Recent Advances

Clinical immunology

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Clinical immunology is a rapidly expanding specialty, and new developments have implications for many doctors since patients with immunological diseases are treated by general practitioners and by clinicians in various specialties. We will therefore consider recent advances in clinical immunology with regard to immunodeficiency, complement, treatment with intravenous immunoglobulin, and infection and vaccines.

Immunodeficiency

Recent developments in the study of genetically determined immunodeficiency have broadened our understanding of the immune system and, in doing so, have extended the possibilities for treatment. The initial description of isolated humoral immunodeficiency, Bruton's agammaglobulinaemia, showed the consequences of insufficient antibody production—repeated attacks of severe infections against which antibodies are the main protection. Cellular immunodeficiency leads to another pattern of infections, and severe combined immunodeficiency—in which both arms of the immune system are affected—implies severe early disease usually leading to death within the first or second year of life. The different types of severe combined immunodeficiency are heterogeneous in their genetic basis (recessive or sex linked) and the basic mechanisms involved, and to some extent in clinical appearance. It is in our knowledge of the basic mechanisms that we have seen the greatest developments.¹

COMMUNICATION BETWEEN CELLS

Development of immune responses requires extensive signalling between cells—such as between the antigen presenting cell and responding T cells that produce interleukins, signal substances essential for inducing the required proliferation and differentiation of lymphocytes. The basic reaction is between the specific T cell antigen receptor and processed antigen in the groove of HLA molecules on the surface of the antigen presenting cell. In addition CD4 or CD8 molecules are involved. Recent studies of the hyper IgM immunodeficiency—immunoglobulin deficiency with increased IgM—have shown the fundamental importance of secondary signals provided by other adhesion molecules. CD40 is a surface antigen on B cells that reacts with a ligand (CD40L) present on activated T cells. The interaction between them is synergised by co-stimulatory signals to drive proliferation and differentiation of B cells. In patients with X linked hyper IgM immunodeficiency, expression of CD40L on activated T cells is incomplete because of several distinct mutations of the gene coding for CD40L.² The signals required for switching immunoglobulin class from IgM to IgG are not generated so that a secondary immune response cannot develop, resulting in immunodeficiency.

Summary points

- The genetic basis for many types of hereditary immunodeficiency has now been found, allowing more precise diagnosis and giving hope for future treatments
- Manipulation of proteins that regulate complement activation has exciting therapeutic implications, such as ameliorating the hyperacute rejection of xenografts
- Deficiencies in complement regulators have been implicated in several types of kidney disease, and soluble complement receptor 1 may be useful in future treatments
- Intravenous immunoglobulin is now used to treat several systemic inflammatory conditions, and its effects include modulating proinflammatory cytokines and complement activation
- Use of new technologies is allowing development of more effective vaccines and avoidance of adverse effects such as found with whole cell pertussis vaccine

Several interleukins are now known, at least from interleukin 1 to interleukin 17. The interactions between them are complex, but some features stand out. There is a hierarchy, with some interleukins being more important than others, and there is much redundancy. Interleukin 2 is a main T cell growth factor in vivo and is essential for in vitro work with T cells, including generation of T cell clones. However, "knock-out" mice in which the gene for interleukin 2 has been disrupted do not present with overt immunodeficiency. Other interleukins can obviously take over.

In one form of X linked severe combined immunodeficiency there is an almost complete absence of T cells. The genetic basis has been precisely identified and is a mutation in the gene coding for the γ_c chain common for the receptors for interleukin 2, interleukin 4, interleukin 7, interleukin 9, and interleukin 15. The mutation leads to formation of premature stop codons, probably resulting in production of truncated γ_c chains and interruption of the signalling pathways for these five cytokines with extensive loss of function. In a clinically less severe form of X linked combined immunodeficiency, the same gene is affected but at a different site with a missense mutation in the region coding for the cytoplasmic portion of the γ_c polypeptide chain—resulting in less severe disruption of the signalling processes.³

The study of genetically determined immunodeficiency has now reached the stage where deficiencies

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have been identified in different groups of proteins—such as membrane proteins, kinases, other cytoplasmic proteins, transcription factors, and transactivators—providing new possibilities for molecular dissection and identification of their individual roles in the differentiation of lymphoid cells and development of immune responses.¹ Furthermore, the identification of the genetic defects allows more precise diagnosis, at the prenatal stage in several cases. This is, of course, a prerequisite for future development of gene therapies for these severe diseases.

