Premises for immune interventional therapy in rheumatoid arthritis

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Summary: Consideration of rheumatoid arthritis (RA) as an autoimmune disease includes initiating event(s), genetic predisposition, immune regulatory derangements, and effector cycles of articular damage. The initiating event is still unknown. Collagen type 2 has good claims as a rheumatogenic autoantigen which perpetuates disease. The association of HLA DR4 with rheumatoid arthritis is in part explainable by the affinity of binding of the rheumatogenic antigen to a hypervariable portion of MHC Class II molecules with selective presentation of this complex to T cell receptors. Immune regulatory derangements include lymphokine-induced aberrant expression of MHC Class II molecules on synovial tissues, the presence of a 'resistant' subset of B cells (CD5+ve), failure of anti-idiotypic control of autoantibodies (not well established as yet in rheumatoid arthritis), and defective immune suppression, revealed by low counts in synovial fluids of a suppressor-inducer subset of CD4+ve T cells. The many possibilities for therapeutic immune intervention would include polyclonal or monoclonal antibody to block (a) receptors for antigen on B or T lymphocytes (but this would require knowledge of the rheumatoid arthritis-inducing antigen), (b) the CD4 complex on helper T lymphocytes, (c) MHC Class II (Ia) molecules, for which there are excellent prototypes in experimental immunopathology, or (d) lymphokines or their receptors. Induction of suppression by 'tolerogenic vaccines' is experimentally validated, but only for diseases for which an autoantigen can be identified.

Introduction

A recent paper on Type I diabetes mellitus (Type I DM) contained the comment 'Only when the innermost mechanisms of immune reactions are understood, specific immunotherapy will become a standard tool in the clinical management of diabetes'. Since an understanding of immunological dysfunction in the pathogenesis of Type I DM¹ is probably closer than for many other autoimmune diseases, including rheumatoid arthritis,² it could be premature even to consider immunotherapy for rheumatoid arthritis. Yet many current therapies of immune-mediated diseases are based on no more than a general principle of reduction of lymphocyte activity, the expectation being that the particular treatment will attenuate the activity of pathogenic autoreactive lymphocytes without being overly prejudicial to the function of normal lymphocyte populations.

The cause of rheumatoid arthritis and the 'innermost mechanisms of immune reactions' in this disease has been investigated from many directions,

notably immunology, genetics, biochemistry, pharmacology, microbiology and epidemiology, with the following pathogenetic scenarios constructed:

1. an initiating event presumed to be infectious, and which may contribute a residual intrasynovial antigen, although this has never been convincingly demonstrated;
2. a genetic predisposition contributing up to 30% of the risk for the disease;
3. an immune regulatory disorder in which suppressor systems fail to limit an unwanted immune response to the postulated intrasynovial antigen;
4. immunopathogenetic events sequential to 1-3 which create secondary cycles (immune complexes) and tertiary cycles (destructive lymphokines) of articular damage.

The initiating process: the intrasynovial antigen

No serious consideration is being given to any persisting infectious agent other than the Epstein-Barr virus, and the evidence for this as a causal

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agent is insecure.³ Perhaps the AIDS epidemic will encourage improved technologies and enthusiasm for demonstrating retroviral infections in hitherto obscure diseases. However the question is open as to what happens on day 1 in the course of rheumatoid arthritis (RA), and whether a postulated initiating infection is transient or persistent and, if persistent, whether it acts by causing ongoing tissue damage in its own right, or provides a new antigenic particle which elicits a damaging immune response, or creates a milieu in which autoimmunity takes over. This uncertainty pertains to various of the autoimmune diseases in which no tissue-specific autoantigen can be identified.

