

(higher concentrations) route of progestin delivery. Another possibility is that when a polyp did appear after 12 months it was in a patient who had had a polyp removed before treatment. If so, the LNG-IUS only prevented (or delayed) two polyps from reappearing in the treatment arm. It is, however, reassuring that new polyps did not develop over the 1 year period.

As has happened in other settings, local progestins in combination with tamoxifen led to prolonged vaginal bleeding, especially in the first six months, in Gardner's study. This effect on bleeding has been recorded by others¹⁶ and may reduce treatment compliance with tamoxifen. I suspect that this bleeding is probably related not only to mechanical irritation but also to chronic down-regulation of the progesterone receptor.¹⁷

Several issues remain unresolved. The exact signalling pathways and long-term effects of low serum concentrations of levonorgestrel on hormone-sensitive organs remain undefined. Breast tension, although rare, has been linked with LNG-IUS. What about low doses of synthetic progestins and breast cancer risk and do they interfere with tamoxifen's antitumoral effect? What about lipids and cardiovascular consequences? What percentage of tamoxifen users really stands to benefit since most do not develop endometrial polyps? How does a chronic down-regulation of the progesterone receptor fit with continuous prevention of bleeding and an ongoing endometrial protection?

Gardner and colleagues report 100% decidualisation of tamoxifen-exposed postmenopausal endometrium after a single application of LNG-IUS, which points towards tamoxifen's oestrogen-like effect. Their study also shows that one year of local progestins prevents endometrial polyps appearing or reappearing. The LNG-IUS may induce more vaginal bleeding but it does not alter the ultrasonographic appearance of tamoxifen-exposed endometrium. On the evidence available, a randomised trial of the LNG-IUS in women on tamoxifen who have an endometrial polyp hysteroscopically removed (eg, after three years of tamoxifen intake because this group is at most risk¹⁸) is justified. The primary endpoint should be the prevention of endometrial polyps and cancers; effects on the breast and on lipids should also be looked at.

P Neven

Algemene Kliniek St-Jan, Broekstraat 104, B-1000 Brussels, Belgium

- 1 Neven P, Vernaëve H. Guidelines for monitoring patients taking tamoxifen treatment. *Drug Safety* 2000; **22**: 1–11.
- 2 Bergman L, Beelen MLR, Gallee MPW et al. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. *Lancet* 2000; **356**: 881–87.
- 3 Neven P, Vergote I. Should tamoxifen users be screened for endometrial lesions? *Lancet* 1998; **351**: 155–57.
- 4 Gardner FJE, Konje JC, Abrams KR, et al. Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system: a randomised controlled trial. *Lancet* 2000; **356**: 1711–17.
- 5 Suvanto-Luukkonen E & Kauppila A. The levonorgestrel intrauterine system in menopausal hormone replacement therapy: five year experience. *Fertil Steril* 1999; **72**: 161–63.
- 6 Thijs I, Neven P, Van Hooff I et al. Oestrogen and progesterone receptor expression in postmenopausal endometrial polyps and their surrounding endometrium. *Eur J Cancer* 2000; **36**(suppl 4):108–09.
- 7 Brechin S, Cameron ST, Paterson AM et al. Intrauterine polyps. A cause of unscheduled bleeding in women using the levonorgestrel intrauterine system. *Hum Reprod* 2000; **15**: 650–52.
- 8 Elkas J, Armstrong A, Pohl J et al. Modulation of endometrial steroid receptors and growth regulatory genes by tamoxifen. *Obstet Gynecol* 2000; **95**: 697–703.
- 9 Powles TJ, Bourne T, Athanasiou S et al. The effects of norethisterone on endometrial abnormalities identified by transvaginal ultrasound screening of healthy postmenopausal women on tamoxifen or placebo. *Br J Cancer* 1998; **78**: 272–75.

