Sir Keith Peters

Will Basic Immunology solve Immunological Diseases?

Abstract

Progress of immunotherapy is disappointing, despite the fascinating gains of knowledge in the past decades about general humoral and cellular processes in immunological defence. Therapy still mainly aims at the abrogation or modulation of harmful immune responses, such as in allergy or rejection of grafts, by immunosuppressive agents. Growth of knowledge about general immunological processes however initiated the concept that these may be harmful as a result of pathophysiological aberrations in the immune system, of which the nature and cause is as yet unknown. Alluded is to systemic disorders such as lupus erythematosus or organ specific diseases as insulin-dependent diabetes, nephritis or rheumatoid arthritis. Animal models have until now mostly disappointed. At present the physiology of antigen processing and lymphocyte signalling is emerging. This hopefully will enable industry in the future to develop disease specific drugs. It will require close cooperation between industry and clinical investigation.

Introduction

Few would disagree that the eradication of smallpox by vaccination represents the greatest triumph of preventive medicine and that in more recent times organ transplantation has transformed the lives of patients with irreversible organ failure. Against this background of success it may seem churlish even to hint at disappointment in progress in treatment of immunological disease. I believe, however, that this may reflect two considerations. The first is the explosive growth of immunology and the second, the realisation that immunological disease represents a major public health problem in the Western world being responsible for a great deal of morbidity and mortality – in organ specific diseases such as multiple sclerosis, insulin-dependent diabetes, rheumatoid arthritis, nephritis and various systemic disorders such as lupus erythematosus.

Indeed immunological disease probably ranks only after cardiovascular disease and cancer as a cause of morbidity in the developed world. Yet the

principal therapies available for immunological disease have hardly changed in the past several decades. Steroids were introduced in the late 1940s, azathioprine in the early 1960s, plasma exchange and cyclosporin in the 1970s as were a variety of non-steroidal anti-inflammatory agents; the 1980s have produced FK 506 and rapamysin. Control of the immune response by anti-lymphocyte globulin, although much refined in recent years by the development of monoclonal antibodies and their humanisation by genetic engineering, was advanced by, amongst others, Sir Peter Medawar in the 1960s. Much recent activity centres on the striking advances being made in elucidating the nature of the cytokines and their receptors – an area of intense interest to the pharmaceutical and biotechnology industry which is only just emerging in clinical practice.

The selective abrogation of harmful immune responses

It has long been clear that the aim of therapy in immunological disease (here I exclude of course the deficiency diseases) is the selective abrogation or modulation of harmful immune responses. This is the case for the autoimmune diseases, for allergy, and for control of the rejection of allo or xenografts. Selective control of the immune response has, until recently, represented a formidable task and in the early days caused fundamental immunologists such as Medawar to doubt whether organ transplantation in man was practicable (Professor Sir Roy Calne, personal communication); – indeed it is fair to say that this area of therapeutic advance was achieved in spite rather than because of the advances in understanding the basic science of immunology – driven by surgeons intent on helping patients for whom no alternative therapy was available.

In relation to spontaneous immune disease in man a central question concerns the identification and quantification of such harmful immune responses. Their identification is necessary for targeting of therapy and their quantification for its monitoring. This has long been recognised as a difficult area: it is only rarely in man that it is possible to be confident that a particular immunological phenomenon is indeed pathogenetic. Striking examples are occasionally seen in antibody-mediated diseases when transplacental transmission of antibody may give unequivocal evidence of pathogenicity; and in other circumstances transfer of disease to experimental animals may provide strong support for pathogenicity. However, in many conditions the evidence of pathogenicity is by association: it is daunting to reflect that after many years of research in systemic lupus erythematosus, the nature and pathogenetic mechanisms of vascular and renal injury remain controversial.

Quantification of pathological immune responses is also important since it is now clear that a complex interlinking series of events occurs in which immunopathology engages inflammatory mechanisms which in turn lead to scarring and disorganisation of tissue function. Therapy needs to be tailored

to these processes; apparent failure of immunological therapy may simply reflect that it has been applied at the wrong stage in the natural history of disease. It is clear, therefore, that elucidation and quantification of pathogenetic mechanisms of human disease is needed for rational and selective therapy. A particular difficulty here is that immunopathology rarely represents a single process. There are examples in man of diseases which are seemingly exclusively mediated by antibodies, and others in which T cells appear to be predominantly responsible, but in most instances multiple processes and mediators are involved. The evolutionary drive that created the immune system has ensured that there is much redundancy in its mechanisms. Clearly this is an advantage for defence against microbial invasion, but in relation to immunopathological inflammation selective blocking of a particular mediator system may provide little protection.

Animal models of immunological disease

Because of the difficulties in elucidating mechanisms in human disease a large body of research has been conducted on experimental models of disease and also on spontaneous immunological disease in animals. It is not my purpose to detract from the substantial body of knowledge that has accrued from these experiments but to highlight certain difficulties. Brief consideration of the experimental immunopathology of the kidney highlights the way in which this approach can mislead.

