In rheumatoid arthritis (RA), the aetiology is a mystery. We know that joint destruction occurs because of host activity, but we do not know what triggers this self-destructive process and why it persists. The best clue to the initiating event in RA is provided by genetic studies. Familial clustering occurs and the genes known to be partly responsible for this are HLA genes [1]. Many clinical studies, both transverse and longitudinal, showed that HLA molecules are associated both with the initiation and the progression of RA [2, 3]. Furthermore, it was shown that 75% of the RA patients in North America and Europe carry the motif Q(K/R)RA in the antigen-binding DRB1-HV3 region of the T-cell antigen receptor (TCR) [4]. This observation is the basis of the ‘shared epitope hypothesis’. These associations strongly point to a role of T cells in RA since the only known function of these molecules is to present antigens to T cells as the first step of the activation. Further evidence of in situ stimulation of T cells stems from observations that these cells carry markers of stimulation. T cells isolated from rheumatoid synovial tissue differ from circulating T cells by the increased expression of CD45RO and CD27, markers of prior exposure to antigens, and by the increased expression of activation markers like VLA or HLA class II molecules [5]. Owing to the lack of evidence for T-cell proliferation in synovial tissue, it is supposed that T cells are continuously recruited. This recruitment is facilitated by the high expression of adhesion molecules on synovial endothelium and the local production of chemotactic cytokines.

The T-cell centred hypothesis has been challenged firstly because attempts to define distinct T-cell subsets that drive the autoimmune process have not been successful and secondly because T-cell-derived cytokines, cytokines that should drive the rheumatoid inflammation, are scarce in synovial tissue [6]. The functional disability of synovial T cells is underscored by results of ex vivo studies wherein it is demonstrated that synovial T cells are in a state of hyporesponsiveness. These T cells respond poorly to mitogenic stimulation and display decreased Ca$^{2+}$ responses [7, 8]. The hyporesponsive state of synovial T cells in RA directly correlates with impaired TCR-mediated signalling transduction. In-depth biochemical analysis of the most proximal TCR signalling events revealed severely diminished phosphorylation of TCR zeta chain and p38 [9]. Defective phosphorylation of TCR zeta chain was found to be accompanied by a decrease in TCR zeta chain expression. These features are reminiscent of those of anergic cells, as previously described by others. Another feature of synovial T cells is their relatively low concentration of the intracellular antioxidant glutathion (GSH) [10].

In association with a decreased concentration of intracellular GSH in synovial T cells, high levels of thioredoxin (TRX), a major cellular antioxidant previously found to be released by lymphocytes and other cells under conditions of oxidative stress, were found in RA synovial fluid. These data are in line with current thinking that conditions of chronic oxidative stress markedly inhibit synovial T-cell function.

A similar hypothesis is put forward to explain reduced T-cell responses in HIV-infected individuals. In analogy with RA T cells, T cells of HIV-infected individuals have decreased intracellular levels of GSH, and impaired TCR signalling with concomitant loss of TCR zeta chain expression [11]. These observations suggest a close relationship between oxidative stress and TCR zeta chain downmodulation. Evidence for this hypothesis is provided by the observation that reactive oxygen intermediates inhibit the effector function of melanoma-specific cytotoxic lymphocytes and induce downregulation of TCR zeta chain [12].

The critical issue to address is whether the above-mentioned features of synovial T cells provide strong enough arguments to exclude a major role of T cells in RA. One could argue that in order to control the inflammation, the system works towards an active suppression of T-cell function, but fails to do so adequately. Consequently, a low level of T-cell function is still detrimental. In line with this reasoning, the disturbed balance between Th helper 1 (Th1) and Th helper 2 (Th2) cells may be held responsible for a pathogenic role of T cells. If such a balance is critical for arthritis, then the preponderance of Th1 cells in rheumatoid synovial tissue [13] may be important for the persistence of inflammation in the RA synovium. Synovial T cells comprise functionally heterogeneous T-cell subsets. Correction of an abnormal Th1/Th2 balance may be accompanied by a restoration of several T-cell functions. In this context, it is of interest to learn that beneficial effects on disease activity in RA upon in vivo administration of neutralizing anti-tumour necrosis factor alpha monoclonals are associated with restored T-cell responses to mitogens and antigens [14].