- 10 Kennedy MM, Baigrie CF, Manek S et al. Tamoxifen and the endometrium: review of 102 cases and comparison with HRT-related and non-HRT-related endometrial pathology. *Int J Gynecol Pathol* 1999; **18**: 130–37.
- 11 Elkas J, Gray K, Howard L et al. The effects of tamoxifen on endometrial insulin-like growth factor-1 expression. *Obstet Gynecol* 1998; **91**: 45–50.
- 12 Pekonen F, Nyman T, Lähteenmäki P et al. Intrauterine progestin induces continuous insulin-like growth factor-binding protein-1 production in the human endometrium. *J Clin Endocrinol Metab* 1992; **75**: 660–64.
- 13 Berezowsky J, Chalvardjian A, Murray D. Iatrogenic endometrial megapolyps in women with breast carcinoma. *Obstet Gynecol* 1994; **84**: 727–30.
- 14 Cohen I, Figer A, Altaras MM et al. Common endometrial decidual reaction in postmenopausal breast cancer patients treated with tamoxifen and progestogens. *Int J Gynecol Pathol* 1996; **15**: 17–22.
- 15 Rose PG, Brandewie EV, Abdul-Karim FW. Failure of megestrol acetate to reverse tamoxifen induced endometrial neoplasia: two case reports. *Int J Gynecol Cancer* 1999; **9**: 362–64.
- 16 Ballard P, Turnbull L, Richmond L, Tetlow R. The effect of a levonorgestrel intrauterine system on the endometrium of patients receiving long-term tamoxifen treatment for breast cancer. *Brit J Obstet Gynaecol* 1998; **105** Suppl 17: abstr 299.
- 17 Critchley HOD, Wang H, Kelly RW et al. Progestin receptor isoforms and prostaglandin dehydrogenase in the endometrium of women using a levonorgestrel-releasing intra-uterine system. *Hum Reprod* 1998; **13**: 1210–17.
- 18 Berlière M, Charles A, Galant C et al. Uterine side effects of tamoxifen: a need for systematic pretreatment screening. *Obstet Gynecol* 1998; **91**: 40–44.

Parasites, atopy, and the hygiene hypothesis: resolution of a paradox?

See page 1723

In this issue Anita van de Biggelaar and colleagues¹ report that infestation of children with helminth parasites, which are potent stimuli for allergen-associated T-helper 2 (Th2) immunity, is paradoxically associated with reduced susceptibility to atopy. This finding superficially appears to challenge some of the basic tenets of the Th1/Th2 paradigm and of the hygiene hypothesis for atopy. However, it is becoming clear that atopic disease is a two-stage process, involving a discrete phase for induction (ie, immunological memory development favouring allergic sensitisation) which is regulated via interactions between Th1 and Th2 cytokines, followed by a second and more complex effector phase involving the expression in target tissues of sensitised individuals of highly variable levels of Th2-mediated inflammation.² As discussed below, the key effects of helminths in this context appear targeted at cellular mechanisms central to the effector phase of atopy, which are operative beyond the stage in the disease process involving Th1/Th2 regulation. But, more importantly, the paper's linking of parasite-induced interleukin-10 production in children with reduced capacity to respond in vivo to allergens against which they are "sensitised", has important theoretical implications for the therapeutic control of allergy.

The hygiene hypothesis arose from attempts to explain differences in allergy prevalence related to socioeconomic and geographical factors. Its major focus has been upon viruses and bacteria, the broad proposal being that exposure to these classes of microbial stimuli in early life has a significant role in regulating the allergen-specific immune responses which underlie atopic disease. The agents implicated include respiratory and gastrointestinal pathogens, the normal commensal flora of the gastrointestinal tract,^{3–5} and, recently, bacterial cell-wall products in respirable dusts.^{4,5} The underlying cellular mechanisms are incompletely understood, but a variety of evidence suggests that the effects of these microbial agents

derive largely from their influence on the postnatal maturation of immune function.⁶ In the newborn, Th-cell activity is constitutively biased towards production of the Th2 cytokines, which predispose to allergy; and this Th2 bias is greatest amongst those at high genetic risk of allergy.⁷ Programming of Th-cell memory against allergens commonly occurs during early childhood,^{2,7} the period during which the balance between Th1 and Th2 functions “matures” from the Th2-biased fetal phenotype towards the relative Th1 dominance which characterises the adult immune system. Thus the risk of allergy-associated Th2-biased immunological memory may be directly related to the kinetics of postnatal development of capacity to generate Th2-inhibitory Th1 cytokines.^{2,7}

It is also recognised that the environmental signals which trigger maturation of Th2 function are specific microbial “signature” molecules not encountered during fetal life.³ One of the most potent of these is bacterial lipopolysaccharide which is recognised by cells of the innate immune system via the CD14 receptor. A polymorphism in the CD14 gene has been identified which predisposes to high-intensity atopy.⁸ Additionally, the CD14 receptor has also recently been linked with recognition of viral proteins by the innate immune system.⁹