One concept is that an infectious agent with a tropism for synovial tissues causes an initial acute synovitis and then provides an intrasynovial antigen which provokes a chronic inflammatory response. A model for this is the arthritis induced in rats by intraperitoneal injection of cell wall fragments from streptococci or other bacteria.⁴ There is a biphasic response in which the second chronic phase is characterized by a pathology resembling that of rheumatoid arthritis, and is dependent on the abundant T helper cell infiltration into synovial tissues. The disease is genetically based, in being strain-specific in rats. Chronicity requires the continued presence of the cell-wall antigen in synovial tissues, and one role for the infiltrating helper T cells is to augment the expression of MHC Class II molecules on cells throughout the synovium. Another way in which a new and non-tolerated antigen could be introduced would be by incorporation of microbial or viral DNA into the genome of synovial cells, and its expression as a new cell membrane antigen. However, lacking in human RA is any clinical evidence for a relevant antecedent infection, or histological evidence in the diseased synovium for an extrinsic antigen equivalent to bacterial cell wall. Moreover, in the well studied synovitis due to infection of humans with Ross River virus, delayed recovery certainly occurs yet evolution to a rheumatoid synovitis is not reported.⁵

The question of the *agent provocateur* for rheumatoid synovitis merits deep consideration because it raises one of the most testing questions facing immunopathology – is the immune response in various putative autoimmune diseases antigen-directed and antigen-driven? This question is particularly applicable to those tissue-specific autoimmune diseases in which there is no evident relationship between the marker antibodies and the tissue(s) affected, examples including antibody to La nucleoprotein in Sjögrens syndrome, mitochondrial antibody in primary biliary cirrhosis, antibody to centromere in scleroderma etc., not to

mention rheumatoid factor in rheumatoid arthritis. Indeed, the failure to identify an extrinsic intra-synovial antigen relevant to rheumatoid arthritis has led authors to invoke non-antigen driven processes to explain self-perpetuation, by suggesting that there develops an autologous mixed lymphocyte reaction (AMLR) in the rheumatoid synovium.^{6,7} In this AMLR, T lymphocytes can respond to antigens presented by B lymphocytes or other cells, with resulting cycles of polyclonal B cell activation and production of immunoglobulins which activate the down-stream features of RA, immune complexes and release of lymphokines, which culminate in articular destruction. The idea of a self-sustaining synovial AMLR depends strongly on immunoregulatory deficiency, for which there is substantial evidence in RA (*vide infra*).

The next alternative for consideration is a relevant autoantigen as an endogenous initiator: the prime candidates are the Fc piece of immunoglobulin G (the reactant for rheumatoid factor), and collagen type 2. Rheumatoid factor has received immense attention, without a conviction being recorded, and hence discussion here will be directed exclusively to antibody to collagen, first of all noting that collagen type 2 is present within the joint as the major collagen type of articular cartilage.

Autoimmunity to collagen has had a long and undulating history. The earliest protagonist was Steffen, whose studies track back to 1954, and whose writings in the 1970s led to definitive claims for RA as a 'collagen autoimmune disease'.⁸ These claims fell on rather deaf ears, since in the mid-1970s there could be conferences held on RA,⁹ and chapters written,¹⁰ with no mention at all of 'collagen autoimmune disease'. The reasons were, as Ziff³ states, that about 40% of patients with RA did not have collagen antibody, and that collagen antibodies were detectable in patients with articular diseases other than RA. The later reawakening of interest was stimulated by reports of the association of collagen antibodies with severe erosive rheumatoid disease,¹¹ the demonstration in patients with RA of cell-mediated immunity to collagen,¹² with an immunogenetic association with HLA-DR4 and attribution to deficiency of suppressor T cells,¹³ and the establishment of a strain-specific animal model in rats and mice based on immunization with native collagen.¹⁴

We have investigated autoimmunity to collagen type 2, and particularly heat-denatured collagen type 2 rather than native collagen, using a sensitive solid-phase radioimmunoassay.¹⁵ The antibody, referred to hereafter as 'collagen antibody', is seen to be comparable with most other disease-associated autoantibodies for which levels in serum

form a continuous variable from health to disease. Thus, in severe rheumatoid arthritis, there is more collagen antibody than in healthy sera, but comparable increases are not seen in other articular diseases, osteoarthritis¹⁵ or epidemic polyarthritis¹⁶ and, in particular, collagen antibody is not increased in any form of juvenile arthritis,¹⁷ a disease now regarded as different from RA. It is a fact that serum levels of collagen antibody are not increased in all cases of RA but, in studies in which paired samples of synovial fluid and serum were examined, there was a significant excess of collagen antibody in synovial fluid over serum,¹⁸ indicative of local synovial synthesis of antibody which may or may not spill over into serum.

