second event in the somatic cell, homozygosity or hemizygosity of a recessive mutation is obtained, leading to the formation of a tumor. As shown by the group of Cavenee (9,10) and others, besides mutation or chromosome deletion, this second step may also involve abnormal chromosomal segregation events during mitosis. As both Wilm's tumor and retinoblastoma are embryonic tumors it is tempting to speculate that the genes involved play a part in the development of the target tissues during embryogenesis.

References:

- 1 De Klein A et al 1982 Nature 300: 765
- 2 De Klein A, Hagemeyer A 1984 Cancer Surveys 3: 515
3. Gale RP, Canaani E 1984 Proc Natl Acad Sci USA 81: 5648
4. Stam K et al 1985 New Engl J of Med 313: 1429
5. Canaani E et al 1985 Nature 315: 550
6. Grosveld G et al 1986 Mol Cell Biol 6: 607
7. Orkin SH 1984 Cancer Surveys 3: 465
8. Sparkes RS 1984 Cancer Surveys 3: 479
9. Cavenee WK et al 1985 Science 228: 501
10. Koufos A et al 1984 Nature 309: 170

MOLECULAR GENETICS OF THE IgE RESPONSE IN MAN
R.K.B. Schuurman, R.W. Hendriks and J.D.L. Schot
Dept. Immunohaematology & Blood Bank, University
Medical Center Leiden, the Netherlands

At least two regulators of the IgE response have been distinguished. One is involved in the production of allergen specific IgE antibodies. This regulator segregates in families in linkage to determinants encoded by the major histocompatibility gene complex (HLA). Thus this regulator has been proposed to be encoded by HLA genes. Moreover increased IgE responses have been found to segregate in families. The patterns of inheritance suggest multifactorial expression in spite of more or less clear autosomal dominant or recessive segregation patterns. The hyper IgE syndrome, an immunodeficiency disease accompanied by recurrent infections of the skin in particular, is not associated with allergy. In this syndrome there is evidence that the defect resides in T lymphocytes, involved in the regulation of the IgE level. We have started investigations on regulatory sequences within the immunoglobulin heavy chain complex on the long arm of chromosome 14. As a first step we try to characterize the V (= variable) genes involved in the IgE response. For this purpose we have performed experiments to establish human IgE producing B cell lines, the results of which to be discussed.

IMPROVED TOLERANCE TO INHALANT ALLERGENS DURING AN INTENSIVE COURSE OF RUSH-IMMUNOTHERAPY

K. Ende, R. Urbanek, G. Klein
University Children's Hospital, Freiburg, FRG

Significant reduction in asthmatic symptoms and use of medication was reached by a short term course of allergen immunotherapy. In vivo and in vitro parameters were investigated for their predictive value. Six patients with allergic asthma, 5 sensitized to housedust mite and one with allergy to grasspollen underwent a rush immunotherapy of 8 to 14 days under clinical observation until a maintenance dose was tolerated.

Titrated skin test, conjunctival provocation test (CPT), bronchial provocation test (BPT) and allergen-

specific IgE and IgG antibodies were examined before and 8 weeks after the dose build-up period. A significant improvement was demonstrated clinically by a decrease in reported symptoms and use of medication as well as by increasing the threshold of tolerance 10 to 100 fold in skin test, CPT and BPT. Specific IgG antibodies increased in all patients. An intensive short term course of allergen-immunotherapy was shown to be effective in reducing allergic symptoms in patients sensitized to inhalant allergens already within 2 months. Titrated skintest, BPT and specific IgG levels were of predictive value.

Genetics in Allergy: A Model for Studying the Genetics of Human Immune Responsiveness

DAVID G. MARSH

Division of Clinical Immunology, Department of
Medicine, Johns Hopkins University School of
Medicine, Good Samaritan Hospital, Baltimore, MD
21239, USA

Allergy serves a particularly good model for understanding the genetics of human immune response and its relationship to disease, since one can establish a clear causal relationship between specific IgE antibody responses and the expression of specific allergies (1). There is evidence for at least two types of genetic control of IgE responses in man, namely, HLA-linked control of specific responses and non-HLA-linked control of the overall production of IgE, where high IgE is inherited as a recessive trait.