It can be argued that the hygiene hypothesis provides plausible mechanisms within the framework of the Th1/Th2 paradigm for how allergy prevalence has risen in industrial countries in recent generations, concomitant with improvements in public health and hygiene practices which have resulted in reduced exposure to Th1-trophic microbial stimuli during early life.³ However, this model appears less plausible in relation to the wide discrepancy between prevalence rates in first and third world tropical countries. In the latter the dominant source of immunostimulatory signals in postnatal life is provided via parasites, particularly helminths, which, unlike most bacteria and viruses, selectively stimulate Th2 function. Why, then, is allergic disease less frequent in these countries?

The report by van den Biggelaar and colleagues¹ may hold the key to this puzzle. This study of 520 schoolchildren in Gabon, where helminthic parasitism is endemic, generated two seemingly contradictory findings. The frequency of raised total serum IgE and specific “sensitisation” to allergens was very high (eg, 32% of children were IgE antibody positive to mite), indicating that endemic parasitism is indeed associated with high frequency of development of Th2-polarised immunological memory against allergens. Secondly, and of greater interest, is the finding that in vivo skin-prick test (SPT) reactivity to the mite allergen was demonstrable in less than one-third of these IgE positive children. This major dissociation between production of sensitising IgE antibody and in-vivo expression of SPT reactivity contrasts markedly with experiences in first-world countries, in which these indices are consistently highly correlated in individuals. However, a comparable disassociation has been observed amongst children in Estonia,¹⁰ a second-world country in which the overall prevalence of allergy is low, and parasitism is infrequent, but bacterial and viral infection rates are high.

Reciprocal relations between parasitic infestation and in vivo manifestations of allergy have been reported previously in tropical environments, and eradication of helminths can unmask SPT reactivity in previously unresponsive individuals.¹¹ It has been proposed that saturation of mast cell IgE receptors by “non-specific” antibody stimulated by the parasites underlies these effects.¹¹ However, no significant relation between total serum IgE and SPT reactivity to specific allergen amongst sensitised children was observed in the large Gabon study group.¹ Instead,

failure to respond to challenge with specific allergen was associated with high level production of anti-inflammatory interleukin-10 by peripheral blood mononuclear cells stimulated by parasite antigen, and the authors propose that this cytokine dampens allergen-induced responses in vivo. They cite several papers on the anti-inflammatory role of interleukin-10 in asthma and allergy which are consistent with this mechanism, including those suggesting deficient interleukin-10 production in atopic individuals with active disease. Of particular relevance to the interpretation of their results is a recent report from our group indicating that amongst non-parasitised white children from a first-world country who were sensitised to mite, the diameter of mite-specific SPT wheals was inversely related to the magnitude of the interleukin-10 component of their in-vitro mite-specific Th-cell responses.¹²

Thus, the Gabon study suggests that while helminth parasitism may be permissive or even stimulatory towards Th2-mediated sensitisation to environmental allergens, it additionally triggers powerful anti-inflammatory mechanisms which limit the magnitude of ensuing in-vivo responses to these allergens. The findings provide compelling evidence to support the suggestion that interleukin-10 plays an important part in determining the severity of allergic disease in individuals, and the paper provides further impetus for research aimed at harnessing the potent effects of this anti-inflammatory cytokine for therapeutic purposes.

The current upsurge of interest in the role of microbial exposure in modulating atopic disease was sparked by a 1989 report¹³ suggesting an inverse relation between respiratory infections and allergic sensitisation in first-world populations, but much less attention has been paid to the possibility of a similar role for parasites. However, back in 1976, in a paper on allergy in the Metis Indians of northern Canada, Gerrard and colleagues reported that mean serum IgE levels in the white community were much lower than they were in the Metis community.¹⁴ Asthma, eczema, and urticaria were less common in the Metis Indians, contrasting with an increased prevalence of helminth infestation and untreated viral and bacterial diseases. Gerrard et al suggested: “atopic disease is the price paid by some members of the white community for their relative freedom from diseases due to viruses, bacteria, and helminths”.

