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DEBATE

The hygiene hypothesis revisited

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At the end of 2002, I published an article that related 'the clinical observation, empirically cited over the centuries', that 'inhibition of acute disease manifestation in childhood can predispose to future chronic diseases', according to distinct lines from medical thought: homeopathy (Hahnemann, Burnett, French school), anthroposophic medicine, experimental pathology (Maffei).[1] This theory assumed a modern scientific guise in the 'hygiene hypothesis', suggesting 'an inverse relationship between atopic diseases and an environment that leads to increased pathogen exposure'.

Contrary to the hygiene hypothesis, Adler publishes in this edition of Homeopathy a review of the epidemiological literature concluding that 'childhood infections do not protect against atopy, on the contrary, they increase the risk of allergic disease' and 'vaccination is not a risk factor for the development of the atopy'.[2]

Adler does not review that indirect markers of exposure to infections, mentioned in the hygiene hypothesis (climatic and social-economic differences; farm environment; exposure to domestic animals; number of siblings and age at admission to a day care centre; use of antibiotics; positivety to hepatitis A virus antibodies and bacterial endotoxins; etc), have limited the comprehensiveness of the analysis even more.

In the first *quantitative systematic review* on 'infections and atopy', Randi *et al*[3] carried out 'an exploratory study for a meta-analysis of the hygiene hypothesis', examining differences concerning the association with a history of infectious events, in terms of magnitude and homogeneity of global risks estimates (indirect markers of exposure to infections) among the three major atopic diseases (atopic dermatitis, asthma and allergic rhinitis). Using a standardised protocol to select and analyse papers cited in an authoritative review[4] (among 133 references, 37 articles provided pertinent information, and only 10 studies had useful information for a quantitative statistical analysis), the authors concluded: 'with this exploratory study, we obtained a quantification (probably optimistic due to the publication bias for negative results) of the inverse association between infectious events and atopic diseases corresponding to a 20% protection for atopic dermatitis, 30% for allergic rhinitis and 40% for asthma'. Although the authors have followed the explicit descriptions of systematic methods, they are cautious in their conclusions, emphasising that 'any measure of association cannot be interpreted as an unbiased estimator of the potential association infections-atopic disease; the value of this study is essentially as a test of a statistical methodology for data combination rather than an approach to the study of potential associations.'

In recent *qualitative systematic review* of the epidemiological literature (1966–2004), focusing exclusively on atopic dermatitis (AD) and the hygiene hypothesis,[5] using Odds ratios (OR) and 95% confidence intervals (CIs) as a measure of the association between exposure and AD, results showed that there was prospective evidence to support an inverse relationship between AD and endotoxins, early day care and animal exposure. Two well-designed cohort studies have found a positive association between infections in early life and AD and measles vaccination and AD; antibiotic use was consistently associated with an increase in AD risk even into the antenatal period; a few small randomised-controlled trials have suggested that probiotics can reduce AD severity and may also be able to prevent AD to some degree. The authors concluded that with the majority of studies uses non-validated questionnaires rather than physician diagnosis to identify AD cases, the results are prone to bias.

In other systematic reviews, using recent findings (2003–2004),[6] the critical evaluation of the 111 papers selected for the authors' shows that the number of favourable opinions largely exceeds the number of contrary ones, although there is still no unanimous consensus: 'The association between a reduced exposure to infectious agents and a higher prevalence of atopy seems now to be confirmed by consistent evidence. Mechanisms underlying this association,

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however, are not yet completely clear (immune deviation or immune regulation).'

A review of the effects of BCG immunisation on the development of atopy concludes that 'at this moment, there is insufficient evidence to accept or reject a causal relation between early BCG vaccination and the development of allergic diseases', because 'methodological flaws, different vaccine strains and dosages used and varying ages at vaccination have been suggested to be responsible for the conflicting results of the studies investigating the question at issue'.[7,8] In spite of most of the studies being related to BCG, the same can be enlarged for other vaccines.