To reiterate the evidence implicating reactivity to collagen in rheumatoid arthritis: high levels in serum and especially synovial fluid; immune complexes containing collagen antibody in articular cartilage;¹⁹ cell-mediated immunity to denatured collagen by lymphokine release assay; and the animal model established by immunization with collagen type 2, albeit with native rather than denatured collagen type 2.

Genetic predisposition to rheumatoid arthritis

A genetic component in RA rests on aggregation (weak) within families, and a concordance (~30%) in monozygotic twins.²⁰ This degree of concordance, of the same order as that seen in other autoimmune diseases, e.g. systemic lupus erythematosus or Type I diabetes mellitus, represents the germline genetic component of the disease, and the ~70% non-concordance represents the 'random' or 'bad-luck' component usually taken as synonymous with the effect of a ubiquitous environmental agent. However, as stated by Eisenbarth²¹ in the context of Type I diabetes mellitus, the random component could be explained by somatic genetic changes (mutations) which influence the binding affinities of antibody-products of germ-line genes.

The ascertained genetic association of rheumatoid arthritis with HLA genes of the major histocompatibility complex (MHC) would explain an uncertain proportion of the overall genetic risk; this association is with the HLA-Dw4 locus determined by the mixed lymphocyte reaction, or the related HLA locus DR4. Representative frequencies for DR4 in rheumatoid arthritis and health would be, say 60%–70% and 20%, giving a relative risk for the disease of 6–8. The risk conferred by DR4 does not depend on rheumatoid factor which, in the absence of rheumatoid arthritis has no association with DR4, but may depend in part on collagen

antibody. The relative risk cited of 6–8 conferred by HLA DR4 is a minimal figure, since this serologically-defined specificity comprises a number of subtypes definable by other procedures. Thus DR4+ve lymphocytes may include Dw4 or Dw14 which are strongly associated with RA, and Dw10 which is not; the difference between Dw4 and Dw10 amounts to only a few amino acids.²² With the use of T cell clones to identify the Dw14-associated 'susceptibility antigens' on lymphocytes of patients with rheumatoid arthritis,²³ or the monoclonal antibody 109db which likewise identifies such antigens on cells of DR4+ve subjects,²⁴ the figures for relative risk are greatly amplified. These results have led to the 'disease-epitope' hypothesis which holds that there is a sequence or sequences, on the hypervariable regions of MHC class II molecules which can associate with and present a 'rheumatogenic' antigen to helper T cells in such a way as to establish an immune response which determines the occurrence and/or perpetuation of the disease.

The observations of Solinger and Stobo¹³ on cell-mediated immunity to collagen measured by lymphokine release take us along another path. They found that all DR4+ve subjects, with rheumatoid arthritis or not, respond to denatured collagen; such subjects were held to lack a population of CD8+ve suppressor cells which could limit cell-mediated immunity to collagen type 2. Subjects lacking DR4 possessed CD8+ve suppressor cells (for which the restricting element should be a Class I MHC specificity) which would modulate the T cell dependent antibody response to collagen. In studies on serum antibody to denatured collagen type 2 it was found that (presumed) extended haplotypes were increased in frequency in patients with rheumatoid arthritis and high levels of collagen antibody (Rowley, M.J., *et al.*, submitted); these HLA haplotypes contained A2, certain B locus antigens commonly found in linkage with DR4, and DR4, with a class I specificity assumed to be the restricting element.