The primary focus will be on our recent studies of specific IgE and IgG antibody responses to the low mol. wt. *Ambrosia* (ragweed) allergens, *Amb V* (Ra5; refs. 2-5) and *Amb VI* (Ra6; ref. 6). Three species of *Amb V* (mol. wts. 4400-5000 D) have been isolated, *Amb a V* (from *A. artemisiifolia*, short ragweed), *Amb t V* (from *A. trifida*, giant ragweed) and *Amb p V* (from *A. psilostachya*, western ragweed), as well as another allergen species, *Amb a VI* (mol. wt. 11,500 D). Immune responsiveness toward all of the *Amb V* homologues was found to be significantly associated with the Dw2 subspecificity of HLA-DR2 (4,5,7,8), even though these molecules show little, or no, antigenic crossreactivity (6). The association with the *Amb t V* molecule is less striking than with *Amb a V* and *Amb p V*, where 95% or more responder subjects possess DR2/Dw2. In the case of *Amb a VI*, 80% of responders possess HLA-DR5 (9).

We have used a refined version of conventional allergen immunotherapy in a prospective genetic study of immune response to ragweed pollen allergens (10) which, to our knowledge, is the first such study. Twelve matched pairs of DR2+ and DR2- patients were immunized sequentially with giant, western and short ragweed extracts containing known amounts of *Amb t V*, *Amb p V* and *Amb a V*, respectively. Serum was taken before and 12 times after increasing dosages (0.033-11 µg) of each *Amb V*. Eight of 12 DR2+ subjects made IgGAb responses to *Amb t V* (G.M. = 38 ng/ml), whereas 4/12 DR2- subjects made low levels of IgGAb (G.M. = 3.7 ng/ml); $p < 0.05$ by t test. Three of the four DR2+ nonresponders have atypical MLR responses toward Dw2 typing cells. Preliminary data show that 8 DR2+ subjects have positive immune responses to *Amb p V* and to *Amb a V*, with the exception of one DR2+/Dw2- subject who failed to respond to *Amb p V*. However, all 8 DR2- subjects who have completed the *Amb p V* regimen, and all 5

DR2- subjects who have completed the *Amb a V* regimen, show no IgGAb. These data confirm the DR2/Dw2 association with immune response to *Amb t V* and suggest that concordant response toward all three *Amb V* species is associated with the presence on the person's lymphocytes of the immune-associated (Ia) molecule, DR2/Dw2. The data also provide evidence that a similar "Ia determinant" on all *Amb V* molecules is recognized by DR2/Dw2 (or by an Ia specificity encoded by a gene in linkage disequilibrium with DR2/Dw2 in Caucasoid subjects).

Information concerning the structure of the *Amb V* Ia determinant can be inferred from the known amino acid sequences of *Amb a V*(3) and *Amb t V*(4), which show high degrees of homology at positions 17-26 and 31-35 (11). These two regions are probably linked by a disulphide bond and are also relatively hydrophobic. The latter property may stabilize the presence of the Ia determinant in the lipid bilayer of an appropriate antigen-presenting cell (APC), optimize a DR2-restricted antigen presentation to T cells and lead to an immune response. Further information regarding the structure of this putative Ia determinant comes from a comparison of the structures of the *Amb V* molecules with that of wheat germ agglutinin domains, which exhibit significant homology, especially in regard to the positions of their half-cystine residues (11,12). In regard to the Ia molecular structure, we are currently looking for differences in restriction (RFLP) maps of

the *DRβ*, *DQβ* and *DQα* genes in DR2+ persons who have different immune response phenotypes to the *Amb V* allergens. We believe that these studies will lead to important new information concerning structure-function relationships determining human immune responsiveness.

References

1. Marsh, DG et al, N. Engl. J. Med. **305**:1551, 1981.
2. Lapkoff, CB and Goodfriend, L, Int. Arch. Allergy, **46**: 215, 1974.
3. Mole, LE et al, Biochem. **14**: 1216, 1975.
4. Goodfriend, L et al, Mol. Immunol. **22**:899, 1985.
5. Roebber, M et al, J. Immunol. **134**:3062, 1985.
6. Roebber, M et al, J. Immunol. **131**:706, 1983.
7. Marsh, DG et al, J. Exp. Med. **155**:1439, 1982.
8. Marsh, DG et al, J. Exp. Med. **155**:1452, 1982.
9. Marsh, DG et al, Fed. Proc. **45**:490, 1986.
10. Marsh, DG et al Proc. Int. Congress Immunol., 1986 (Abs.#5.11.16).
11. Marsh, DG Proc. Intern Allergol Congress, Washington, D.C., 1985. (CE Reed, ed.) C.V. Mosby Co., St. Louis, Mo. In press.
12. Drenth, J et al, J. Biol. Chem. **255**: 2652, 1980.