Another point of consideration is the importance of the presence of functional active T cells in the inflammation. In other words, the release of soluble factors may not be essential. Although cytokine expression is suppressed, synovial T cells were shown to express molecules that can activate other cells in the synovial tissue. Evidence exists that the direct contact between T cells with an activated phenotype and macrophages or fibroblasts may be important in the pathogenesis of rheumatoid synovitis [15].
The functional heterogeneity of the synovial T cells is discussed in a new way by the hypothesis developed by Zanelli and David. This hypothesis was formulated in the first place because the ‘shared epitope hypothesis’, based on observations in Caucasianoid populations, does not explain the association of HLA with RA in other ethnic groups [16]. A re-evaluation of the role of HLA-DQ in the new hypothesis provides a solution to this problem. It is suggested that HLA-DQ molecules regulate the immune response by presenting self-HLA peptides [17, 18]. This model was initially based on the observation that peptides derived from the HV3 region of some H2-Eβ alleles (DRB1 equivalent) protect mice susceptible to collagen-induced arthritis from disease development. Eventually they found in transgenic mice expressing functional HLA-DQ8 genes an inverse correlation between T-cell responses to DRB1 HV3 peptides and arthritis susceptibility. On the basis of these observations, it was proposed that a predisposition to RA is mediated by HLA-DQ and that a HLA-DR-protective determination is modulating this predisposition either through the induction of specific regulatory TH2 cells or through impaired presentation of autoantigens. Protections mediated by the former mechanism has been designated ‘antigen-specific bystander suppression’ [19].

Regardless of what might increase or decrease the risk of RA, clinical evidence indicates that the mere presence of articular cartilage is essential for the perpetuation of arthritis [20]. Moreover, there is evidence that cartilage degradation is associated with the development of cartilage-responsive T cells [21]. In the search for the autoantigen and T cells that drive RA, Verheijden et al. [22], working at the Department of Immunology of Organon, focused on the human cartilage glycoprotein-39 (HC-gp-39) which is a major secretary product of articular chondrocytes. They used a DR4 peptide-binding motif to select potential self-reactive peptides within HC-gp-39. High-affinity binders were then tested for their capacity to stimulate PBMC responses in RA patients and healthy donors. HC-gp-39-derived, motif-based peptides were indeed selectively recognized by peripheral blood mononuclear cells from RA patients and no responders were found in the healthy donor group. Of high interest was the observation that injection of the intact protein in Balb/c mice resulted in immunity to HC-gp-39 which was found to be associated with the development of a chronic relapsing arthritis. These data indicate that HC-gp-39 is a target of the T-cell-driven immune response in RA.

Finally, clinical observations provided new information on the role of T cells in rheumatoid inflammation. Until recently, the results of T-cell-targeted interventions have met with unfavourable efficacy-toxicity ratios. In particular, the clinical experience with CD4 monoclonal antibodies that deplete T cells from the circulation was disappointing [23]. Several explanations were put forward to explain this observation. Synovial biopsies of RA patients treated with CD4 monoclonal antibodies revealed that a significant number of lymphocytes with an activated phenotype persisted in the synovial tissue [24]. Others pointed to the low dosage of antibodies used when compared to the favourable clinical effects observed in rodent models of induced autoimmune diseases. Blockage of CD4 molecules with monoclonal antibodies given at higher dosages for prolonged periods may, therefore, be an alternative strategy. Such antibodies should be non-depleting since severe lymphocytopenia restricted the use of high dosages of antibodies investigated so far. Recently, preliminary results of two clinical trials investigating the effect of such antibodies have been presented [25, 26]. Both studies found that the majority of patients fulfilled the pre-defined response criteria when CD4 monoclonal antibodies were given at dosages above 500–1000 mg/patient.

In conclusion, evidence has been provided that T cells at the site of inflammation in RA patients are hyporesponsive due to an altered signalling capacity. This not necessarily inhibits the T cell to regulate the inflammatory process either by releasing cytokines or by affecting the function of contiguous cells involved in inflammation by direct cell–cell contact. The recent observations on the clinical efficacy of CD4 monoclonal antibodies further illustrate this. Synovial T cells can be divided into several subsets that either promote or inhibit inflammation. Which population dominates may depend on the autoantigens recognized. These important observations indicate the value of antigens as modulators of RA. Both the administration of peptides that stimulate protective T cells and the administration of autoantigens to induce antigen-specific immune tolerance will eventually be investigated in human clinical trials.

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Electronic mail "E-mail" is the term given to communication across a network and, in its simplest form, is a text message with no predefined format. It can be read on the screen, filed, or printed as a text document. E-mail communications can be directed to one individual or another and will wait in the recipient's repository until he or she checks access to E-mail. This reduces the need for messages to be relayed by telephone and pager; thus reducing the number of interruptions experienced. It is also possible to direct an E-mail message to a number of individuals, when it will be deposited in several repositories. The Internet depends upon depositing messages in repositories to which numerous individuals have open access.