Sasazuki and colleagues²⁵ proposed that associations of HLA with immune responses depend on dominantly inherited immune response (Ir) and immune suppression (Is) genes: the presence of the Ir gene, and lack of the Is gene as a recessive trait, is associated with a high-responder status. In their studies on the human immune response to schistosomal antigen,²⁶ the restricting element for the Is gene was identified with the class II DQw1 molecule, rather than with a class I MHC molecule as might be expected if the suppressor response were determined by CD8+ve cells. Accordingly regulation of the immune response to collagen type 2 could depend on two interacting

and HLA DR4-linked genes, one coding for a Class II epitope or epitopes identified by the T cell clones of Goronzy *et al.*²³ or MAb 109db,²⁴ and required for the 'rheumatogenic' recognition of an antigen by a CD4 positive 'helper' cell, and the other coding for recruitment of a population of CD8+ve suppressor cells which could modulate T dependent cell-mediated and humoral antibody responses to denatured collagen. In other words increased levels of collagen antibody in rheumatoid arthritis would result from the effects of an MHC class II-associated Ir gene coding for a response of denatured collagen, and the absence of an Is gene, class I or II-associated, leading to a deficiency of suppressor cells.

There are likely to be immunogenetic determinants other than HLA in rheumatoid arthritis. Some studies have shown a weak association of rheumatoid arthritis with immunoglobulin Gm allotypes, and a marked interactive effect between HLA DR4 and the Gm(1,2,3;5) phenotype.²⁷ In mice, susceptibility to collagen-induced arthritis depends on MHC genes and also on the presence of particular V β genes for the T cell receptor.²⁸ It would therefore be of interest to investigate DNA from cases of rheumatoid arthritis for polymorphisms of T cell receptor genes, using variable region probes.

Immune regulatory dysfunction in RA

Whatever may be the inciting antigen in rheumatoid arthritis, a fault in immune regulation is well agreed-upon as a contributing mechanism of disease. However, among the numerous observations attesting to this, primary events and secondary or consequential effects of the disease are not easily dissociated.

The first of the regulatory effects to be considered is that of HLA Class II molecules which can be aberrantly expressed on tissues affected by autoimmune disease. This has been shown for thyroid cells, pancreatic islet cells, biliary epithelial cells and others, as well as for the rheumatoid synovium.²⁹ Normally, antigen presentation to helper T lymphocytes is limited to a very select population of macrophage-type cells which constitutively express an MHC Class II gene product with which the antigen associates. Exposure to lymphokines, in particular interferon γ which is released by activated T cells, results in the induction or up-regulation of expression of HLA Class II molecules on various other cells, including parenchymal cells of tissues, which thereby acquire the capability for presentation of tissue-specific autoantigens which may be concerned in processes of autoimmunity. Rheumatoid synovial cells could

phagocytose cartilage fragments, and these cells express MHC Class II molecules and contain mRNA for MHC Class II;²⁹ chondrocytes also are susceptible to aberrant MHC Class II expression.³⁰ Thus the setting is there for an ongoing response to a disease-inducing antigen, denatured collagen or whatever else this may be.

The second aspect of regulation is that related to a particular subset of B lymphocytes marked by the presence of a surface antigen normally associated with T cells, CD5 (Leu-1). The CD5 marker is associated with an early stage of B cell differentiation, and CD5+ve B cells are highly represented among fetal B cells and the B cells of lymphocytic leukaemia. It is of much interest that patients with rheumatoid arthritis have higher than normal numbers in blood of CD5+ve B cells, and this discrete subset of B cells is the source of rheumatoid factor, and other autoantibodies.^{31,32} The suggestion is that CD5+ve B cells, being less susceptible to regulatory controls, may be expanded by various influences independently of antigen drive.

The efferent side of immune regulation can be discussed from the humoral aspect, anti-idiotypic antibody, and the cell-mediated aspect, T suppressor cells.

'Idiotypic' designates the antigenic specificity of antibody molecules raised in the course of an immune response to antigen: such antibody molecules are themselves immunogenic and the resulting response is 'anti-idiotypic'. What is usually studied is the reactivity of anti-idiotypic antibody with the binding site of antibody, but reactivity could equally be with the antigen-receptor on B cells which has an equivalent configuration. The reality of anti-idiotypic antibodies (anti-id) is well-accepted and, moreover, under defined conditions, the waning of an immune response to a given antigen is associated with the appearance in serum of anti-idiotypic antibody.³³ However there is uncertainty over the degree to which anti-id actually down-regulates immune responses under physiological conditions, and whether a defect in (or resistance to) the anti-id response is an important factor in autoimmunity.

