

children have continued to grow satisfactorily their anatomical bony abnormalities if present, (as in MPS I, II, IV and VI) have not improved after grafting. Thus children with Morquio Disease (MPS IV) (9) and Maroteaux-Lamy Disease (MPS VI) (10) have a disappointing result following BMT, although at first one might have thought they would have been ideal for this treatment, as they have no neurological involvement. There are case reports in the literature of about another thirty inborn errors of metabolism that have been successfully corrected by bone marrow transplantation. (11)

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DNA ANALYSIS AND THE DIAGNOSIS OF INHERITED DISEASE
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The availability of human DNA sequences in recombinants has transformed human genetics. There are now approximately five hundred coding gene sequences, and innumerable localised anonymous probes, cloned and available pure and in unlimited amount. These can be used by clinical molecular pathologists to study genes in a person-specific way, since any cloned gene sequence is unique to the person from whom it is isolated. Therefore, all of the heritable parameters of individuality, whether representing pathological or normal variation, can be studied by comparing gene sequences.

Many of the cloned human coding genes which have been isolated and characterised to date are also involved in single gene pathology. These include the sequences known to be mutated so as to cause known and characterised Mendelian disorders, such as thalassaemia, PKU or haemophilia. In such cases, the underlying molecular nature of the defect can be determined, and the probe can be used for population-based carrier testing and for unequivocal prenatal diagnosis. Other common single gene defects of unknown biochemistry, such as cystic fibrosis and Duchenne muscular dystrophy, have been linked either to known DNA coding sequences, or to anonymous DNA probes which are chromosomally localised. In these cases, carrier detection and prenatal (or presymptomatic) diagnosis is only available to informative families with living affected members.

A complete map of the human genome will soon be

available, which will simplify the task of determining which gene is mutated and the reason why each causes a characteristic pathology. This is particularly true for those diseases which are locus-heterogeneous, or where more than one gene is involved jointly. Conditions such as coronary artery disease, diabetes and hypertension will be obvious candidates for mapping studies, if accurately diagnosed families of sufficient size are available. For the application of these data, however, it will also be necessary to develop new and inexpensive diagnostic methods for rapid gene analysis using small human tissue samples if these developments are to be applied in community-wide clinical practice.

ONCOGENES AND ANTI-ONCOGENES

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At least two classes of genes have been identified, which are important in the pathogenesis of cancer. The first class was originally discovered by the work on acutely transforming RNA tumor viruses and consists of the oncogenes. Activation of these genes by mutation, chromosome translocation or by other means, provides an essential step in the multistage process of malignant transformation. The second class which includes the so-called anti-oncogenes, has been identified in studies of hereditary cancers, in particular Wilms' tumor and retinoblastoma. Whereas oncogenes behave dominantly (one activated copy is sufficient for producing cancer), the anti-oncogenes show a recessive mode of cancer initiation both alleles have to be inactivated.

An example of the first class is the abelson oncogene (c-abl) which seems to play an essential role in chronic myeloid leukemia (CML). CML is characterized by the presence of the Philadelphia (Ph¹) chromosome in the leukemic cells of 96% of all CML patients. The Ph¹ chromosome (22q-) is the result of a reciprocal translocation between chromosome 22 and chromosome 9, t(9q34,22q11). Previously we described the localization of the human c-abl oncogene on chromosome 9 and demonstrated its translocation to the Ph¹ chromosome in CML patients (1). The cloning and analysis of breakpoint fragments revealed that the breakpoints on chromosome 22 all cluster in a very limited area, the breakpoint cluster region, bcr (2). Breakpoints on chromosome 9, however, are scattered over a large area. The detection of a chimeric mRNA (5' bcr and 3' abl sequences) in the leukemic cells of CML patients (3,4) and the cloning of chimeric cDNAs from a CML derived cell line K562 (5,6) strongly indicate that bcr and c-abl coding sequences are linked by RNA splicing, independent from the distance between the two genes on the Ph¹ chromosome. These findings suggest an important role for the altered c-abl product in the generation and/or maintenance of CML.

Strong evidence for the existence of the second class of genes the so-called anti-oncogenes comes from studies of Wilms' tumor and retinoblastoma. Both tumors seem to be the result of loss or inactivation of the two alleles of a wild type gene located on 11p13 in the case of Wilms' tumor (7) and 13q14 in retinoblastoma (8). In the hereditary form of these tumors the first inactivation event is present in the germ line as a mutation or chromosome deletion, whereas in the non-hereditary cases (mostly unilaterally affected) the first inactivation event occurs in the somatic cell. As a result of a

second event in the somatic cell, homozygosity or hemizyosity 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.

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MOLECULAR GENETICS OF THE IgE RESPONSE IN MAN

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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

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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

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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