Even among reviews that criticise the hygiene hypothesis, it is evident that natural infections may regulate the immune system (Th1 response), in ways that immunisation does not, protecting against the development of allergic and autoimmune diseases: 'Since modern subunit vaccines mostly lack these microbial antigens, they may not activate dendritic cells efficiently. Likewise, microbial antigens such as heat shock proteins seem to have an intrinsic capacity to trigger Tr cells. As a result, the absence of microbial antigens from vaccines may also impair regulation of the adaptive immune response. Recent advances in understanding how cell-mediated immunity is regulated have indicated substantial differences between responses after natural infections and vaccination that may contribute to the induction of Th1 responses after vaccination. Infants with a positive family history of atopy have a reduced Th1 response capacity. Vaccination of these genetically predisposed infants is unlikely to stimulate upregulation of Th1-type responses.[…] Therefore, the challenge is to construct vaccines that not only prevent infectious diseases, but also mimic infection-mediated immune stimulation to protect against the development of allergic and autoimmune diseases'.[8]

Since most of the researches are observational studies, which are prone to confounding bias, additional experimental and clinical evidences in well-designed controlled studies (with special reference to the time, duration and intensity of exposure to any specific infectious agent), systematic reviews and meta-analysis are needed to evaluate the reality and magnitude of the hygiene hypothesis.

In 2002–2005 a number of further papers have been published. Perhaps the progress made by the hygiene hypothesis in the 15 years following its introduction is best summarised by Strachan himself: 'The hygiene hypothesis remains a credible but non-specific explanation for observed variations over time, place and person at risk for developing atopic allergic disorders. More prospective studies are needed to unravel which infectious agents exert a protective effect and the time period of importance for sensitisation. The clinical implications of these advances in understanding the etiology of atopic allergic disorders are currently limited.'[9]

Revisited Hygiene Hypothesis (2002–2005)—Favourable Papers

Systematic Reviews

[*Curr Opin Allergy Clin Immunol* 2005; 5: 147–151; *Br J Dermatol* 2005; 152(2): 202–216; *Rev Epidemiol Sante Publique* 2004; 52(6): 565–574]

General Reviews

[*Curr Opin Allergy Clin Immunol* 2005; 5(2): 147–151; *J Pediatr Gastroenterol Nutr* 2005; (Suppl): S37–S38; *Allergy* 2004; 59(2): 124–137; *Clin Rev Allergy Immunol* 2004; 26(1): 15–24; *Allergy Asthma Proc* 2004; 25(1): 7–10; *J Allergy Clin Immunol* 2004; 113(1): 179–180; *Br Med Bull* 2003; 68: 227–242; *J Laryngol Otol* 2003; 117(12): 946–950; *Curr Opin Allergy Clin Immunol* 2003; 3(5): 325–329; *Allergy* 2003; 58(9): 844–853; *J Allergy Clin Immunol* 2003; 111(3): 471–478; *N Engl J Med* 2002; 347: 911–920; *Ann Allergy Asthma Immunol* 2002; 89(6 Suppl 1): 69–74; *Curr Drug Targets Infect Disord* 2002; 2(3): 193–199; *Environ Health Perspect* 2002; 110 (Suppl 4): 557–560]

Specific Reviews

The role of microbial antigens (endotoxins) in stimulating immune response (Th1) and protecting the future development of atopic diseases [*J Allergy Clin Immunol* 2004; 114(5): 1051–1054; *Paediatr Respir Rev* 2004; 5 (Suppl A): S65–S71; *Curr Opin Allergy Clin Immunol* 2004; 4(2): 113–117; *Curr Opin Otolaryngol Head Neck Surg* 2004; 12(3): 232–236; *Nat Immunol* 2004; 5(3): 337–343; *Ann Allergy Asthma Immunol* 2003; 90(6 Suppl 3): 64–70; *Pediatrics* 2003; 111(3): 653–659; *J Allergy Clin Immunol* 2003; 112(1): 219–220; *Curr Drug Targets Inflamm Allergy* 2003; 2(2): 187–195].

Contradicting the hypothesis that toxic agents (environmental, alimentary, etc) are responsible for the increase of atopic diseases in last decades [*Pediatrics* 2004; 113 (4 Suppl): 1107–1113; *Curr Opin Allergy Clin Immunol* 2002; 2 (2): 141–145].

Inducing effect of antibiotics in the future development of atopic diseases [*Infect Immun* 2004; 72: 4996–5003].

Inducing effect of vaccines in the future development of atopic diseases [*Med Hypotheses* 2004; 63(5): 875–886; *Acta Derm Venereol (Stockh)* 2003; 83: 445–450].

The protective role of the childhood infections in the future development of autoimmune diseases: DM type 1 [*Clin Dev Immunol* 2004; 11(3–4): 191–194; *N Engl J Med* 2002; 347: 911–920].