The cell-mediated aspect of regulation of immune responses involves T suppressor cells, of which various subsets have been described. In general, T suppressor effects can be non-antigen-specific or antigen-specific. However, the responsible cells and their receptor molecules, and the pathways by which the negative signal of suppression is mediated, remain poorly defined in human systems. It is held that particular epitopes of complex antigens are immunogenic whereas others are 'suppressogenic'.³⁴

The most credible type of T suppressor cell would be that which is anti-idiotypic for a B or T cell receptor for antigen, i.e., the T cell analogue of anti-idiotypic antibody. For the immunopathologist, the reality of T suppressor cells is best sustained by the establishment of 'resistance' to various experimental autoimmune diseases by special protocols of immunization, with transfer of this resistance by spleen cells to normal syngeneic recipients.³⁵

In human systems, the study of suppression depends either on functional assays based on relative recruitment of suppressor cells by mitogens, or enumeration of cells of purported suppressor phenotype. Such procedures in rheumatoid arthritis hitherto have not been informative on the nature of the regulatory defect because assays for suppressor cells depended on the CD8 marker which is not exclusive for a suppressor subset. However monoclonal antibodies to antigens called 4B4 and 2H4 are more informative, since anti-4B4 and anti-2H4 identify reciprocal subpopulations which function as inducers of a helper subset or a suppressor subset respectively.³⁶ In studies by Emery *et al.*³⁷ on blood and synovial fluid lymphocytes and antibodies to CD4, 4B4 and 2H4, with two colour immunofluorescence, the suppressor-inducer CD4+ve 2H4+ve subset was reduced moderately in blood and markedly in synovial fluid, specifically in rheumatoid arthritis and not in other articular diseases. The helper-inducer to suppressor-inducer (HI:SI) ratios (mean $\pm$ s.e.m.) for rheumatoid arthritis and other articular diseases (OAD) were as follows: blood - RA; OAD; controls = 2.8 ± 0.7 ; 1.1 ± 0.1 ; 1.2 ± 0.1 ; synovial fluid - RA; OAD = 9.5 ± 2.1 ; 1.6 ± 0.4 .

The fourth regulatory mechanism in rheumatoid arthritis would be via lymphokines released by helper T lymphocytes which mediate effects of these cells. These lymphokines include interleukin-2 (IL-2), interferons α/β interferon γ and the colony-stimulating factors (CSFs) which have activating effects on mature cells.² We have examined for IL-2 and IFN- α in blood and synovial fluid but neither was demonstrable.^{38,39} Although active phases of autoimmune responses might be expected to be associated with increased expression of IL-2 on T cells, we found that there was a marked down-regulation of high-affinity receptors for IL-2 on synovial fluid lymphocytes,⁴⁰ perhaps a result of these cells being terminally stimulated. In the studies on interferon α in rheumatoid arthritis,³⁹ a remission state was associated with evidence of lymphocytes having been under the influences of an interferon stimulus.

Immune intervention in rheumatoid arthritis

Each of the numerous therapies for rheumatoid

arthritis confers some degree of benefit, variable from case to case, but none cure the disease. The mode of action for many of the drugs used is not well understood, and may not correspond with the premise on which a given drug was introduced. Adverse effects or a refractory state, cumulative with time, usually limit prolonged treatment with any one agent. Combination therapy to achieve multiple effects, as in oncology, has not been wholly adopted by rheumatologists. Treatments which are cytoreductive, whether by drugs, cell removal (apheresis) or radiation, ameliorate the disease, perhaps by selective removal of a cell population with deleterious properties; however removal of a large number of normally functional lymphocytes may be needed in order to deplete adequately a critical but small subpopulation of harmful lymphocytes. Finally, given our data on deficiency of a suppressor-inducer subset, or a suppressor subset, replenishment rather than reduction could be the more appropriate strategy.

