

EDITORIAL

Allergy to furred animals

In the United Kingdom, pet ownership is very common and $\approx 1/3$ of homes have a cat and $1/4$ a dog [1]. Whilst the popularity of the dog and cat is generally reversed in other countries, these figures are similar throughout the western world and it is estimated that between 60 and 70% of households have pets (including birds) [2,3]. As cat and dog allergen can be detected in public places and homes without current pet occupation [4], the majority of the population may be at risk of sensitization to domestic animals. Exposure to animals also occurs at work. Laboratory animals and farm animals such as cows, pigs and horses are all well recognized causes of occupational allergy. Recent reports have also implicated the urine of mink [5] and the dander of deer [6] as causes of occupational asthma. In this issue Savolainen *et al.* have investigated the IgE responses of seven individuals occupationally sensitized to mink and other animals farmed for their fur [7]. By using the techniques of immunoblotting and RAST inhibition, they have demonstrated that, in common with other animal species, albumin and other low molecular weight allergens are present in the dander and urine and contribute to cross-reactivity between these species.

There has been an enormous amount of work reported which describes the allergens involved in allergy to different mammalian species. The pelt (or dander), saliva and urine are the most common sources of the major allergens and the chief observations up until the early 1990s have been comprehensively reviewed by Schou [8]. Since then, further advances have been made in understanding the biochemistry of the allergens which have potentially important implications for the understanding and treatment of animal allergy.

The biochemistry of the major cat allergen, the heterodimer Fel d 1, is particularly well understood and the recent production of recombinant Fel d 1 has facilitated the determination of the importance of conformational epitopes in IgE binding to this allergen [9–11]. Evidence that a 'Fel d 1-like' molecule exists in other cat species suggested that this molecule may have biological significance [12] and in 1994, Vailes demonstrated that one epitope on chain 1 of the 'Fel d 1-like' molecules is conserved between these *Felidae* species [13]. Chain 1 of the Fel d 1 molecule has now been identified as a member of the lipocalin family of proteins [14]. These globular proteins are of low molecular weight (typically 17–20 kDa) which bind hydrophobic ligands such as steroids. They are present in secretions (such as those found on skin and in urine and saliva) and the resulting ligand complexes may be involved in the protection of epithelia or have pheromonal properties. Chain 1 of Fel d 1

has some sequence homology with rabbit uteroglobulin (28%, [14]) and a mouse salivary protein (50%, [15]). The tertiary structure of these molecules however, may be diverse; whilst chain 1 of Fel d 1 is in antiparallel topography with chain 2 to form a heterodimer, the lipocalins present in the urine of rats and mice (Rat n 1 and Mus m 1) are comprised of one chain only [16,17]. The latest allergen to be identified as a member of the lipocalin family is the major 20 kDa cow allergen Bos d 2 [18]. It too is comprised of one chain and the amino acid sequence homology with Rat n 1 and Mus m 1 is 28 and 25%, respectively.

Examination of the factors affecting the excretion of Fel d 1, Rat n 1 and Mus m 1 suggest that the production of these lipocalins may be under complex hormonal control. This has been clearly demonstrated for the urinary secretion of Rat n 1 and Mus m 1 where the influence of testosterone make adult male animals an abundant source of the major urinary allergens [19,20]. Zielonka *et al.* have also shown that testosterone increases the skin secretion of Fel d 1 [21]. These hormonal effects may be tissue-specific; the salivary production of allergenic rat and mouse proteins for example, is less influenced by testosterone levels [22–24]. This differential regulation may explain in part, why female animals are still capable of secreting significant levels of allergen [20,25]. The existence of multiple copies of the genes coding for rodent proteins may help to explain the existence of allergen isoforms [26].

It is clearly an exciting development that major allergens from at least four allergenically important animal species have been identified as belonging to the same super-family of proteins. Whilst there is still a lot to be understood, as the urine and pelts of so many species appear to contain low molecular weight allergens, including those identified by Savolainen *et al.* in fur animals [7] and the currently unsequenced Can f 1, it is of interest to see if further members of this family can be identified. Should the conserved regions of this family of proteins code for IgE binding epitope(s), this would have profound implications for those with pre-existing animal allergy when domestic or occupational exposure to new animal species is considered.

