

THE FOETAL ORIGINS OF ALLERGY

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ABSTRACT

The dramatic increases in allergy and allergic diseases which have occurred over the past half-century have been strongly associated with changes in early life events. Changes in lifestyle, which have affected nutrition, allergen and microbial exposures, have been strongly implicated as explanations for changing allergy susceptibility. To what extent these influences affect the foetus during pregnancy rather than the infant post-natally is uncertain. In all probability there is a sequence of events through pregnancy and early post-natal life which in combination change the outcomes. Successful pregnancy is associated with a Th-2, allergy-biased immunological environment which results in virtually all neonates having an apparent allergic pattern of immune responsiveness. Under normal circumstances this is rapidly down-regulated after birth, most likely affected by the evolving human microbiome. Interactions between genetic and environmental variation, both during pregnancy and in the first months of the infant's life, perturb this normal sequence and lead to a sustained Th-2-biased allergic response.

The future for prevention rests in identifying the key influences that should highlight strategies to turn the clock back to an era of low prevalence of allergic diseases.

INTRODUCTION

Allergic diseases have become the commonest chronic disorders to affect children and young people in affluent countries. Over the past half-century the increases in the prevalence of asthma, eczema and allergic rhinitis have reached almost epidemic proportions, with upwards of 30 per cent of whole populations being affected. Whereas the increase in asthma prevalence has plateaued in some countries, this is not the case for eczema or food allergy.¹ Indeed, for food allergy, the increases have become apparent only over the past 20 years,² which has resulted in exponential increases in the prescribing of alternatives to cow's milk formula for infants.³ Furthermore, developing countries that 50 years ago had a very low prevalence of allergic diseases are now experiencing the largest increases commensurate with the adoption of a more affluent lifestyle.¹ Studies of migrating populations have highlighted that lifestyle changes in early life have the greatest impact on the manifestation of allergy and disease. Therefore, Afro-Caribbean and Asian migrants to the United Kingdom, Chinese to Canada and Turkish subjects to Germany all manifest considerable increases in allergic disease – which in the case of asthma predominantly increases in prevalence in the next generation born in the new country rather than in the parents who migrated as adults.^{4,5} This highlights early life environment rather than inherited DNA as being the principal cause. To what extent

the environment is producing epigenetic modifications of DNA rather than directly influencing allergic immune responses has yet to be established. It is also unclear whether the environment is primarily influencing foetal immune ontogeny and disease susceptibility or whether early post-natal events are more important. The present state of knowledge suggests that both antenatal and post-natal influences operate. It follows that developing an understanding of the sequence of events leading to allergic disease will highlight targets for future intervention in order to prevent disease and turn the clock back to an era of low prevalence.

In evaluating published evidence of the early life origins, it is important to discriminate those studies which have investigated influences on allergic sensitisation from those which have focused on specific diseases such as asthma or eczema that may or may not be associated with allergy. In this article care has been taken to ensure the correct interpretation, particularly as it is now clear that independent gene–environment interactions are associated with allergic sensitisation compared to those associated with diseases that are often linked to allergy (see Figure 1).⁶ For the former genes regulating cytokine production, the configuration of IgE receptor, MHC and T-cell receptors have an impact on the allergic status.

Ontogeny of allergic sensitisation and disease

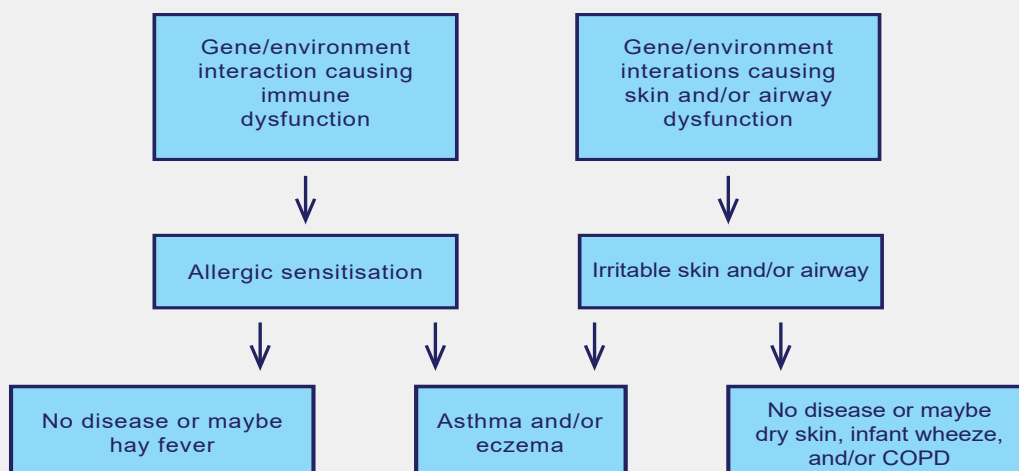


Figure 1: A schematic representation of the separate gene–environment interactions that affect susceptibility to allergic sensitisation, showing how they link to disease-specific interactions that ultimately lead to allergic disease.