The possibilities for intervention include (a) immune interference with (i) receptors for antigen on B or T lymphocytes by anti-idiotypic, (ii) with the CD4 complex on helper T lymphocytes (iii) with MHC class II molecules or (iv) with lymphokines or their receptors, or (b) reinduction of suppression, e.g., by 'negative' vaccines.

Receptors for antigen

The basis for examining anti-idiotypic antibody in therapy is the ready demonstrability in serum of anti-idiotypic antibody in various human and experimental autoimmune diseases. Indeed, there is a reported success in some experimental models with the use of anti-idiotypic, e.g. spontaneous autoimmune thyroiditis in Buffalo rats,⁴¹ induced interstitial nephritis in Brown Norway rats,⁴² and lupus in (NZB/NZW)F1 mice.⁴³ However, in these models, there is an identifiable tissue-specific auto-antibody to which an anti-idiotypic antibody can be directed. Although, in one case of rheumatoid arthritis, anti-idiotypic antibody to rheumatoid factor was held to explain seronegativity,⁴⁴ the therapeutic use of anti-idiotypic to rheumatoid factor would not seem to be promising. Given that treatment with anti-idiotypic requires that the pathogenic antibody is known, it is hard to see prospects at present for antibody directed against idiotypic on either antibody molecules or against B cell or T cell receptor for antigen.

The CD4 complex on T cells

The T lymphocyte subset defined by CD4 is associated with the restricted recognition of MHC class II products on antigen-presenting cells. Hence

antibodies against CD4 should block antigen recognition by CD4 bearing cells and indeed have been shown to suppress immune responses. These include immune responses to soluble antigens,⁴⁵ immune responses responsible for graft rejection,⁴⁶ and also for various immune-mediated diseases, including collagen arthritis.⁴⁷

Antibody to MHC class II (Ia)

The use of monoclonal antibody against MHC class II (Ia) rests on the premise that injection of such antibody in a heterozygote could *selectively* suppress the response to antigens under the control of the relevant DR (Ia) molecule without completely immunosuppressing the individual,⁴⁸ in particular, the blocking MAb should be specific for a single chain of the class II molecule so that, in heterozygotes, there would be two unblocked heterodimers to permit a normal response to foreign antigens. This approach has been pursued with success in various experimental autoimmune diseases.

In studies on experimental autoimmune encephalomyelitis (EAE) induced in the susceptible SJL mouse,⁴⁹ injection of MAb before immunization with brain emulsion prevented the occurrence of disease (3/28 treated mice affected versus 19/28 receiving a control antibody). Moreover, treatment with MAb after the appearance of lesions, or in mice with chronic relapsing EAE, was likewise successful (7/18 relapses and 0/18 deaths in treated mice versus 18/18 relapses and 7/23 deaths in controls). Equivalent data are accruing for EAE in monkeys although acute deaths in some monkeys given anti-DR MAb have occurred.⁴⁸ Beneficial effects of anti-Ia MAb have been shown in various other experimental autoimmune diseases including myasthenia gravis induced by immunization with acetylcholine receptor.⁵⁰ Perhaps of more relevance is the amelioration by anti-Ia antibody of spontaneously developing autoimmunity exemplified by thyroiditis/diabetes in the BB rat,⁵¹ or lupus in mice when treated over the 4th to 8th month of life.⁵² Finally, of interest to the concept that collagen may be an antigen relevant to rheumatoid arthritis, monoclonal and polyclonal anti-Ia antisera suppressed the occurrence of arthritis in mice after immunization with type 2 collagen.⁵³

In concluding anti-Ia therapy, reference could be made to the proposal,⁵⁴ based on recognition of different cytochrome c molecules, that an antigen has a contact area, called an agretope, which binds to the MHC epitope. Conceivably, there could be developed structures which compete for the agretope-binding site of the MHC, thus inhibiting antigen presentation. The following exchange took

place at a recent Ciba conference on autoimmunity:⁵⁵

A M — structures — could potentially compete for the MHCs agretope-binding site and thus inhibit antigen presentation

H M — how would I make a competing molecule — the target antigen is not known?