The protective role of helminth infections (induce strong Th2-type response) in development of inflammatory bowel diseases (Crohn's disease; ulcerative colitis) [*Can J Gastroenterol* 2005; 19(2): 89–95; *Inflamm Bowel Dis* 2005; 11(2): 178–184; *Gut* 2005; 54(3): 317–320; *Can J Gastroenterol* 2005; 19(2): 89–95; *Curr Opin Gastroenterol* 2004; 20(6): 560–564; *Can J Gastroenterol* 2004; 18(8): 493–500; *Clin Rev Allergy Immunol* 2004; 26(1): 35–50; *J Helminthol* 2003; 77(2): 147–153; *Infect Immun* 2002; 70(12): 6688–6696].

The protective role of probiotics in development of atopic diseases [*Gut* 2005; 54(3): 317–320; *Can J Gastroenterol* 2004; 18(8): 493–500; *Trends Microbiol* 2004; 12(12): 562–568; *Ann Allergy Asthma Immunol* 2002; 89 (6 Suppl 1): 75–82; *Br J Nutr* 2002; 88 (Suppl 1): S19–S27].

Proposal of new strategies of treatments, using the microorganisms or their products (endotoxins) in treatment or prevention of atopic diseases [*J Allergy Clin Immunol* 2004; 114(5): 1051–1054; *Pharmacol Ther* 2004; 101(3): 193–210; *Allergy* 2003; 58: 461–471].

Hygiene Hypothesis Enlargement

Hygiene Hypothesis should be enlarged in three aspects: first, the importance of sources of microbial stimulation in causing immune deviance; second, immunomodulatory and suppressive immune responses complement the Th1/Th2 paradigm; third, in addition to protection against atopy, protection against infectious, inflammatory and autoimmune diseases may also depend upon healthy host–microbe interactions implicated in the hygiene hypothesis [*J Pediatr Gastroenterol Nutr* 2004; 38(4): 378–388; *J Allergy Clin Immunol* 2004; 113(3): 395–400; *Immunology* 2004; 112(3): 352–363; *J Pediatr Gastroenterol Nutr* 2004; 38(4): 378–388; *Clin Rev Allergy Immunol* 2004; 26(1): 25–34; *J Clin Invest* 2004; 114(2): 270–279; *Am J Kidney Dis* 2003; 42(3): 575–581].

Hygiene Hypothesis needs to be enlarged in the 'type' of infectious agent, in the 'age', 'time' and 'intensity' of agent exposure, besides the period among the exposure to the infectious and allergic agents [*Curr Opin Allergy Clin Immunol* 2005; *Clin Exp Allergy* 2005; 35(1): 8–17; *Allergy* 2005; 60(2): 226–232; *Curr Opin Pulm Med* 2005; 11(1): 14–20; *Pharmacol Ther* 2004; 101(3): 193–210; *Curr Opin Allergy Clin Immunol* 2004; 4(1):69–74; *J Pediatr Gastroenterol Nutr* 2004; 38(4): 378–388; *Curr Opin Otolaryngol Head Neck Surg* 2004; 12(3): 232–236; *Ann Allergy Asthma Immunol* 2003; 90(6 Suppl 3): 64–70; *Br Med Bull* 2002; 61: 29–43; *Science* 2002; 296(5567): 490–494; *Eur Respir J* 2002; 19(1): 158–171; *Infect Immun* 2002; 70(12): 6688–6696].

Descriptive and Observational Studies

Protecting effect of the childhood infections in the future development of atopic diseases [*Clin Exp Allergy* 2004; 34(8): 178–183; *Int J Pediatr Otorhinolaryngol* 2004; 68(6): 775–778; *Am J Public Health* 2003; 93(11): 1858–1864; *Pediatr Allergy Immunol* 2003; 14(5): 363–370; *J Allergy Clin Immunol* 2003; 111(4): 847–853; *J Allergy Clin Immunol* 2002; 110(3): 381–387; *Arch Dis Child* 2002; 87(1): 26–29].

Protecting effect of the childhood infections in the future development of autoimmune diseases [*Diabet Med* 2004; 21(9): 1035–1040; *Diabetologia* 2003; 46(2): 301–302] and cancer [*Leuk Res* 2004; 28(7): 713–724; *Med Hypotheses* 2004; 62(6): 880–888].