However, independently of allergic sensitisation, a number of eczema-specific genes are associated with epithelial barrier dysfunction; of these, Filaggrin polymorphisms have the greatest impact. Interestingly, Filaggrin polymorphisms leading to eczema may, through impairing the skin epithelial barrier, facilitate allergen penetration and sensitisation, leading to food and inhalant allergy and a subsequent higher risk of asthma. This could in part explain the allergic march from eczema to food/inhalant sensitisation and subsequent asthma/rhinitis and food allergy (see Figure 4). Similarly, there are a number of genetic polymorphisms that affect airway form and function which are associated with asthma independently of allergic status. These polymorphisms interact with environmental airway stressors such as tobacco smoke and other pollutants.

THE IMMUNOLOGY OF PREGNANCY

The paradigm underlying allergy is this: dominant helper T-lymphocytes' expressing Interleukins (IL)-4, -5 and -13 (known as TH-2 cells) and reduced TH-1 activity associated with the generation of interferon-gamma (IFN- γ). TH-1 and TH-2 responses are counter-regulatory; additional regulation is exerted by regulatory T-cells' expressing the Foxp3 transcription factor or generating IL-10 or transforming growth factor beta (TGF- β). In addition, the cytokines and co-stimulatory signals from antigen presenting cells affect the immunological balance of T-cell responses (see Figure 2).

Foetal development is facilitated in an environment

that biases responses towards T-lymphocyte 2 (TH-2) activity which is characterised by the generation of IL-4, -5 and -13. In addition, T-regulatory cell-like activity is also increased with high levels of IL-10 and TGF- β . Decidua tissues and the foetus express paternal as well as maternal antigens that should stimulate a maternal tissue/graft rejecting immune response. This is primarily through activation of T-helper-1 (TH-1) lymphocytes expressing among other cytokines IFN- γ . IL-4 suppresses TH-1 activity, whereas IFN- γ has a mutually exclusive down-regulatory effect on TH-2 responses. In both murine and human pregnancies, the maternal TH-1 response to foeto-paternal antigens is associated with recurrent early miscarriage or intrauterine growth retardation. This clearly does not occur in the majority of pregnancies because of regulation of the maternal immune response, in part, by the generation of TH-2 and regulatory cytokines at the materno-foetal interface.⁷ There are additional factors that provide immune protection, including the expression of HLA-G rather than classic HLA-A and HLA-B on cytotrophoblasts. HLA-G ligates the natural killer (NK) cell inhibitory receptor, preventing NK-induced cell death. It is not recognised as foreign by maternal lymphocytes⁸ (see Figure 3). IL-37, a potent anti-inflammatory cytokine, is generated in the placenta and is reduced in mothers who have pre-eclampsia.⁹ It may also play a role in damping inflammatory responses at the materno-foetal interface.

It is inevitable that the cytokines regulating the maternal immune response during pregnancy will also have an impact on the foetus. They affect both foetal growth and

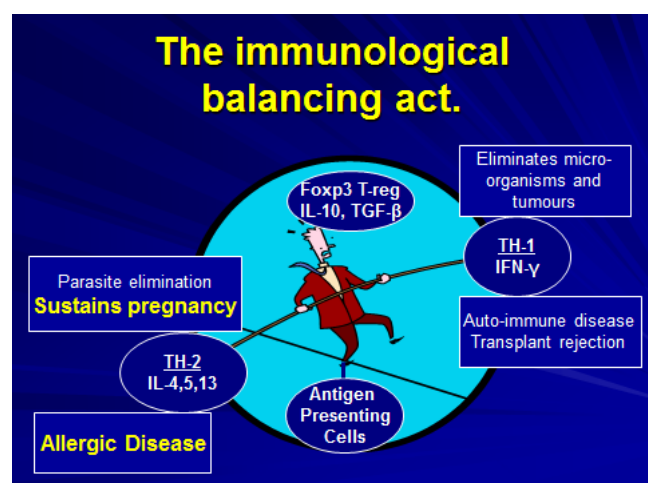


Figure 2: A diagrammatic representation of the control of helper lymphocyte responses to antigen/allergen exposure.