A M — the question is which approach has the better long-term future — monoclonal antibodies have had a good run for their money —

H M — the approach you suggest would be ideal, if it were feasible —.

Lymphokines and their receptors

IL-2 is the lymphokine involved in the clonal expansion of T cells, by acting on a specific high affinity membrane receptor. Accordingly a blockade of the IL-2 receptor (IL-2R) should prevent recruitment of activated T cells and so have immunosuppressive effects, perhaps akin to those of cyclosporin; this was shown in a model which depended on injection of activated T lymphocytes from a cell-line specific for myelin basic protein derived from Lewis rats.⁵⁶ Also, rat IgG_{2a} MAb to IL-2R was shown to retard rejection of human renal allografts.⁵⁷ Reservations about the use of anti-IL-2R in rheumatoid arthritis hinge on two points. First, it would need to be established that the disease is antigen-driven, and IL-2 dependent. Second, there would need to be a clearer understanding of the state of the IL-2 system in rheumatoid arthritis; IL-2 is not demonstrable in serum or synovial fluid, and there is only weak expression of high-affinity IL-2R on blood and synovial fluid lymphocytes⁴⁰ — hardly a premise for treatment with an exogenous source of antibody to the receptor for IL-2.

IFN- γ is a lymphokine released by T lymphocytes which induces normal expression of Class II MHC molecules on antigen-presenting cells and aberrant expression on tissue cells, including cells of articular structures in rheumatoid synovitis. A monoclonal antibody to the interferon- γ molecule induced significant remission of lupus in (NZB/NZW)F₁ mice.⁵⁸ Also cells which can be influenced by IFN- γ have a surface receptor which enables the IFN- γ to be internalized. Monoclonal antibody to this receptor can be raised⁵⁹ and hence interaction of IFN- γ with this receptor could be susceptible to antibody blockade.

Induction of suppression

What has been stated hitherto has dealt with

reduction of positive influences on immune responses – abrogation of ‘help’. Amplification of suppressor mechanisms could have some prospects, albeit still remote from clinical application. As one example, there have been derived, from animals immunized for a given autoimmune disease, lymphocyte cell lines which usually transfer disease; however when ‘autoimmune’ cells from such lines are ‘attenuated’ in various ways, the animal is rendered specifically resistant to a subsequent disease-inducing immunization.⁶⁰ This tolerogenic ‘vaccination’, which experimentally has been proven effective in EAE, thyroiditis, and arthritis, is thought to induce a type of suppressor T lymphocyte which inactivates (?deletes) effector cells with the receptor idiotype.

Another possibility rests on the assumption that macromolecular autoantigens contain particular epitopes that are suppressogenic. There is much current interest in the cloning of genes for autoantigens with, as one premise, the identification of particular epitopes which could serve as a ‘negative’ vaccine to stimulate dormant suppressor mechanisms.⁶¹ It must be noted that these approaches to induction of suppression require that the relevant autoantigen is known – a requisite still unfulfilled in rheumatoid arthritis, as so often mentioned in this essay.

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Epilogue

Lest rheumatoid arthritis seem too unpromising a subject for immune intervention, the closing comment can be made that there is no other autoimmune disease in which the site of the pathology, the synovial cavity, is so readily and ethically accessible to the clinical investigator. Synovial fluids and synovial tissues should be a rich source of material for research into the pathogenesis of rheumatoid arthritis, and the injection of monoclonal antibodies or other agents intra-synovially does not present the constraints associated with parenteral use.

Many rheumatologists express such pessimism about the identification of a rheumatogenic antigen that one is reminded of the Greek philosopher Diogenes who wandered the streets of Athens by night with his lantern in a fruitless search for an honest man. Fortunately lanterns with brighter lights are now available, so that the search, at least for the elusive rheumatogenic antigen(s), should soon be rewarded. The achievement of this should open up new approaches to treatment of rheumatoid arthritis, with immunotherapy prominent among these.

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