Patrick G Holt

TVW Telethon Institute for Child Health Research, and Centre for Child Health Research, University of Western Australia, Perth, WA 6872, Australia

- 1 van den Biggelaar AHJ, van Ree R, Rodrigues LC, et al. Role for parasite-induced interleukin-10 in children infected by *Schistosoma haematobium*. *Lancet* 2000; **356**.
- 2 Holt PG, Macaubas C, Stumbles PA, Sly PD. The role of allergy in the development of asthma. *Nature* 1999; **402**: B12–17.
- 3 Holt PG. Environmental factors and primary T-cell sensitisation to inhalant allergens in infancy: reappraisal of the role of infections and air pollution. *Pediatr Allergy Immunol* 1995; **6**: 1–10.
- 4 Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000; **30**: 187–93.
- 5 Gereda JE, Leung DYM, Thatayatikom A, et al. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. *Lancet* 2000; **355**: 1680–83.
- 6 Martinez FD, Holt PG. The role of microbial burden in the aetiology of allergy and asthma. *Lancet* 1999; **354**: 12–15.
- 7 Holt PG, Macaubas C. Development of long term tolerance versus sensitisation to environmental allergens during the perinatal period. *Curr Opin Immunol* 1997; **9**: 782–87.
- 8 Baldini M, Lohman IC, Halonen M, Erickson RP, Holt PG, Martinez FD. A polymorphism in the 5'-flanking region of the CD14 gene is associated with circulating soluble CD14 levels with total serum IgE. *Am J Respir Cell Mol Biol* 1999; **20**: 976–83.
- 9 Kurt-Jones EA, Popova L, Kwinn L, et al. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. *Nature Immunol* 2000; **1**: 398–401.

- 10 Julge K, Vasar M, Björkstén B. Development of allergy and IgE antibodies during the first five years of life in Estonian children. *J Allergy Clin Immunol* (in press).
- 11 Lynch NR, Hagel I, Perez M, Brisco MC, Lopez R, Alvarez N. Effect of antihelminthic treatment on allergic reactivity in children in a tropical slum. *J Allergy Clin Immunol* 1993; **92**: 404–11.
- 12 Macaubus C, Sly PD, Burton P, et al. Regulation of T-helper cell responses to inhaled allergen during early childhood. *Clin Exp Allergy* 1999; **29**: 1223–31.
- 13 Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259–60.
- 14 Gerrard JW, Geddes CA, Reggin PL, Gerrard CD, Horne S. Serum IgE levels in white and Metis communities in Saskatchewan. *Ann Allergy* 1976; **37**: 91–100.

Minimising discomfort with fine-needle aspiration cytology of the breast

The history of aspiration of tissue for diagnostic purposes dates back to 1853, when James Paget aspirated tissue from a breast tumour. In 1925, Hayes Martin and Bradley Corley, with the assistance of a technician Edward Ellis, did likewise with various human organs at the Memorial Hospital for Cancer and Allied Disease. They used an 18G needle connected to a 20 mL syringe. Because of concern about dissemination of disease through the needletrack and about the possibility of a pneumothorax because of the large needle, the aspiration technique fell out of favour in the USA. 20 years later, the aspiration technique was revived in Scandinavia, where it flourished. It was not until the early 1970s that the fine-needle aspiration (FNA) technique was repopularised. Now FNA has proved to be an accurate, efficient, and cost-saving procedure as an adjuvant tool in the “triple-test approach” and management of breast lesions.¹

A 21G needle is generally recommended, but there is no consensus on whether a local anaesthetic is necessary, so what is the experience like for the patient? I R Daltrey and M W Kissin have done a randomised trial to examine the effect of needle size (21G or 23G) and local anaesthetic on discomfort produced during FNA. The greatest discomfort was produced by the 21G needle used without an anaesthetic. There was no difference in discomfort among the other three groups (23G needles alone or either needle with an anaesthetic), so the investigators recommended that the use of a 23G needle even without local anesthetic as first choice for breast FNA.² Previous work has shown that accuracy of diagnosis and yield of the material are similar whether a 21G or 23G needle is used.³

In our practice at Saint Vincents Comprehensive Breast Center, a surgeon and a cytopathologist are in attendance, with the cytopathologist usually performing the procedure. On average, 30–40 FNAs are done each week with a 25G needle and 10 mL syringe attached to a syringe holder (Precision Dynamics) and without an anaesthetic. The number of passes varies with the lesion that is being biopsied. The average is about two passes whereas Daltrey and Kissin report ten. The difference might be due to the attendance of cytologists to assess adequacy of cellularity while the procedure is being done. Although neither we nor Daltrey and Kissin, recorded the degree of discomfort according to the number of passes, our experience is that patients accept this procedure very well. Bleeding is rare (one patient out of 1500 had a haematoma, treated expectantly) and other complications such as cellulitis and pneumothorax were seen not at all.

