8. Schleimer RP, MacGlashan DW, Peters SP, Naclerio R, Proud D, Adkinson NF, Lichtenstein LM 1984 *J Allergy Clin Immunol* 74: 473-481
9. Lewis RA, Austen KF 1984 *J Clin Invest* 73: 889-897
10. Mencia-Huerta JM, Benhamou M 1986 In Kay AB (ed) *Asthma, clinical pharmacology and therapeutic progress*. Blackwell, Oxford pp 237-250
11. Rodger IW 1986 In Kay AB (ed) *Asthma, clinical and pharmacology and therapeutic progress*. Blackwell, Oxford, pp 114-127
12. Szentivanyi A 1968 *J Allergy* 42: 203-232
13. Vries K de, Gökemeyer JDM, Koëter GH, Monchy JGR de, Bork LE van, Kauffman HF, Meurs H 1982 In Morley J (ed) *Bronchial hyperreactivity*. Academic Press, London pp 107-121
14. Koëter GH, Meurs H, Kauffman HF, Vries K de 1982 *Eur J Respir Dis* 63 (suppl 121): 72-78
15. Meurs H, Koëter GH, Vries K de, Kauffman HF 1982 *J Allergy Clin Immunol* 70: 272-280
16. Meurs H, Kauffman HF, Timmermans A, Monchy JGR de, Koëter GH, Vries K de 1986 *Int Archs Allergy Appl. Immunol.*, in press.
17. Meurs H, Kauffman HF, Timmermans A, Amsterdam FThM van, Koëter GH, Vries K de 1986 *Biochem Pharmacol*, in press.

PRODUCTION OF, AND INTERACTIONS BETWEEN, IMMUNOGLOBULINS

R.C. Aalberse, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service and Laboratory for Experimental and Clinical Immunology, University of Amsterdam, Amsterdam

Immunoglobulins are the product of plasma cells. Plasma cells are derived from lymphocytes by a complex differentiation pathway that involves both antigen-independent and antigen-dependent stages. All the early differentiation steps are antigen-independent; this is understandable because the cells do not yet have the capability to recognize the antigen until a number of differentiation steps have taken place. Some of these differentiation steps require DNA rearrangements, notably the joining of a V- (= variable region) gene to a D- (= diversity region) gene and subsequently the joining of the VD gene to a J (= joining region) gene and thus to the C- (= constant region) gene. This DNA rearrangement generates a gene for a heavy chain of an IgM molecule. After another set of DNA rearrangements on a different chromosome an immunoglobulin light chain gene is generated. After this event the cell starts to synthesize surface-bound immunoglobulin, predominantly of the IgM type. This surface-bound immunoglobulin enables the cell to recognize a fitting antigen, so from now on the cell is immuno-competent. Interaction with such an antigen under suitable conditions results in cell proliferation and differentiation. During the cell divisions a further DNA rearrangement may take place: the isotype switch, or class-switch. In this DNA rearrangement the VDJ-gene on the heavy-chain chromosome is linked to another C-region gene, e.g. the IgG₁ or the IgE-C region gene.

The differentiation leads to plasma cells committed to the production of one single type of immunoglobulin and to the production of secondary (memory) B cells which may respond upon a subsequent antigenic stimulation.

Factors governing the isotype regulation are largely unknown. Some regulation is evident in the isotype switch event; further isotype specific regulation occurs at the level of the isotype-committed B-cell.

If we take the regulation of the IgE production as an example of isotype-specific regulation, it is clear that certain parasitic infections stimulate the production of IgE B-cells, presumably by stimulating isotype-switching to IgE; a further stimulus for the enhanced production of IgE are IgE-binding factors, produced by certain activated T-cells, which acts by stimulating IgE-bearing B-cells to differentiate into IgE-producing plasma cells.

In the response to environmental non-microbial glycoprotein antigens, three immunoglobulin isotypes are prominent: IgG₁, IgG₄ and IgE. IgE is prominent only in allergic individuals; IgG₄ is prominent only after prolonged antigen exposure. The role of antibodies of the IgG₄ isotype is still controversial; presumably IgG₄ antibodies protect against the potential harmful effects of IgE- and IgG₁ antibodies by preventing mast cell degranulation and complement activation.

GENETIC DISEASE: PATIENTS; MOLECULES AND PREVENTION

H. Galjaard

Erasmus University, Head Dept. Clinical Genetics, University Hospital, Rotterdam

Congenital disorders become the major cause of infant mortality and morbidity in an increasing number of countries. The possibilities of primary prevention are very limited and the main emphasis has therefore been on newborn screening and early treatment, and on the early identification of couples at risk, genetic counseling and prenatal diagnosis followed by selective abortion. Enzyme replacement therapy has been attempted in patients with various types of lysosomal storage diseases and "gene therapy" is foreseen in patients with genetic disorders of the haemopoietic system. It seems, however, that in this area more basic research is needed about the exact nature of the molecular defect involved, the routing of gene products within the body, the efficiency of their uptake by various types of mutant cells and the corrective effect on cell metabolism of exogenous (enzyme) protein. Some of these aspects will be illustrated by experimental work on the genetic, molecular and cellular background of a number of lysosomal storage diseases.

At present the most effective approach towards prevention of handicaps is the early diagnosis of index patients with a chromosomal aberration, a genetic disease or other types of congenital anomalies followed by genetic counseling of relatives at increased risk. Various follow-up studies indicate that a high proportion of couples who are informed about an increased risk of affected offspring are deterred from a (next) pregnancy. For those who still want to reproduce, there is the option of chorion analysis, amniotic fluid (cell) analysis or ultrasonography in each pregnancy. The scope of prenatal diagnosis will be further widened by the possibilities of demonstrating gene mutations or polymorphisms closely linked to disease using recombinant DNA technology. Also for genetic diseases with a relatively high incidence, carrier screening programmes will enable couples to prevent the birth of a first affected baby in their family. In the future, the technology will also allow the prediction of diseases or of increased susceptibility to environmental factors. Such developments require timely attention to psychological, social and educational aspects. Such factors also play a major role in the participation of presently available technology as will be illustrated by