immune ontogeny. Some of the cytokines play an important role in promoting tissue growth and organ development. TGF- β , for instance, is a potent stimulator of fibroblasts and is strongly expressed during branching morphogenesis in early bronchial tree development.¹⁰ It is co-expressed in foetal airways with 'a disintegrin and metallo-protease 33' (ADAM33), and polymorphisms of the ADAM33 gene are associated with a higher risk of asthma.¹¹

FOETAL IMMUNE ONTOGENY AND ALLERGY OUTCOMES

While there is a common misconception that the neonate is immunologically naïve, the foetus is capable of mounting a significant immune response. Paediatricians will be familiar with the demonstration of immunoglobulin M (IgM) antibodies following maternal infection early in pregnancy with rubella, cytomegalovirus (CMV) and toxoplasma, as well as similar responses after maternal immunisations.¹² Foetal baboons directly immunised with recombinant hepatitis B surface antigen mount an IgG antibody response when none has occurred in the mother. This is associated with an enhanced post-natal response to repeat immunisation.¹³

Antigen presenting cells (APCs) and T and B lymphocytes are detectable from 14 weeks' gestation in rudimentary lymphoid follicles in the foetal small bowel. Molecules identified on their cell membranes suggest that antigen presentation has occurred with co-stimulatory signalling to promote a sensitising immune response by T lymphocytes.¹⁴ Both allergen and IgE of maternal origin are detectable in amniotic fluid at around 10 per cent of maternal circulating levels. Dendritic cells in the foetal gut express both high- and low-affinity IgE receptors, which means that IgE-facilitated antigen focusing will occur, resulting in sensitisation to extremely low concentrations of allergen.¹⁵ The swallowed maternal IgE, inevitably higher where the mother is also allergic or infected with parasites, will bind to high- and low-affinity IgE receptors on foetal

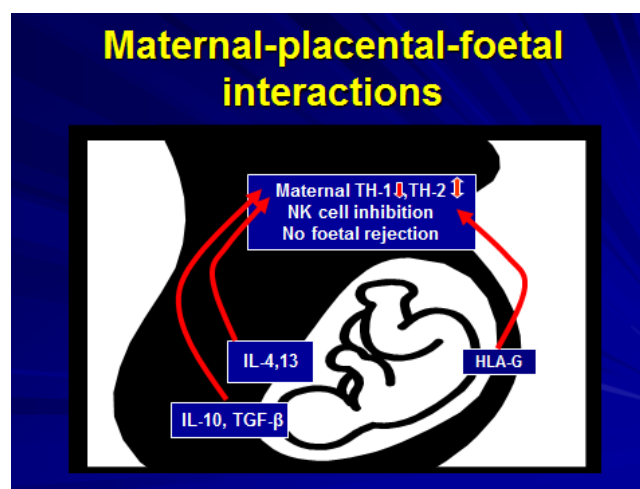


Figure 3: The factors protecting the foetus against a maternal TH-1 immunological rejection paternal antigens which will be expressed by the foetus and all decidual tissues.

dendritic cells in the small bowel and facilitate the pick-up of allergens. This will enable them to respond to a 100- to 1 000-fold lower concentration than would be the case in the absence of IgE. This potential sequence is corroborated by a study using proteomic techniques to detect low levels of IgE antibody to specific cow's milk proteins. It showed a strong association between the presence of cow's milk IgE antibodies in the mother during pregnancy and that in the cord blood of the resulting infant.¹⁶ Because IgE does not cross the placenta into the foetal circulation, it must have been generated *de novo* by the foetus.