Others have also investigated whether local anesthesia should be used for FNA. A study on the aspiration of neck masses showed that there was no difference in the ease of FNA, complication rates, and accuracy whether patients received ethyl chloride spray, lidocaine infiltration, or no

anaesthesia. However, patients' perception of pain and satisfaction rates were better in the ethyl chloride and lidocaine groups than in the no-anaesthesia group.⁴

Another study has shown the preference of patients undergoing breast FNA for the Biojector 2000 needle-free lidocaine injection system (Bioject, Portland, OR). This pneumatically powered needle-free injection system delivers a high-pressure stream of anaesthetic either subcutaneously or intramuscularly. 83% of patients preferred the Biojector 200 to either no anaesthesia, ethyl chloride spray, or lidocaine injection with a needle and syringe. The limitation of the Biojector 2000 system is that it is not suitable for breast masses located close to the chest wall because inadvertent infiltration of the costal periosteum is painful and because of fear of introduction of lidocaine into the pleural space. The Biojector 2000 is also not recommended for neoplastic breast lesions in case the positive lidocaine stream “pushes” the neoplastic cells into the vascular system.⁵

On the basis of our experience, a small needle (25G) should be the choice for FNA of breast lesions, even without local anaesthesia. If there is a cytopathologist available on site for immediate Also, the availability of an on-site cytopathologist for immediate assessment of how adequate the aspiration has been should reduce the number of aspirations and thus help lessen discomfort for patients.

Sutini Ngadiman, Christina E Vallejo, Beth Siegel, Deborah Axelrod

St Vincents Comprehensive Breast Center, New York, NY 1001, USA

- 1 Koss LG. The palpable breast nodule: a cost-effective analysis of alternate diagnostic approaches: the role of the needle aspiration biopsy. *Cancer* 1993; **72**: 1499–502.
- 2 Daltrey IR, Kissin MW. Randomized clinical trial of the effect of needle gauge and local anesthetic on the pain of breast fine-needle aspiration cytology. *Br J Surg* 2000; **87**: 777–79.
- 3 Walker SR. A randomized controlled trial comparing a 21 G needle with 23 G needle for fine needle aspiration of breast lumps. *J R Coll Surg Edinb* 1998; **43**: 322–23.
- 4 Cannon CR, Replogle B. Fine needle aspiration biopsy: is anesthesia necessary? *Otolaryngol Head Neck Surg* 1999; **4**: 458–59.
- 5 Florentine BD, Frankel K, Raza A, et al. Local anesthesia for fine-needle aspiration biopsy of palpable breast masses: the effectiveness of a Jet injection System. *Diag Cytopathol* 1997; **6**: 472–76.

Being equipped for clinical PET

Positron emission tomography (PET) has made the transition from research into clinical practice, especially into oncology. This rapid expansion is primarily attributable to the production and availability of the radiotracer ¹⁸F-fluorodeoxyglucose (FDG). This analogue of glucose mimics the cellular uptake and initial metabolism of glucose, enabling those cells using an excess of glucose to be visualised. An increase in glucose metabolism is most commonly seen with malignant tissue¹ (although it can also occur in some benign disorders²). The techniques used to image the FDG distribution in vivo can locate functionally active tissue much more accurately than can conventional nuclear-medicine imaging techniques. From the high-quality images acquired with state-of-the-art dedicated PET scanners, semiquantitative and quantitative measures of glucose metabolism can be obtained. Because of the radioactive decay of the tracer, PET scanning is generally done at a site within 2 h of an FDG-production facility.

PET is forcing a reassessment of conventional staging with computer tomography (CT) and magnetic resonance imaging (MRI) in certain cancer groups. The greatest impact on patient management has been with lung tumours, colorectal tumours, and lymphomas.

FDG PET is cost-effective in the assessment of