Complement

The complement system is composed of more than 30 proteins and is an important part of the humoral host defence system. It has a unique ability to distinguish between self and non-self in that it is activated as soon as it recognises foreign structures—either directly or through recognition of antibodies. Complement can react even with the host's own cells, but this is normally prevented by fluid phase regulators and the expression on cell membranes of inhibitory proteins responsible for homologous restriction. Examples of these proteins are complement receptor 1 (CD35), membrane cofactor protein (CD46), decay accelerating factor (CD55), and protectin (CD59). The last two belong to a group of proteins linked to cell membranes by the glycosylphosphatidylinositol anchor. It has long been known that a defect in the glycosylphosphatidylinositol anchor—with consequent lack of CD55 and CD59 on cell membranes—is associated with paroxysmal nocturnal haemoglobinuria, and animal studies have shown that blocking of complement regulatory proteins on endothelial cells leads to vascular leakage. These observations support the concept that complement is detrimental to the host whenever its regulatory mechanisms are disturbed.

COMPLEMENT'S REGULATORY MECHANISMS AND ORGAN TRANSPLANTS

A major breakthrough in manipulating complement's regulatory mechanisms was the transferring of glycosylphosphatidylinositol anchored proteins (CD55 and CD59) from erythrocytes to endothelial cells *in vivo*.⁴ This has exciting therapeutic implications, such as the transfer of human complement regulators to pig endothelial cells, which has been shown to delay the hyperacute rejection of pig organs transplanted into human (xenotransplantation).⁵ This type of hyperacute rejection is mediated by naturally occurring antibodies to the α (1-3) galactosyl residue exposed on pig, but not human, endothelium.

An alternative approach to avoid hyperacute rejection is to produce transgenic pigs by incorporating human genes into the pig genome. This was recently shown to be successful by the histological demonstration of human CD55 in endothelial cells of various organs of transgenic pigs.⁶ Enzymatic removal of the α (1-3) galactosyl residue is another promising way of reducing hyperacute rejection.^{7,8} Production of genetic "knock-out" animals lacking the enzyme necessary for galactosylation, combined with gene transfer of human complement regulators into the same animals, may be an even better way to solve this problem.

ROLE OF COMPLEMENT IN INFLAMMATORY TISSUE DESTRUCTION

Pathological activation of complement contributes to tissue damage in diseases typically mediated by abnormalities in the immune diseases. In addition, it can cause general tissue damage when the internal homeostasis is disturbed and tissues are no longer protected by an intact endothelial lining—such as in reperfusion injury after ischaemia.

Activation of complement leads to formation of biologically active products like the anaphylatoxin C5a and the terminal C5b-9 complement complex. Specific inhibition of the terminal pathway by use of monoclonal antibodies to C5 leads to substantially reduced activation of leucocytes and platelets during extracorporeal circulation.⁹ This supports the view that complement is a primary and major inductor of the cell mediated proinflammatory effects known to contribute to the whole body inflammatory reaction with multiorgan failure that occasionally occurs after cardiopulmonary bypass.

C5a has long been known to mediate important effects through C5a receptors on granulocytes and other myeloid cells. Recently, C5a receptors were also found on endothelial cells and on various cells of liver, lung, and kidney tissue,¹⁰ indicating that C5a may play a role in activating a variety of human cells. In fact, binding of C5a to its receptors on liver cells induced hepatic acute phase gene regulation.¹¹ C5a and the terminal C5b-9 complex induce proinflammatory effects in endothelial cells by increasing the expression of P selectin and E selectin respectively,^{12,13} thereby enabling attachment of leucocytes. In addition, the C5b-9 complex mediates disorganisation of endothelial cells, leading to gaps forming between the cells and subsequent vascular leakage.¹⁴ Finally, the impact of activated complement on endothelial cell function was emphasised by the observation that the C5b-9 complex caused release of tissue factor, with subsequent activation of the coagulation system.¹⁵

COMPLEMENT AND KIDNEY DISEASE

Factor H is a fluid phase regulator of complement, and a genetic deficiency of this protein in pigs was recently shown to be the cause of membranoproliferative glomerulonephritis type II that was lethal in all affected animals.¹⁶ Deposition of C3 and the C5b-9 complex in capillary walls preceded electron microscopic changes (dense deposits) and light microscopic changes with cellular infiltration and proliferation (fig 1). Thus, this animal type of glomerulonephritis is mediated by complement without other causal factors, and this has clear implications for human membranoproliferative glomerulonephritis.