Circulating B lymphocytes with surface IgM can be detected by 16 weeks' gestation. Circulating peripheral blood mononuclear cells (PBMCs) are capable of mounting a specific proliferative response to allergens such as hen's egg ovalbumin and the major house-dust mite allergen, Der P1, from 22 weeks' gestation.¹⁷ By full term, the overwhelming majority of neonates are able to mount specific responses to common environmental factors; and a high proliferative response with a different cytokine expression profile to an allergen at birth associated with a higher probability of allergic disease later in childhood.¹⁸⁻²⁰ The presence of TH2-promoting cytokines around the foetus biases virtually all neonatal responses to a TH-2 phenotype. This response may not be only a bystander effect of foetal protection against maternal TH1 responses; it is likely also to have had an evolutionarily relevant role in protecting the neonate against its mother's parasites. This process orchestrates a foetal response to maternal helminths. Infants born to helminth-infected mothers have enhanced specific TH2-biased immune responses to maternal helminth antigens, and high levels of IgE antibodies to these antigens are detectable in cord blood. Although the neonate has a 'face-down' exposure to its mother's parasites, it is exceedingly rare for the infant to become infected by these parasites; this implies an efficient adaptive immune response to preventing such infection. It

is likely that the molecular configuration or, more likely, the biological activity of allergens has counterparts to parasite antigens, leading to the activation of an identical immune response in a parasite-free environment.²¹

ALLERGEN EXPOSURE AND FOETAL SENSITISATION

While primary sensitisation to allergen in pregnancy is via the foetal gut, detectable during the second trimester of pregnancy, there are third-trimester counter-regulatory events that may re-balance responses. Active transportation of IgG antibody across the placenta complexed with antigens and allergens has the potential, via inhibitory IgG receptors, to prevent APC activation. This will result in antigen presentation without co-stimulation, which will produce clonal deletion of the relevant allergen-sensitised T-cells. Higher IgG antibody levels to an allergen are associated with a lower subsequent rate of allergic sensitisation to those allergens.²¹ If this is the case, it follows that the timing and concentration of exposure during pregnancy will have subtly different influences on outcomes.

One study of Birch and Timothy pollen exposure in pregnancy has substantiated this hypothesis. The foetus mounted a sensitising cellular response only if the pollen season coincided with the first six months of pregnancy, whereas exposure in the last three months resulted in tolerance.²² Concentration of exposure affects the maternal IgG antibody levels with high doses and therefore high IgG antibody levels, having a greater potential to induce tolerance.

There are several clinical observational studies which substantiate this hypothesis. Children of mothers who had undergone rye grass allergen immunotherapy during pregnancy with consequently high IgG antibody levels compared with children born to rye grass-allergic mothers who did not receive immunotherapy had fewer positive skin tests to rye grass three to 12 years later.²³ Neonates with high IgG antibody levels to cats and/or pollens have a lower probability of generating IgE antibodies to those allergens up to eight years later.²⁴ My group's study of egg exposure during pregnancy showed that both very high and very low dose exposure was associated with lower allergy prevalence in the offspring than in those where the mother had a moderate exposure.²⁵ This phenomenon has been well documented from murine studies, where oral ovalbumin in pregnancy induces ovalbumin tolerance in infant BALBc mice. The protective effect is abrogated by the inhibition of either placental IgG transfer or infant memory T-cell IFN- γ production.²⁶

These clinical observations imply that attempts to reduce allergen exposure in pregnancy might be equally likely to have an adverse rather than favourable effect. Many antenatal allergen exposure studies have suggested that

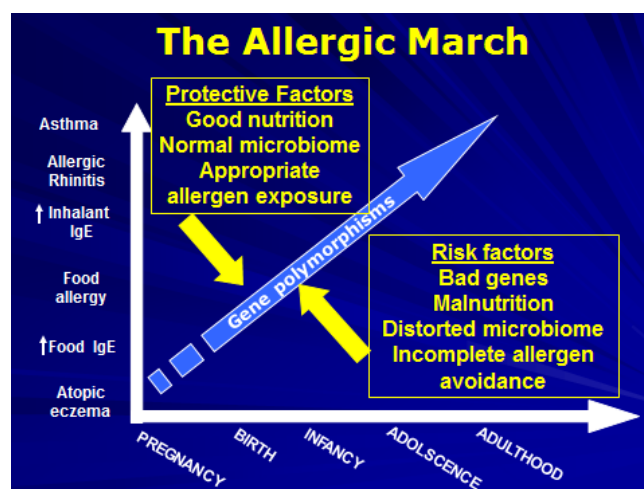


Figure 4: A representation of the allergic march and factors which increase or decrease susceptibility.

this may indeed be the case. At one year of age, low house-mite exposure has been associated with somewhat less wheezing by three years of age, but there is either no effect or an increased rate of later sensitisation to house-dust mite. Most studies have failed to demonstrate any consistent effect of house-mite avoidance in preventing either sensitisation or asthma and low-level exposure to house mite has been associated with a greater risk of IgE sensitisation and asthma than higher levels.^{27,28}

In conclusion, there is no justification for making any recommendations about environmental modification during pregnancy to prevent allergic sensitisation or allergic disease.