The other biologically important group of molecules found in mammals are the serum proteins. Albumin has been identified as a minor allergen in most species [8] and is generally accepted as an important cause of crossreactivity between a variety of species, such as cat, dog and horse [27]. The observations of Savolainen *et al.* show that albumin contributes significantly to the crossreactivity between both urine and dander extracts from species as diverse as mink, silver fox, blue fox, raccoon dog and fitchew [7]. Their

paper provides another example of how renal disease may influence the allergenic composition of mammalian urine. Serum proteins may be present in urine or dander extracts although the relative quantity is dependent upon the extent of renal disease and the method of preparation. Other mammalian serum proteins which have been shown to be allergenic are transferrin and immunoglobulins [4,28,29].

Although allergenic crossreactivity may contribute to the development of hypersensitivity to multiple animal species, the basic atopic predisposition of the subject is likely to be of greater importance. Atopy is consistently identified as a risk factor for the development of allergy to laboratory animals [30,31] and the role of existing cat and dog allergy has recently been examined in more detail. Hollander *et al.* found that a history of symptoms associated with pets, a positive skin-prick test response to cat or dog, and an elevated total IgE level were risk factors for the presence of allergy to rats or mice in a cross-sectional study. When two or more of these factors were present, an individual was 25 times more likely to have rat allergy (defined as symptoms and specific IgE) and 40 times more likely to report mouse allergy [31]. Preliminary evidence has also been reported, again from a cross-sectional study of laboratory animal workers, that 73% of the 15 subjects with rabbit specific IgE also had co-existing cat hypersensitivity [32]. It is significant that 80% of the subjects used in the present study of fur animal allergens were also atopic. The recent case reports of allergy to more 'exotic' species including mink urine [5], deer [6,32] and raccoon [33] are also often described in those who are atopic.

In conclusion, the paper in this issue by Savolainen *et al.* illustrates the complexities of the factors determining animal allergy. As hypersensitivity to multiple species of animals is not uncommon, future research is needed to determine whether the increased risk is due to the individuals inherent ability to produce IgE (atopy), due to a specific predisposition to mount an IgE response to these types of proteins, or whether common dominant epitope(s) exist between mammalian species. With a greater understanding of the biochemistry of the major allergens, how the existence of allergy to domestic animals may be associated with an increased risk of developing allergies to other animal species may be clarified.

References

- 1 Cullinan P. Personal communication. Based upon figures for 667 homes surveyed in 1994–5 in Ashford, Kent.
- 2 Brunekreef B, Groot B, Hoek G. Pets, allergy and respiratory symptoms in children. *Int J Epidemiol* 1992; 21:338–42.
- 3 Beck AM, Meyers NM. The pet owner experience. *NER Allergy Proc.* 1987; 8:185–8.
- 4 Munir AKM. Environmental factors influencing the levels of indoor allergens. *Pediatr Allergy Immunol* 1995; 6 (suppl 7):13–21.
- 5 Gómez IJ, Antón E, Picáns I, Jerez J, Obispo T. Occupational asthma caused by mink urine. *Allergy* 1996; 51:364–5.
- 6 Nahm D-H, Park J-W, Hong C-S. Occupational asthma due to deer dander. *Annals Allergy* 1996; 76:423–6.
- 7 Savolainen J, Uitti J, Halmepuro L, Nordman H. IgE response to fur animal allergens and domestic animal allergens in fur farmers and fur garment workers. *Clin Exp Allergy* 1997; 27:501–9.
- 8 Schou C. Defining allergens of mammalian origin. *Clin Exp Allergy* 1993; 23:7–14.
- 9 Bond JF, Brauer AW, Segal DB, Nault AK, Rogers BL, Kuo M-C. Native and recombinant Fel d 1 as probes into the relationship of allergen structure to human IgE reactivity. *Mol Immunol* 1993; 16:1529–41.
- 10 Keating KM, Segal DB, Craig SJ et al. Enhanced immunoreactivity and preferential heterodimer formation of reassociated Fel d 1 recombinant chains. *Mol Immunol* 1995; 32:287–93.
- 11 Slunt JB, Rogers BL, Chapman MD. IgE antibodies to recombinant forms of Fel d 1: Dichotomy between fluid-phase and solid-phase binding studies. *J Allergy Clin Immunol* 1995; 95:1221–8.
- 12 de Groot H, van Swieten P, Aalberse RC. Evidence for a Fel d 1 like molecule in the 'big cats' (Felidae species). *J Allergy Clin Immunol* 1990; 86:107–16.
- 13 Vailes LD, Li Y, Bao Y, de Groot H, Aalberse RC, Chapman MD. Fine specificity of B-cell epitopes on *Felis domesticus* allergen 1 (Fel d 1): Effect of reduction and alkylation or deglycosylation on Fel d 1 structure and antibody binding. *J Allergy Clin Immunol* 1994; 93:22–33.
- 14 Morgenstern JP, Griffith IJ, Brauer AW et al. Amino acid sequence of Fel d 1, the major allergen of the domestic cat: Protein sequence analysis and cDNA cloning. *Proc Natl Acad Sci* 1991; 88:9690–4.
- 15 Karn RC. The mouse salivary androgen-binding protein (ABP) alpha subunit closely resembles chain 1 of the cat allergen Fel d 1. *Biochem Genetics* 1994; 32:271–7.
- 16 Adams P, Sawyer L. Structure of rodent urinary proteins. *Biochem Soc Trans* 1990; 18:936–7.
- 17 Bayard C, Holmquist L, Vesterberg O. Purification and identification of allergenic α_{2u} -globulin species of rat urine. *Biochim Biophys Acta* 1996; 1290:129–34.
- 18 Mäntyjärvi R, Parkkinen S, Rytkönen M et al. Complementary DNA cloning of the predominant allergen of bovine dander: A new member of the lipocalin family. *J Allergy Clin Immunol* 1996; 97:1297–1303.
- 19 Longbottom JL. Purification and characterization of allergens from the urines of mice and rats. In: A Oehling et al. eds. *Advances in Allergology and Immunology*. Pergamon Press Oxford. 1980; 483–90.
- 20 Gordon S, Tee RD, Newman Taylor AJ. Analysis of rat urine proteins and allergens by sodium dodecyl sulphate-polyacrylamide gel electrophoresis and immunoblotting. *J Allergy Clin Immunol* 1993; 92:298–305.
- 21 Zielonka TM, Charpin D, Berbis P, Luciani P, Casanova D,