The well known rat model of passive Heymann nephritis is induced by the nephritogenic antibody Fx1A. This antibody has been shown to inhibit the complement regulators Crry (analogous to human CD46 and CD55) and CD59, which may explain the nephritogenicity and increased activity of complement associated with this antibody.¹⁷

Soluble complement receptor 1, which resembles factor H in structure and function, is a specific and effective inhibitor of complement activation. It was recently used as a complement inhibitor to show the fundamental role of complement in the pathogenesis of three different animal models of glomerulonephritis.¹⁸ Soluble complement receptor 1 and other complement inhibitors may be useful in the future as treatments for diseases where activation of complement contributes to the tissue damage. Conjugates of soluble complement receptor 1 and sialyl Lewis(x), a ligand for L selectin, are being developed in the hope that the complement inhibitory effect can be combined with inhibition of L selectin dependent adhesion of leucocytes to the endothelium.

Intravenous immunoglobulin

Intravenous immunoglobulin has been used in replacement therapy for patients with immunoglobulin deficiency and in specific passive immunisation against certain infectious diseases. It is now also used in high doses to treat several autoimmune and systemic inflammatory conditions. The mode of action is incompletely understood, and indications for its clinical use are not well defined.

POSSIBLE MODES OF ACTION

There are several possible mechanisms by which immunoglobulins might affect the immune system. Effects dependent on the variable region (antibody binding part) of the immunoglobulins include interaction with the idiotypic network—the immunoglobulins include antibodies to autoantibodies and may thereby modify autoimmune diseases—and neutralisation of microbial superantigens—which may partly account for their effect on Kawasaki disease. Anti-idiotypic antibodies are particularly prevalent in the dimer fraction of the immunoglobulins,¹⁹ indicating that a preparation with high dimer content may be of benefit in treating conditions where the anti-idiotypic effect is desired. Effects dependent on the Fc fragment (constant region) of the immunoglobulins include

Fig 1—Kidney glomeruli from pigs aged 3–5 weeks with hereditary deficiency of factor H and membranoproliferative glomerulonephritis type II. Top panel: Immunofluorescence shows deposits of terminal C5b-9 complement complex in capillary walls. Middle panel: Electron micrograph showing intramembranous dense deposits in capillary basement membrane. Bottom panel: Light micrograph showing thickened capillary walls and pronounced mesangial hypercellularity. The morphological changes occur in this sequence and are typical for this type of glomerulonephritis. (Figures provided by Johan H Jansen and Kolbjørn Høgåsen, Oslo, Norway)

blocking of Fc receptors—shown in vivo to account for their effects on idiopathic thrombocytopenic purpura—and inhibition of complement. Purification of Fc fragments may therefore be a possible specific treatment when these effects are desired.

Other effects of intravenous immunoglobulin include modulating production and release of proinflammatory cytokines and cytokine antagonists and regulating B cells, T cells, and NK cells. Our knowledge of its effects on cytokines was recently extended by the demonstration that it inhibited production of tumour necrosis factor and interleukin 6 induced by staphylococcal enterotoxin B by neutralising the enterotoxin.²⁰ Antibodies to cytokines have been found in intravenous immunoglobulin, and high avidity neutralising antibodies to interferons were recently demonstrated.²¹ It has been reported to selectively induce interleukin 2 receptor antagonist and interleukin 8 in human monocytes—dependent on both variable and constant regions—and it was suggested that this effect contributes to the anti-inflammatory effects of intravenous immunoglobulin in vivo.²²

Intravenous immunoglobulin has been shown to modulate complement activation in several animal models, and this may be important in human dermatomyositis.²³ This effect has traditionally been regarded as a scavenger mechanism whereby immunoglobulins bind and neutralise activated C3 and C4 (the effect on C4 depends on the immunoglobulin isotype²⁴). Recent data indicate that intravenous immunoglobulin may have an inhibitory effect on C1 as well.^{25, 26} An interesting application of this effect is in xenotransplantation²⁷: the inhibition of complement delays hyperacute rejection of transplants from guinea pig to rat²⁸ and from pig to primate.²⁹