FACTORS MODIFYING THE IMMUNOLOGICAL BALANCE IN PREGNANCY

The almost universal Th-2-biased neonatal immune response normally down-regulates rapidly after birth. The current hypothesis, arising from the much-investigated hygiene hypothesis, is that the developing diversity of the gut microbiome of the infant post-natally is the major contributor. However, there are some differences in the maternal microbiome in pregnancy related to later variations in immunological and eczema outcomes in the infant.²⁹ Furthermore, an increasing use of antibiotics by the mother during pregnancy is associated with a higher risk of asthma in the off-spring.³⁰ Whether this observation represents a different neonatal inoculum from mother to infant during delivery or an antenatal effect on maternal immune priming of the foetus remains to be established. The post-natal diversification of the microbiome is facilitated by oligosaccharide pre-biotics present in human milk.³¹ These matters are discussed in accompanying articles in this issue.

However, there are antenatal environmental influences that commit the neonate to a more entrenched TH-2 response which is less likely to be abrogated after birth.

Many studies have shown that if the mother is allergic, her infant is far more likely to show allergy and allergic disease from an early stage in life compared to merely inheriting allergy genes from the father. Maternal allergy must in some way prime the foetus to be more prone to becoming allergic. This is likely to be due to maternal IgE in the amniotic fluid facilitating antigen focusing. There may also be differences in the levels of amniotic fluid cytokines from allergic compared to non-allergic mothers, which is certainly the case for IL-10.²¹

NUTRITION AND ALLERGY

Foetal growth and nutrition may well also have an impact on the ontogeny of immune responses. There have been some unusual direct associations between large head circumference at birth and levels of total IgE in childhood and even in adulthood. It has been hypothesised that a large head circumference at birth is representative of a rapid foetal growth trajectory because of good nutrient supplies in early pregnancy. The foetus is subsequently programmed to continue on a rapid growth trajectory and retains a high nutrient demand. If this is not met in the later stage of pregnancy, head growth continues at the expense of relatively poor nutrition to the body, with consequent adverse effects on rapidly developing tissues such as those in the immune system. The key question raised by these observations is whether there are any specific nutrients of importance in protecting immune responsiveness.

A high intake of fresh fruit and vegetables during pregnancy has been associated with a lower rate of allergic sensitisation, and high intakes of fish in pregnancy have also been associated with less subsequent allergy in the offspring. Both of the above group of foods are prominent in the so-called 'Mediterranean' diet and a systematic review of published studies confirms a significant effect on a reduced prevalence of wheezing.³³ Low cord selenium and iron have been associated with a higher subsequent risk of persistent wheeze alone for selenium and both wheeze and eczema for iron. To what extent low selenium, as a marker of anti-oxidant activity, increases allergy risk or merely predisposition to airway inflammation and wheeze, with or without allergy, remains to be clarified.

Trials of dietary supplementation in pregnancy are now required. A number of studies have focused on lipids as being important in immune ontogeny. Fatty acids have a crucial role as a source of energy, as the principal component of cell membranes and as substrates for the synthesis of prostaglandins and leukotrienes. Minor variations in the levels of these dietary supplements could have a profound effect on immune responses. Fish oils have a high level of omega-3 polyunsaturated fatty acids (n-3PUFAs). Western diets have a diminished intake of n-3PUFAs, with corresponding increases in n-6PUFAs. This change has been associated with increasing rates of allergic disease and asthma.

Three randomised controlled studies have employed administration of a fish oil dietary supplement to mothers throughout pregnancy and then monitored of outcomes in the offspring in high-risk cohorts where at least one parent or sibling had atopy with or without asthma. One study aimed only to detect differences in cord-blood immune profiles and it showed reductions in cytokine release from allergen-stimulated cord-blood mononuclear cells, with marginal effects on clinical outcomes at one year in relation to atopic eczema, wheeze and cough. Another, much larger study employed fish oil supplementation in pregnancy with or without additional house-mite avoidance, and demonstrated a significant reduction in wheeze at 18 months of age. By three years of age there was a significantly lower prevalence of respiratory symptoms. In comparison, house-mite avoidance had an effect on house-mite sensitisation but no effect on any respiratory symptoms. As proof of concept, the fish oil supplementation in pregnancy studies at least demonstrated an effect, and further studies are certainly indicated. To what extent this will affect subsequent allergic sensitisation and disease remains to be established.

