigrants and their children are thus at a particular disadvantage on entry to Australia with its current enforced emphasis on sun-avoidance, cleanliness and overabundance of calories.[8] Moreover, our architecture is based on Northern European models and is sun-minimising. Is this the explanation for the increased prevalence of asthma and atopy in SE Asian immigrants to Australia and Tokelau Islander immigrants to New Zealand, T2D in SE Asian and Pacific Island immigrants to Australia and cardiovascular disease in African Americans compared to white Americans?[8]

What can we do about environmental factors and chronic diseases? A wish list

Intervention measures of different kinds at several life stages are required to reduce the burden of environment-driven chronic disease.

Pre-natal

Education of pregnant women is crucial, perhaps most effectively through campaigns in public hospitals and via obstetricians and gynaecologists. The current strong evidence for vitamin D sufficiency in optimising immune and other functions in mother and foetus is particularly relevant for women who are dark skinned and/or covering for cultural reasons. These women are tested in Melbourne by gynaecolo-

gists. However, also at risk are light-skinned, non-covering but sun-avoiding mothers who live in places where vitamin D deficiency is common, such as in Australia below 35° latitude (Canberra level), or anywhere in New Zealand. Thus, serum vitamin D (25 OH D3) should be measured in all pregnant women, with the aim to maintain a concentration of at least 70 nmol/L either by supplement or judicious sun-exposure. Several studies provide evidence that vitamin D sufficiency is not only important for the fetus, but early in pregnancy may diminish the risk of pre-eclampsia and later the risk of caesarean delivery, presumably by increasing muscle tone.

In infancy

Vitamin D does not enter the breast milk unless 6000 international units (IU)/day are consumed by the mother. Education of the mother in the need for vitamin D for herself and the infant is therefore desirable. Mothers can either take this amount as a supplement or provide exclusively breast-fed infants with 300 IU/day of vitamin D as drops.[5] Education would be most effective via community health nurses, who also provide encouragement of young mothers and support for breast-feeding. At the level of local government, the provision of sun-exposed areas in leisure centres, especially for otherwise covering women, would be very helpful. Play areas for children, particularly in high-rise apartment zones, are critical for several reasons, including for activity and sun exposure. In the home, education is needed to encourage physical activity by children (including restricted access to television), to avoid pollution from cigarette smoke and to avoid foods high in fat and sugars, including fructose (in Australia, mainly from pure fruit juices). Especially in families of small size and with first-born infants, mixing of infants with other children and less concern for scrupulous cleanliness of their environment are to be encouraged, particularly in the first nine months of life when maternal antibodies are still present. Doctors should avoid inappropriate prescribing of oral antibiotics for infants, which could disturb development of the normal gut microbial flora.

At primary school

Modification of the 'Sun Smart' program for schoolchildren in Victoria is needed, so that children with pigmented skin do not necessarily have to wear a hat or other protective clothing during playtimes in the sun at school. This is politically sensitive, and in the meantime routine supplementation of such children with vitamin D (as occurs at the Refugee Clinic at the Royal Children's Hospital, Melbourne) may be more feasible, perhaps at the school that so carefully avoids the sun.

In New Zealand, a study by Dr Robert Scragg encouraged consumption of healthy foods in the school canteen. Sugary drinks were banned and water drinking increased. This was implemented by education of school leadership students who then decided what they would change and how. Well-designed school water bubblers enhanced water drinking and implementation of activity programs encouraged weight loss. Schools need to be sited away from sources of air pollution. Teachers should encourage limits on time spent watching television or playing computer games. Establishment of school gardens is a brilliant initiative by Stephanie Alexander throughout Victoria to educate and motivate children about healthy lifestyle choices.

In adolescence

Ongoing campaigns against smoking, for healthy food at schools, and so on, need to continue, but may be more successful if run by students themselves. Being healthy must be promoted as 'cool' and 'sexy' and linked with image and status. Local government should provide areas in parks to encourage adolescent involvement in unsupervised, non-team physical activities (e.g., skate-boarding, BMX bike-riding). Television programs on cooking and eating narrated by young people may be more helpful if TV producers would allow them to be slanted towards healthy foods, as promoted by Jamie Oliver. A campaign on Facebook, designed as a survey on 'What did you eat today?' might help raise awareness of food issues.