CLINICAL USE

Intravenous immunoglobulin is relatively safe for clinical use, but it is prepared from humans, and, although it is treated to inactivate viruses, no full guarantee against infectious transmission can be given.³⁰ In addition, patients deficient in IgA risk being immunised against IgA, with resultant production of antibodies to IgA and a potential risk of anaphylactic reaction. Because of these aspects, as well as high costs and, most important, the lack of data from controlled clinical trials, treatment with intravenous immunoglobulin should continue to be restricted to treating idiopathic thrombocytopenic purpura, Kawasaki disease, steroid resistant dermatomyositis, and probably a few selected patients with acquired haemophilia, intractable asthma, myasthenia gravis, and Guillain-Barré syndrome.³¹ Although not confirmed in human studies, intravenous immunoglobulin caused clinical and laboratory remission in mice models of systemic lupus erythematosus and primary phospholipid syndrome.³² Long term prospective studies in humans are needed before the clinical use of intravenous immunoglobulin is extended to these and other autoimmune and systemic inflammatory diseases.³³

Infection and vaccines

In recent years interest in infectious diseases has increased because of problems concerning infections in immunocompromised patients, increasing occurrence of drug resistant strains of many microorganisms, and the effects of the HIV epidemic. Vaccination remains an essential component of preventive medicine. It is well established that an effective vaccine is the most cost effective tool to control an infectious disease. It can lead to virtual eradication of an infectious disease—such as smallpox—or to a pronounced reduction in the incidence of a disease with almost complete arrest of transmission—as with polio and measles. These effects

show the importance of continuing effective vaccination programmes. Priority should be given to the study of vaccines and development of new vaccines.

DEVELOPMENT OF NEW VACCINES

Several of our most effective vaccines are still based on empirical findings. Recent developments have been possible because of our increased knowledge of microbial pathogenesis and the immune system.

Capsular polysaccharides are often poor immunogens, and vaccines based on them fail to induce immunological memory, particularly in children. Vaccines based on chemical coupling of capsular polysaccharides to protein carriers have proved to be valuable, like the *Haemophilus influenzae* type b polysaccharides coupled to tetanus toxoid. In this form it becomes a T cell dependent antigen and induces immunological memory, resulting in a considerable decrease in the disease in children under 5 years old.³⁴

Whole cell vaccines are used extensively—for example, suspensions of killed *Bordetella pertussis* organisms, usually incorporated in combined vaccines against diphtheria and tetanus as well. Although these vaccines have been effective, adverse effects can occur and the safety of whole cell pertussis vaccine in particular has been questioned. Studies have identified four main pertussis antigens that induce formation of protective antibodies: pertussis toxin, filamentous haemagglutinin, pertactin, and fimbrial antigens. On the basis of this information, acellular pertussis vaccines have been developed and have shown excellent protection in extensive clinical trials,^{35,36} presenting a major advance in vaccine technology.³⁷

Local administration of antigen usually results in a systemic response by the immune system, but local responses do occur, particularly with the mucosal immune system.³⁸ In enteric infections local responses by the mucosal immune system are essential for induction of protective immunity. This is one of the most active fields of basic immunology and is of particular importance in the development of new vaccines. An essential feature is how antigen should be delivered to ensure an optimal and selective response by the mucosal immune system. The techniques being tested include nasal immunisation,³⁹ expression of selected recombinant protein on the surface of oral commensal bacteria,⁴⁰ oral vaccination with attenuated recombinant enterobacteria like *Vibrio cholerae*,^{41,42} and new delivery systems for oral vaccines.⁴³

In recent years there has been renewed interest in tuberculosis, and new information has come from recombinant DNA technology.⁴⁴ *Mycobacterium tuberculosis* kills more people than any other human pathogen, and the increasing prevalence of strains with multiple drug resistance shows the urgent need for development of a new tuberculosis vaccine. Insufficient knowledge of mechanisms of protective immunity and the basis for the pathogen's characteristic dormancy and reactivation are major problems, but new technologies have opened up new avenues for the development of vaccines.⁴⁵