Another hypothesis related to nutrition has gained popularity: it suggests that vitamin D insufficiency increases the risk of allergic sensitisation. The geographical distribution of allergy prevalence can to a certain extent be associated with reduced vitamin D levels. Vitamin D receptors have been identified on immune active cells and particularly regulatory T-cells, suggesting a novel immune-regulatory function to this nutrient. However, this potentially beneficial effect on allergy is balanced by dendritic cell production of IL-12 being inhibited and IL-10 being increased by exposure to vitamin D. This in turn would down-regulate T-helper-1 responses and allow T-helper-2 activity to predominate – which, of course, based on the Th-1 and Th-2 paradigm, would be associated with a greater probability of allergy and allergic disease. These conflicting effects could explain the lack of effect on allergy or any disease outcome in a controlled trial of vitamin D supplementation in pregnancy.³⁴

DISEASE-SPECIFIC GENE–ENVIRONMENT INTERACTION

While most studies of the gene–environment interactions that affect susceptibility to allergy and/or disease have elaborated on post-natal influences, there are some intriguing studies of the effects during pregnancy. Paracetamol/acetaminophen intake by pregnant mothers and/or their infants has been associated with, and even correlated to, an increased risk of asthma. When metabolised, this analgesic/antipyretic reduces anti-oxidant activity. One study has shown an interaction which increased asthma in five-year-olds born to mothers having frequent courses of paracetamol during pregnancy and a co-existent polymorphism in the anti-oxidant glutathione S-methyl transferase P1 gene.³⁵

A meta-analysis of cigarette smoking identified only three of 43 studies which claimed to evaluate pregnancy smoking alone, while in the rest smoking occurred during pregnancy and post-natally. The greatest impact was on infant wheeze, with less certain effects on later allergy or asthma.³⁶ However, smoking during pregnancy certainly has an impact on infant lung function and subsequent risk of wheezing, in all probability by impairing alveolar development, which in turn reduces small airway elastic tissue support.³⁷ Furthermore, any perturbations which compromise late pregnancy foetal growth with subsequent rapid post-natal weight gain are associated with impaired lung function and an increased risk of infant wheezing.³⁸ As obesity is also a longer term consequence in this situation, perhaps the early associated lung function deficit could explain the link between asthma and obesity. There may well be interactions with genetic polymorphisms, as has been demonstrated for paracetamol exposure. One intriguing observational study has shown that grand-maternal smoking during pregnancy with the mother increases asthma risk in the subsequent grandchild, irrespective of whether the mother smoked.³⁹ This is very

likely to be an epigenetic effect of grandmothers ETS exposure.

Folic acid is a methyl donor and epigenetic modification of human DNA translation is either suppressed by methylation of the 30 million CpG motifs or enhanced by methylation of the 30 million histone nucleosomes around which DNA is coiled. Three studies suggest a weak effect of folic acid in later but not early pregnancy on the risk of early respiratory symptoms. However, several other studies have shown no effect.⁴⁰

DECLARATION OF CONFLICT OF INTEREST

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This article has been peer reviewed.

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ERRATUM

The references to the article “Multiple Chemical Sensitivity – two illustrative case reports” by Dr Hilary A Carman published in the Vol 30 No 1 (2017):40-43, were incorrectly listed. Herewith please find the correct references. We apologise to the authors and the readers for this error.

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RECOMMENDED FURTHER READING

1. Multiple Chemical Sensitivity – the end of controversy. Martin_pall@wsu.edu 2016. www.laleva.cc/environment/mcs_en.html This discusses Professor Pall's ongoing research into the role of nitric oxide on neural sensitisation.
2. Sparks PJ (editor). Multiple Chemical Sensitivity/Idiopathic Environmental Intolerance. *Occupational Medicine: State of the Art Reviews* 2000;15. This is a 170-page publication which covers many aspects of MCS, including its aetiology, diagnosis and treatment.
3. Black DW, Temple S. Overview of idiopathic environmental intolerance (multiple chemical sensitivity) UpToDate 2015. www.uptodate.com/contents/overview-of-idiopathic-environmental-intolerance-multiple-chemical-sensitivity
4. Gibson PR, Elms AN, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. *Environmental Health Perspectives* 2003;111:1498–1504.