Rheumatoid arthritis

A paradigm of inflammatory disease of the musculoskeletal system

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Where we stand today

The spectrum of disease

In the category of inflammatory rheumatic diseases we include local and systemic disorders that mainly affect anatomical structures of the musculoskeletal system as well as disorders in which symptoms and signs referable to the musculoskeletal system (arthralgia, arthritis, myalgia) are a prominent and constant feature of the disease. In the former group belong metabolic diseases such as gout, infections of joints and spine, reactive arthritis, rheumatoid arthritis and spondyloarthropathies; in the latter group are connective tissue diseases (*syn.* multisystem autoimmune diseases; connective tissue or collagen diseases) such as SLE, scleroderma, poly- (and dermato-) myositis, Sjögren's syndrome, polymalgia rheumatica; and systemic vasculitides, such as giant cell arteritis, Wegner's granulomatosis, polyarteritis nodosa, Henoch-Schoenlein syndrome and other forms of vasculitis. An essential component of these diseases is the presence of inflammation, as detected by the presence of the classical (Hippocratic) clinical features—i.e., dolor, calor, rubor and tumor—and characteristic tissue involvement as assessed by microscopic features—i.e., polymorphonuclear and/or mononuclear cell infiltration and activation, exudation of plasma proteins and variable degree of breakdown and regeneration of connective tissue cells and matrix. In this paper the focus will be on rheumatoid arthritis (RA).

Historical background

The definition of the different inflammatory diseases of the musculoskeletal system recognised as diagnostic entities today has been continuously evolving over the past two centuries. Clinical description of recurring patterns is the cornerstone of the original syndromal description. For example, as observed in adults, children or the elderly, with a gender predilection (rheumatoid arthritis in adult women, Still's disease in juveniles, gout in adult males, ankylosing spondylitis and polyarteritis nodosa in young males, giant cell arteritis in the elderly), with one, a few or many joints being involved. Usually the pathology and causation of diseases becomes incorporated in the criteria for classification later on—for example, the inclusion of synovitis, myositis, vasculitis as judged by histopathogical features; infectious causes being linked to causation on the basis of a microbiological diagnosis (direct isolation of bacteria, viruses from joints or from distant sites or detection of microbial antigen and specific humoral or cellular immune responses); or syndromes requiring the inclusion of the presence of autoantibodies with a high degree of diagnostic specificity (e.g., rheumatoid factor for RA and anti-DNA antibodies for SLE). The accuracy and reproducibility of disease classification usually requires a set of criteria to be formulated on the basis of retrospective data, validated and refined by prospective application in epidemiological studies and clinical trials. The American College of Rheumatology criteria for RA and SLE are examples of attempts at classification which have undergone major revisions and still leave room for further development (Arnett et al. 1987, Tan et al. 1982).

In regard to RA, it is of interest to scholars of the history of medicine that a credible description of this nosological entity, of unknown aetiology, began to appear in the European literature only in 17th and 18th century, with the term RA being coined by Garrod in 1859 (Garrod 1859). This relatively recent description has prompted the speculation that RA is a new disease (Short 1974), which, if true, does provide an argument in favour of the emergence of an environmental causative factor. Be that as it may, it is un-

deniable that the basket of classification into which RA was placed has been emptied over the past few decades of rheumatic diseases which are now recognised as nosological entities in their own right—for example, polyarticular gout, haemochromatosis, pyrophosphate arthropathies, the spondlyoarthropathies, chronic forms of reactive arthritis, chronic infections (of which Lyme disease is a striking recent example), polyarthritis of SLE, mixed connective tissue disease, scleroderma and Sjögren's syndrome. In the residual category of RA, arguments persist about the possibility of further heterogeneity. Heterogeneity in this context might suggest that each syndrome has a specific causation, different from the cause of others. Thus it has been suggested that persistently (rheumatoid factor) 'seronegative' disease is a different disease from 'seropositive' disease (the latter being more frequently associated with nodules, serositis, vasculitis, lung fibrosis etc.). However, it is equally possible that the presence of genetic factors—e.g., HLA-DR 'shared epitope', may explain such a difference in disease expression. If this was generally true then apparently different syndromes may result from a single causative agent. The trend towards diagnostic 'splitting', rather than 'lumping', could thus confound the search for aetiological agents, even though it is operationally useful in defining prognosis and guiding therapy.

Table 1. Incidence and prevalence of RA in different populations

Population		Incidence [a] per 1000 persons/year (range)	
Western Europe/ North Americans (whites)		Women 0.24–3.34	Men 0.1–1.50
		Prevalence [b] per 100 persons[c]	
Western Europe/ North Americans (whites)		0.8–1.1	
Amerindians (Chippewa, Pima)		5–8	
Chinese		0.3–0.4	
Parts of Nigeria		0–1	
South Africa	urban	0.9	
	rural	0.12	

[a] Definition: New cases occurring in a population during a defined period.
[b] Definition: The proportion of the population suffering from RA at a time point—including patients with past disease, now inactive.
[c] The ratio of female : male is approximately 2–3 : 1

Incidence and prevalence

The foregoing discussion gives an important perspective in the difficulties experienced in estimating the incidence and prevalence of RA and other inflammatory rheumatic diseases. The importance of obtaining accurate incidence and prevalence figures of these diseases lies in evaluating their burden in the individual and society. Such data ultimately influence judgements on allocation of currently available resources for research and provision of health care as well as planning for the future. However, even when robust and standardised diagnostic criteria have been applied, the true incidence and prevalence of these diseases may be subject to variation due to other factors. For example, estimates are influenced by the natural history and severity of disease, response to therapy, the age structure of populations and whether surveys are performed retrospectively or prospectively in the community or in the primary care settings or in hospitals.

