Immunology

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Sixty years of progress

Nobel prize awards in medical immunology over the past 60 years reflect the immense recent progress made. Burnet and Medawar were recognised in 1960 for their work on “acquired immunological tolerance”. Skin grafting in mice of different inbred strains showed that graft rejection is an immunity phenomenon, including key features such as specificity, memory, and amplification (second set phenomenon). Medawar subsequently demonstrated that mice accepted not only self but also foreign tissue whenever the latter was first artificially introduced during fetal life, giving insights into mechanisms of immunological tolerance.

Edelmann and Porter (1972 prize) defined “the chemical structure of antibodies”. In the 1950s they showed that immunoglobulins (antibodies) were composed of two “light” and two “heavy” protein subunits. Enzyme cleavage studies helped relate structure to function. Antigen binding resided in the “Fab” but not the “Fc” fragments. They correctly predicted that “antibodies” were Y shaped bivalent molecules.

Benacerraf, Dausset, and Snell (1980) in differing ways worked on “genetically determined structures on the cell surface that regulate immunological reactions”. Snell used inbred mouse strains to demonstrate that “histocompatibility genes” or H genes regulated transplantation of normal tissues. Dausset noticed that multiply transfused patients developed antibodies that killed donor but not host leucocytes. Realising that this was not autoimmune, he concluded that there must be human leucocyte antigens analogous to H gene products in mice. Benacerraf found that the magnitude of the immune response against certain antigens (immunogens) varied greatly between different animal strains. This was genetically based, and interestingly, the immune responsiveness (Ir) mapped to the same region as H genes.

In 1984, Jerne, Kohler, and Milstein shared the prize for “theories concerning the specificity, development, and control of the immune system and the discovery of the principle for production of monoclonal antibodies (in vitro)”.

Jerne’s “network theory” proposed that each antibody molecule carries a unique signature (idiotypic) itself capable of acting as an immunogen. A network of idiotype/anti-idiotypic interactions might “internally” mirror all possible antigens in the outside world. The theory correctly predicted that antibodies carrying the appropriate mirror image could actually replace foreign antigen completely when inducing immunity.

“I predict that we will see an expansion of immunotherapy”

Kohler and Milstein used novel in vitro techniques to combine the immortality of non-secretory myeloma cells with immune B cells to produce “hybridomas”—immortalised biological factories capable of producing monoclonal antibodies. By prior immunisation of mice, and subsequent selection of splenic B cells producing desired antibody specificity, “designer” antibodies had arrived.

By 1987, Tonegawa had defined “the genetic principle for the generation of antibody diversity”. In the 1970s he solved the paradox of how our limited genetic material is capable of generating almost limitless diversity. On the chromosome where the presumed “light” chain gene was expected to be located, he found not one single gene, but rather, a series of V (variable) and J (joining) genes. After removal of the intervening segment of DNA, any random combination of these genes allows the generation of many alternative light chains. Subsequent studies showed that equivalent V, J, and D (diversity) genes on the heavy chain chromosome also randomly reassemble themselves. The combined effect of these gene rearrangements accounts for our ability to manufacture literally millions of different antibody specificities.

Murray and Thomas (1990 prize) were rewarded for “discoveries concerning organ and cell transplantation in the treatment of human disease”. Murray carried out the first successful human kidney transplant in the 1950s. He used police fingerprint techniques to make sure that donor and recipient were true

identical twins. Murray later used total body irradiation to prevent allograft rejection. He and others also showed that azathioprin was an effective immunosuppressant capable of delaying or preventing graft rejection.

Thomas pioneered the use of bone marrow transplantation in the treatment of leukaemia. Tumour cells were eradicated by bone marrow ablative total body irradiation. Normal donor bone marrow could then be infused into a peripheral vein, allowing seeding to the host bone marrow. Methotrexate was used successfully to combat graft versus host disease.

Zinkernagel and Doherty (1996 prize) looked at “the specificity of cell mediated immune defence”. Killer T cells from one mouse strain only recognised and killed virus infected target cells from different mouse strains when both mouse strains shared the same H-2 or major histocompatibility genes. Hence, major histocompatibility genes are not primarily designed to impede transplantation; rather, they are crucial antigen (peptide) presentation structures with a key role in determining T cell immune responses.

Looking to the future, I predict that we will see an expansion of immunotherapy. New immunosuppressant drugs have already improved the success rates in solid organ transplantation. Cyclosporin (1970s) was the first “calcineurin” blocking (enzyme found primarily in T cells) agent, and analogues such as Tacrolimus have followed. More recently, “biologics” (humanised monoclonal antibodies such as anti-CD25) have been used in human transplantation and look extremely promising. Similar “magic bullets” such as anti-tumour necrosis factor α are now commonly and successfully used in district general hospitals to treat inflammatory/autoimmune conditions such as rheumatoid arthritis and Crohn’s disease. However, caution is always necessary with newer treatments. Thus, Campath (a humanised monoclonal, lytic, anti-lymphocyte agent), although effective in treating patients with multiple sclerosis, resulted in some patients unexpectedly developing autoimmune Grave’s thyrotoxicosis.² Gene therapy has been used successfully in severe combined immunodeficiency or “bubble” babies with single gene defects such as X linked severe combined immunodeficiency³ (although sadly, a small number of the successfully treated children subsequently developed leukaemias). Vaccination is not “new” but novel uses can be predicted. BCG vaccination can prevent or reverse the tendency towards atopic disease (so called T helper type 2 bias).⁴ In the context of

autoimmunity too, peptide immunotherapy has been used successfully in animal models of human autoimmune disease (for example, multiple sclerosis models) to prevent and even reverse ongoing autoimmune diseases.⁵

Careers in clinical immunology are expanding. Sixty years ago, most medics interested in immunology were primarily university academics. Immunopathologists (forerunners of today's "clinical" immunologists) were first appointed in the UK around 50 years ago. These pioneers attempted to move immunology from the hypothetical/academic to something with direct applicability in terms of patient diagnosis and

treatment. In 2005, there are more than 50 jobbing National Health Service clinical immunologists involved in hands on care of inpatients and outpatients with immunodeficiency, allergy, or autoimmune disease, and in providing laboratory based immunodiagnostics. In addition, the 32 immunology (specialist registrar) training posts in the UK will ensure that the specialty continues to expand. The future looks bright.

J Clin Pathol 2005;**58**:791–792.
doi: 10.1136/jcp.2005.030619

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