Inducing effect of vaccines in the future development of atopic and chronic diseases [*Leuk Res* 2004; 28(7): 713–724; *Acta Derm Venereol* 2003; 83(6): 445–450; *Allergy* 2002; 57(6): 472–479].

Inducing effect of antibiotics in the future development of atopic diseases [*J Epidemiol Community Health* 2004; 58(10): 852–857; *Am J Resp Crit Care Med* 2002; 166: 72–75; *Am J Resp Crit Care Med* 2002; 166: 827–832; *J Allergy Clin Immunol* 2002; 109: 43–50].

Protecting effect of childhood infectious fever in the future development of atopic diseases [*JAMA* 2005; 293(4): 463–469; *J Allergy Clin Immunol* 2004; 113(2): 291–296; *Eur Respir J* 2002; 20(2): 391–396].

Protecting effect of gestation infectious in the future development of atopic diseases in children of atopic women [*Allergy* 2004; 59(9): 961–968].

Protecting effect of household crowding in the future development of atopic diseases [*BMC Public Health* 2004; 34(1): 19; *J Epidemiol Community Health* 2002; 56(3): 209–217; *Clin Otolaryngol* 2002; 27(5): 352–358].

Protecting effect of farm style in the future development of atopic diseases [*Eur Respir J* 2002; 19(5): 853–858].

Experimental Studies

Mice experimental model that demonstrated the role of antibiotics in driving pulmonary allergic [*Infect Immun* 2005; 73(1): 30–38; *Infect Immun* 2004; 72(9): 4996–5003].

Mice experimental models that demonstrated the capacity of the *Mycobacterium bovis* Bacillus Calmette–Guerin (*M. bovis* BCG) infection stimulate Th1 response and

suppress Th2 response [*Curr Opin Allergy Clin Immunol* 2004; 4(1): 57–62; *Eur J Immunol* 2004; 34(3): 631–638; *Clin Exp Allergy* 2003; 33(8): 1083–1089; *J Immunol* 2003; 171(2): 754–760; *Nat Med* 2002; 8(6): 625–629], preventing the development of the Graves' disease experimentally induced [*Endocrinology* 2004; 145(11): 5075–5079] and modifying the course of autoimmune encephalomyelitis experimentally induced [*Immunol Lett* 2002; 82(1–2): 101–110], that mimic the human multiple sclerosis.

Murine experimental allergic-asthma model that evidenced the capacity of *Mycoplasma pneumoniae* infection modulate lung allergic diseases [*Infect Immun* 2003; 71(3): 1520–1526].

Mice experimental models that demonstrated the capacity of the helminth infection protects from anaphylaxis via IL-10-producing B cells [*J Immunol* 2004; 173(10): 6346–6355].

Animal experimental models that suggest the use of pathogenic microorganism genetic materials (CpG oligodeoxynucleotides), that mimic childhood infections, to stimulate Th1 response and suppress Th2 response, preventing the future manifestation of allergic diseases [*J Investig Dermatol Symp Proc* 2004; 9(1): 23–28; *Clin Exp Allergy* 2003; 33(10): 1330–1335].

Congenital experimental model of asthma in mice that identified the family gene TIM-1, related to previous infections for the Hepatitis A, that presents an important role in the modulatory immune response in the development of atopic diseases [*Springer Semin Immunopathol* 2004; 25(3–4): 335–348; *Nature* 2003; 425: 576].

Mice experimental model that related the alleles of the gene Nramp1 with resistance or susceptibility to allergic diseases [*Trends Immunol* 2004; 25(7): 342–347; *J Immunol* 2003; 171(2): 754–760; *FASEB J* 2003; 17(8): 958–960].

Review on the genetic studies that describe the gene CD14, expressed in the monocytes and macrophages membrane, as a multifunctional receiver to endotoxins and other microbial products, waking up the Th1 immune response and preventing the manifestation of atopic diseases [*Curr Opin Allergy Clin Immunol* 2003; 3(5): 347–352].

Review on mice experimental models of Diabetes and Gastritis (*Helicobacter*) that demonstrated the improvement of these diseases for the induction of the Th2 response for parasite antigens [*Curr Top Med Chem* 2004; 4(5): 531–538].

T cell maturation linear model interpreting how changes in cytokine production by T cell populations are regulated [*Clin Exp Allergy* 2005; 35(1): 8–17].

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