- Verloet D. Effects of castration and testosterone on Fel d 1 production by sebaceous glands of male cats: I-immunologic assessment. *Clin Exp Allergy* 1994; 24:1169–73.
- 22 Haars LJ, Pitot HC. Hormonal and developmental regulation of glycosylated α_{2u} -globulin synthesis. *Archs Biochem Biophys* 1980; 201:556–63.
- 23 Laperche Y, Lynch KR, Dolan KP, Fiegelson P. Tissue-specific control of α_{2u} -globulin gene expression: constitutive synthesis in the submaxillary gland. *Cell* 1983; 32:453–60.
- 24 Shaw PH, Held WA, Hastie ND. The gene family for major urinary proteins: Expression in several secretory tissues of the mouse. *Cell* 1983; 32:755–61.
- 25 Wentz PE, Swanson MC, Reed CE. Variability of cat-allergen shedding. *J Allergy Clin Immunol* 1990; 85:94–8.
- 26 Longbottom JL. Crossed radio-immunoelectric focusing as a method of identifying isoallergens: Identification of isoallergens in rat urine extracts. *J Immunol Meth* 1984; 68:297–304.
- 27 Spitzauer S, Pandjaitan B, Söregi G et al. IgE cross-reactivities against albumins in patients allergic to animals. *J Allergy Clin Immunol* 1995; 96:951–9.
- 28 Price JA, Longbottom JL. Allergy to rabbits I Specificity and non-specificity of RAST and crossed-radioimmuno-electrophoresis due to the presence of light chains in rabbit allergenic extracts. *Allergy* 1986; 41:603–12.
- 29 Gordon S, Tee RD, Newman Taylor AJ. Analysis of rat serum allergens. *J Allergy Clin Immunol* 1997; in press.
- 30 Desjardins A, Benôit C, Ghezzi H et al. Exposure to domestic animals and risk of immunologic sensitisation in subjects with asthma. *J Allergy Clin Immunol* 1993; 91:979–86.
- 31 Hollander A, Doekes G, Heederik D. Cat and dog allergy and total IgE as risk factors of laboratory animal allergy. *J Allergy Clin Immunol* 1996; 98:545–54.
- 32 Gordon S, Jones MG, Cook A, Tee RD, Newman Taylor AJ. Hypersensitivity to cat and rabbit; effect of atopy and exposure on specific IgE antibodies. Abstract BSACI 1996. *Clin Exp Allergy*, in press.
- 33 Stöger P, Schmid-Grendelmeier P, Johansson SGO, Wüthrich B. Raccoon epithelium – a new allergen source. *Allergy* 1994; 49:673–4.
- 34 Huwyer T, Wüthrich B. A case of fallow deer allergy. Cross-reactivity between fallow deer and horse allergy. *Allergy* 1992; 47:574–5.

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