In the 1950s and 1960s a substantial body of work led to the recognition that two major systems of immunopathology might account for the spectrum of disorders coming labelled as nephritis (Dixon, Feldman and Vazquez 1961). It was argued that trapping of antigen-antibody complexes in the kidney could produce a variety of inflammatory processes and corresponding histologies; it was also shown that rarely in animals and in man kidney disease might be due to antibodies reacting with determinants on the glomerular basement membrane. In experimental animals immunofluorescent microscopy showed characteristic patterns of deposition in immune complex disease and by analogy it was assumed that the majority of patients with nephritis had the same pathogenetic mechanism. However, it is now clear that although these models are of value for the elucidation of inflammatory mechanisms they reflect poorly the processes that occur in human nephritis – as one example, the commonest cause of nephritis in man in the Western world, IgA nephropathy has no counterpart in these early models. It has also become clear in more recent times that autoimmune processes are much more important in human nephritis than had been earlier considered; I refer, as an example, to the diseases such as microscopic polyarteritis and Wegener's granulomatosis associated with autoantibodies to neutrophil cytoplasmic antigens and the association of autoantibodies to complement

enzymes and membranoproliferative nephritis. These also have no parallel in the animal systems.

One further point: it is now clear also that the emphasis on the role of antibodies in nephritis that arose from experimental models may be inappropriate in man where there is much evidence for T cell dependent inflammation. I can recall how difficult it was for the clinical investigators to convince their colleagues in experimental pathology that their models did not account for human disease. The experimental pathologists had considerable research momentum, a great deal of research support and were centre stage for the very reason that they were in fact conducting informative experiments!

Thus, although much has been learnt through experimental pathology, it is important to understand the limitations of this approach. A great deal of hope is currently pinned on transgenic models of disease, but I believe that the need for elucidation of mechanisms of human disease remains paramount.

Who generates therapeutic advances?

It is a reality of modern medicine that although the majority of advances in therapy can trace their origins to basic medical science (as shown by the classical study of Comroe and Dripps 1976) that advances depend heavily on research in the pharmaceutical industry. As I have mentioned there has been a surprising paucity of novel therapeutic compounds over the past three decades. This cannot be because the industry does not recognise the importance of the diseases that are immunologically mediated. Huge sums are spent on drugs aimed at the suppression of inflammation, for example in rheumatoid disease; but the impression is that the pharmaceutical industry has been prepared to devote enormous resources to research in inflammation, but has been wary of investment in immunotherapy.

I can guess at some of the reasons. First is the well known principle of 'unripe time'. It is always easy to underestimate the delay between elucidation of physiology and the development of pharmacology. For example, for many diseases it is instructive that the importance of autoimmunity has only relatively lately been recognised – I cite here the detection of autoantibodies against the acetyl choline receptor in myasthenia gravis in the mid-1970s, and it was about that time that there was growing acceptance by a diabetologists that insulin-dependent diabetes was also autoimmune in nature. I would guess that the modern ethos of the pharmaceutical industry, fuelled by the successes of specific receptor antagonists such as H2 antagonists and ß blockers, and enzyme inhibitors such as angiotensin converting enzyme inhibitors, would have been disposed to use similar approaches – to develop drugs which would act specifically on unwanted immune responses rather than have general immunosuppressive activity. However, the underlying physiology required for this approach, the elucidation of the mechan-

isms of antigen processing and presentation and the signalling mechanisms of lymphocytes is only just emerging. At present the principal hope for selective depletion or inactivation of lymphocytes depends on targeting by monoclonal antibodies. This is principally the preserve of the biotechnology industry. Antibodies need to be 'humanised' for regular administration, require parenteral administration, and the diseases concerned are usually chronic; I understand why this type of therapy might be treated with considerable caution by the pharmaceutical industry. The monoclonal antibody approach might be regarded as an intermediate technology to be overtaken by drugs which interfere with specific biochemical events in autoimmune lymphocytes.

Problems in clinical investigation of immunological disease

It seems timely to refer here to the work of Edward Ahrens (Ahrens 1992) who draws attention to the progressive decline in human research conducted by clinical investigators because of the inherent difficulties in carrying out such research and the relative ease in obtaining support for laboratory based investigation.

Although I have emphasised the burden of immunological disease, with a few exceptions the diseases are not life-threatening and often reasonably well-controlled by existing drugs. Immunosuppression has considerable real and potential toxicity. In the sphere of organ transplantation the success of existing immunosuppressive agents makes the introduction to new drugs difficult: the gain is relatively small and only likely to be apparent over a long time scale (with organ transplantation currently achieving somewhere between 70 and 80 per cent one-year graft function). Analysis will inevitably require multicentre control trials. In the autoimmune diseases the problem often is compounded by a natural history of relapse and remission, for example, in multiple sclerosis and by ignorance of the mechanisms responsible.

A further difficulty concerns the role of the immunologist; it is not uncommon in the U.K. for organ transplants to be managed in centres where clinical immunology is relatively poorly established and it is in the nature of the organisation of medical practice that organ specialists tend to manage patients with immunological diseases in their disciplines. There are notable exceptions; for example, in allergy and particularly in the United States, in rheumatology, where there is a powerful tradition of basic and clinical research in immunology being conducted in the same laboratories. The problem is not dissimilar to that experienced by clinical pharmacologists who, in an era of specialisation in medicine, usually find themselves forced to concentrate on a particular disease or group of diseases.

However, I am convinced that for the growth in immunological science to be translated effectively into clinical practice we will need clinical investi-

gators capable of harnessing the new knowledge. The responsibility for meeting this challenge lies with university departments of medicine and their associated teaching hospitals.

References

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