Recent developments suggest that we may be able to develop vaccines against a wider range of conditions than just infectious diseases. Malignancies, allergies, and autoimmune diseases are promising candidates for the development of vaccines.⁴⁶

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Lessons from international experience in controlling pharmaceutical expenditure. I: influencing patients

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This is the first of three papers to review international policies to control spending on drugs and improve the efficiency of drug use. Policies can target three main groups: patients, prescribing doctors, and the drugs industry. In this paper we examine policies aimed at patients, particularly restrictions on reimbursement (such as prescription charges). Rigorous experimental and quasi-experimental studies suggest that policies to limit the level of reimbursement of drugs reduce the use of essential as well as non-essential drugs and may do more harm than good.

Spending on drugs in the British NHS represents over 10% of the total NHS budget and has increased steadily over recent decades.^{1,2} Similar increases have occurred in health care systems throughout the developed world, and governments have adopted policies to control drug costs that affect both the supply of and demand for drugs. We reviewed recent policy in several developed countries to provide insights for British health policy. We assessed the impact of these policies on prescribing by examining evaluative studies with rigorous designs that we identified through a comprehensive search strategy.

In this paper we examine the impact of policies intended to reduce patient demand for drugs. In future papers we consider policies aimed directly at prescribers and policies intended to regulate the activities of the drugs industry.

Methods of review

Policies to control drug costs and to improve the cost effectiveness of drug use in the developed world are subject to frequent change. We used published descriptive studies and extensive contact with experts in relevant countries to ensure that our review was up to date and that policy initiatives were interpreted correctly. Where necessary, foreign language publications were translated to enable up to date analysis of policy.

In order to assess the impact of such policies in practice, and gaps in knowledge, we identified evaluative studies of policies in different countries that met predetermined explicit criteria on quality. Randomised studies provide the most valid and reliable estimates of the effectiveness of interventions in health services, but non-equivalent group designs with pre-post measures and interrupted time series designs may also provide reliable estimates of the impact of policy initiatives, enabling attribution of any effect to the intervention.^{3,4} We

made an iterative search of *Medline* and hand searches of *PharmacoEconomics*, *Health Economics*, and selected years of *Social Science and Medicine*, *Health Policy*, and *Scrip*. We also searched the *Cochrane Collaboration on Effective Professional Practice* register of studies—a database derived from electronic searches, hand searches, and contact with experts on the subject that contains evaluative studies which meet specific criteria.³

Policies for influencing patient demand

Various interventions are used to depress the demand for drugs by limiting reimbursement of products and providing an incentive for patients to reduce their consumption of drugs. Copayments require patients to pay a proportion of the cost of a prescribed product or a fixed charge (such as the British prescription charge). Patient caps limit the number of reimbursable prescriptions per patient. The withdrawal of reimbursement of a drug may also be used in attempts to reduce prescribing.

Several countries have copayment systems. In Britain the prescription charge covers about 40% of average prescription costs, but only about 12% of prescriptions are charged,² with exemptions for patients with specific chronic diseases or therapeutic categories, elderly people, and those on a very low income. By contrast, the American Medicare scheme, which provides health care for elderly people, reimburses only certain selected drugs (such as those for patients with end stage renal disease). Medicaid, which provides health care services for some of the poor in the United States, reimburses only drugs that are on the formulary in that state, and various restrictions limit the rate at which products are reimbursed.

The flat rate prescription charge applied in Britain (currently £5.25 per item) is less sophisticated than that applied in some other health systems. In countries with a reference price scheme, where a standard price is allocated to a group of drugs, copayments commonly include a fixed charge plus any difference between the actual price and the reference price. In Germany there is a fixed charge of DM3, DM5, or DM7 (£1.50-£3.50), based on the package size of a prescription item, plus any difference between the reference price and the retail price for drugs that are priced higher than the reference price for their group. In New Zealand and Sweden there is a fixed maximum prescription charge plus a premium for drugs costing more than the reference price.

In France copayments are based on the drug reimbursement rate (assessed by the transparency commission). Drugs for serious and chronic conditions and exceptionally expensive drugs are fully reimbursed. Other drugs are reimbursed at 65% or 35% for

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