On the Internet, these areas are known as 'home-pages' and Internet 'sites'. Many Internet sites are accessible from one individual to another and will wait in the recipient's repository until he next makes access to E-mail. This reduces the need for messages to be relayed by telephone and pager; thus reducing the number of interruptions experienced. It is also possible to direct an E-mail message to a number of individuals, when it will be deposited in several repositories. The Internet depends upon depositing messages in repositories to which numerous individuals have open access.

On the Internet, these areas are known as 'home-pages' and Internet 'sites'. Many Internet sites are accessible.
to all users, but some sources of information, such as journals or university databases, are only accessible to authorized users. E-mail is not confined to simple text messages, and the communication can include graphics and other images, such as photographs and X-rays. A home-page may include the necessary program to help a user browse through its contents. If desired, information can be copied from the home-page onto the user’s personal computer. Home-pages are legion and, therefore, programs which access the Internet include methods to search for particular information. The Internet links many sources of information for clinicians and contains an increasing amount of information aimed at patients [1].

As well as being aware of the Internet, the profession should be aware of the benefits from more local networks which improve access to information at patient level and thus improve clinical care more directly. Ten years ago, 52% of rheumatology departments had computers which were mostly used for word processing or research [2]. By 1994, 93% of departments were found to use computers, mainly for secretarial work and audit [3]. The largest increase in users during this time was among secretaries [3]. Over the last 10 yr, use of computers in general practice has also increased [4] and there have been major developments in hospital information support systems. Several rheumatology departments are using locally developed systems for secretarial work, and to offer decision support for staff who monitor patients on disease-modifying anti-rheumatic drugs [5, 6].

What lessons can these experiences teach us and what new developments will support clinical care in the future? General practice computing is the most well researched of these areas. In 1995, a stringent meta-analysis of world reports of general practice computing from 1984 to 1994 was published [7]. Of 21 studies which examined clinician task performance, three showed an increase in vaccination rates when computers were used. In 11 of the studies, other preventative tasks (test ordering, physician and patient reminders, screening procedures) increased by as much as 50% when computers were used. Of the remaining seven studies: four examined physician prescribing practices and reported a reduction in prescribing costs, two were concerned with the management of diabetes and hypertension and showed an increase in appropriate monitoring, and one study demonstrated improved record keeping. Unfortunately, only one study measured clinical outcome; however, this study was able to demonstrate improved blood pressure control, with fewer visits to the surgery, when computers with decision support were used.

In secondary care, studies of North American hospital information support systems have shown that an easy to access display of past test results reduced testing by 13% [8]. In the San Francisco Medical Center, a computerized flow sheet summarizing care was generated by computer for patients attending a rheumatology clinic. Physicians using the computer-generated flow sheet were better able to predict patients’ future symptom changes and laboratory test results than those using paper medical records [9]. An evaluation of a computerized record at the University of Nebraska showed that secretaries and clerical staff were able to locate records and answer telephone queries more quickly than when they were using a paper system [10].

These studies suggest that computers support clinical care by providing easy access to aspects of the clinical record. It is also likely that delivery of care in rheumatology departments by junior medical and paramedical staff would be improved by access to prompts and guidelines, as has been demonstrated in general practice [7, 11]. What has not been demonstrated in the last 10 yr is the feasibility or desirability of a fully computerized medical record. There are two main reasons for this: one is the impossibility of devising a universal coding system for medicine capable of describing all areas of practice and all models of care [12]; and the second is concerns about possible misuse of data if all information about all patients was held in a structured database. The main fear about having medical data structured and accessible is that data may be collected and used for purposes other than for which consent was given [13].

In the future, computers will be used to improve communication within and between institutions, to improve access to information when care is being delivered, and for the long-term storage of summary information, numerical data and medical images [14]. The Internet or the NHS network could provide the medium for this and E-mail can provide an efficient dissemination system [15]. A recent circular from the Department of Health has outlined how this technology will be used to relay urgent communications to health professionals [16]. If information transmitted over a network is to be incorporated directly into a database, agreement on format is needed. The first standard for data interchange to be adopted by the NHS was EDIFACT (Electronic Data Interchange for Administration, Commerce and Transport) [17]. This standard has been used in UK general practice to transfer administrative data and laboratory reports [17].

Clinical computing has now come of age. Departmental systems exist which are able to demonstrate the benefits of saving all clinic letters on a word processor with facilities to search for information for purposes such as audit and research [5, 6]. Patient care can be improved by having systems that support users in tasks such as drug monitoring [5, 6]. E-mail and the Internet are now widely used for communication. Rheumatologists will need to improve their familiarity with computers in order to use them as tools to access information and organize care, but will need to maintain good clinical and scientific skills in order to make use of this technology.

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