In adulthood

Adults who are parents and role models may have a poor knowledge of environmental factors related to health, including foods. This is particularly the case in lower income groups, where the burden of obesity/diabetes and chronic diseases is heaviest. Education campaigns targeted to these groups would thus be the most effective. Health promotion campaigns (anti-smoking, healthy food, exercise initiatives, the importance of a good night's sleep) sponsored by local football clubs, featuring advertising at sporting venues could synergise with the positive image of sport. The role modelling of athletes to the young, for footballers somewhat tarnished in recent years, would also be enhanced. Swimming stars could be sponsored to wear swimsuits bearing 'ban the fat' or 'ban the sugar' or ' ban obesity' logos to be developed. For ethnically based clubs and societies that include many immigrants, use of free-to-air announcements on ethnic radio stations and in the ethnic newspapers to play health promotion messages would be helpful, as would multilingual brochures in the waiting rooms at relevant community health centres and hospital departments. At the level of health promotion by the government (federal or state), sponsorship of announcements at large football matches and athletics events could be coupled with legislation to restrict advertising and even perhaps the sale of fat-drenched fast foods at these events, as at school canteens. The latter might, however, provoke public outcry at the restriction of the 'bread' portion of 'bread and circuses', so that limiting this approach to the restriction of advertising might be more practical. As with campaigns against cigarettes and alcohol, addition of a govern-ment tax to the sale price of fast foods that contain over a specified limit of fat, sugar or salt might also be considered. At the level of employer responsibility, in workplaces with canteens, this could come under the aegis of their pre-existing Occupational Health and Safety bureaucracy. Shiftworkers need to be made aware by their employers of the need for sunshine or supplementation with vitamin D. This would perhaps be best

monitored by the provision of routine annual checkups of vitamin D blood concentrations of shiftworkers, performed in large workplaces by staff nurses or doctors. Packaging of fast foods needs to include health warnings as well as the statement of the fat, sugar and salt concentrations as already present on many other foodstuffs for sale. The promotion of unhealthy practices is both a commercial and economic issue and thus will take governmental and regulatory will to overcome the resistance expected from vested interests in the food industry. There will be a payoff for all industries in better survival of their workforce with less sick days and more customers. However, the major payoff will be a healthier, happier society with no need for a blowout in taxation due to the otherwise inevitably burgeoning costs of the healthcare system.

At the dawn of the new millennium, chronic non-communicable disorders, promoted by environmental changes are the major cause of morbidity and mortality worldwide. The rising tide of autoimmune and allergic diseases is accompanied by other disorders associated with chronic low-grade inflammation, including obesity, insulin resistance and T2D, atherosclerosis and cardiovascular disease, cancer, arguably Alzheimers's and Parkinson's disease. Expensive drugs for established diseases is not the long-term answer. The situation demands novel preventative and therapeutic approaches aimed in the first instance at reducing adverse environmental exposures. We have attempted to identify in the complex environmental matrix those factors that impact most adversely on health. The task is now to institute public health and political solutions at national and international levels.

Given the information above, what would you recommend, or what would you change? How would you go about implementing some of these recommendations? Over to you!

Endnotes

1   www.WHO.int/chp/en for information on chronic disease incidence and prevalence.
2   http://www.stopdiabetes.com.au/ for information on the intranasal insulin trial to prevent T1D.

3 http://www.nationalasthma.org.au/content/view/372/469/ for information on the rise in asthma in Australia.

4 http://www.sciencedaily.com/releases/2010/08/100816095800.htm for the link between diabetes and obesity.

5 http://www.sunvitamin.org for extensive literature on the effects of vitamin D deficiency, and www.vitamindcouncil.org/ for essays on these topics.

6 www.genome.org/cgi/doi/10.1101/gr.107920.110 for information on the genomic influence of vitamin D.

7 See McGrath JJ, Eyles DW, et al. Arch Gen Psychiatry. 2010;67(9):889-94 for the study linking autism and schizophrenia with vitamin D deficiency.

8 See Grant WB and Peiris AN, J Am Dir Assoc 2010; 11:617-628 for an analysis of the different health outcomes in African and White Americans.

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Margo Honeyman is an immunogeneticist. She was until recently a Senior Research Scientist at the Walter and Eliza Hall Institute of Medical Research. Her main research interests are the role of vitamin D deficiency in disease and the mechanisms which initiate pancreatic islet autoimmunity and type 1 diabetes. She is the author of over 90 research papers.

Len Harrison is a clinician–scientist. He is a Professor in the Department of Human Biology at the University of Melbourne, and heads the Autoimmunity and Transplantation Division at the Walter and Eliza Hall Institute of Medical Research and the Burnet Clinical Research Unit at the Royal Melbourne Hospital. Previously he was Director of the Department of Clinical Immunology and Allergy at the Royal Melbourne Hospital. He is Center Director of one of the four international sites of the US–based TrialNet and designs and implements trials for the prevention of diabetes.