The definition of incidence and prevalence of RA is shown in Table 1 (Isomaki 1989, Silman and Hochberg 1993, Symmons 1998). The incidence figures show up to a ten-fold variation, even in genetically similar Northern Europeans and US whites, thus supporting the contention that we are not dealing with an exact science. Such difficulties make it problematic to assess the veracity of the claims that the severity of RA and its incidence in women may be showing diminishing trends (Linos et al. 1980, Macgregor and Silman 1992, Jacobsson et al. 1994, Symmonds 1998) and whether there are geographic/ethnic differences. Clearly, better designed studies are still required. In contrast, the prevalence figures of RA show a degree of consistency in Northern Europe and amongst US whites with a cumulative life-time figure approaching 0.8% of the adult population and a two- to three-fold preponderance of females. The prevalence data also shows a remarkable increase in certain Amerindian tribes in the USA and lower figures in China, Indonesia and parts of Africa. Of note is the suggestion that in Southern Africa the prevalence of RA in urban blacks is similar to that in Europe and significantly higher than in rural blacks—again hinting at the importance of environmental factors.

Table 2 shows the relative incidence and prevalence data in Europe for rheumatic diseases, an approximation based on a published data. It emphasizes the great burden that RA places on the health of nations. However, it does not bring to the fore the widely held impression that SLE has higher prevalence rates in parts of Asia when compared with Europe, nor the intriguing possibility that people of common African descent, residing for several generations on American continent and in Caribbean islands, appear to have higher prevalence of SLE than their brethren in Africa.

Table 2. The relative incidence and prevalence of inflammatory rheumatic disease (north European)

	Incidence per 1000/yr	Prevalence per 100 adults
RA	0.24	1.0
SLE	0.04	0.03
Scleroderma	0.01	0.01
Ankylosing spondylitis	0.07	0.20
Psoriatic arthritis	–	0.02
Gout	1.0	–

Outcome

Contrary to previous beliefs, evidence has accumulated that RA is a chronic progressive disease with a significant morbidity and mortality, which once established, rarely shows any spontaneous long-lasting remissions. Recent studies emphasize the following points in relation to the prognosis and socioecomonic outcome of RA.

1. Following clinical presentation to specialist centres, disability occurs early and is progressive over the following 10–20 years (Jacoby et al. 1973). Thus, 50% of the patients already exhibit moderate disability in two years and are severely disabled by 10 years (Wolfe and Cathey 1991).
2. Radiological assessment, and more recently, other modalities of imaging, essentially confirm the above clinical conclusion and demonstrate an early development of significant decalcification and erosions of juxta-articular bone and loss of cartilage, with the maximum rate of change occurring in the first two to three years (van der Heijde et al. 1992).
3. Whilst the capacity to continue work employment is determined by the social and cultural background in which the patient lives, it is also related to the type of work, the age and the sex of the patient. The overall trend is for over 50% of patients in employment to become incapacitated within a decade of onset of disease (Markensen 1991).
4. Co-morbidity and a shortened life span due to increased susceptibility to cardiovascular disease, increased incidence of lymphoma, susceptibility to infections, renal failure and complications of drug therapy (e.g., gastropathy of NSAIDS) have been described in many studies. The increased mortality is especially seen in a subset of patients with severe polyarticular, nodular, seropositive disease with extra-articular manifestations (Pincus and Callahan 1993, Erhardt et al. 1989)
5. Prognostic factors which signal rapidity of functional deterioration and premature death include laboratory, clinical and other features, for example, a persistently raised level of acute phase proteins (ESR, C-reactive protein) rheumatoid factor positivity, cryoglobulinaemia, multiple joint involvement, lower socioeconomic status, and in patients of North European descent, the presence of a genetic marker, i.e., the 'shared epitope' (a pentapeptide) in the hypervariable region of the HLA-DR ß chain (present in some subtypes of HLA-DR4 and DR1), especially when present (as a double gene dose) on both pairs of chromosome 6.
6. Quality of life has been defined by WHO as "complete physical, psychological and social well being". It is clear that the health status of patients with RA is impaired in all these areas. Various instruments of measurement have been employed in the assessment of RA (e.g., health assessment questionnaires) which evaluate the degree of physical impairment and psychological well being (fatigue, depression, self image etc.) (Fries 1983, Fries 1991, Bellamy et al. 1995, Kind 1996). Not only do these provide a 'map' of the natural history of RA and the path of progression of the individual, but they provide subjective and objective criteria for evaluation of drug therapies.
7. The understanding of pharmacoeconomics of RA is becoming an increasingly important subject of study as growing pressure on medical resources and innovations in management are applied to preserve the quality of life of patients (Fries et al. 1995, Kavanaugh et al. 1996). Medical costs not only include the cost of drugs, salary of doctors, laboratory tests, imaging of joints, hospital in-patient treatment and involvement of the allied health professional team (physiotherapist, occupational therapist, psychologist, nurse) but also overhead costs of administration, aids and appliances, education and implementation of new developments. There is a growing appreciation that in a chronic disease such as RA, as disease progresses, we should also include the costs of surgical interventions, rehabilitation and provision of care provided in the community (home help, mobility allowance, full time care). All this against a background of escalation indirect and intangible costs—e.g., unemployment benefits, social isolation, anxiety, depression, pressure on family life and loss of dignity.
8. Both for quality of life and pharmacoeconmics, the concept of "cumulative loss" and "cumulative cost" has been emphasized. In other words, the temporal dimension over the two to three decades of disease has to be addressed in calculations and gives a truer picture of the immensity of the strategic problem, than an assessment dictated by the need for balancing of annual budgets of the social welfare and insurance agencies.

Aetiopathogenesis of RA

Our knowledge of the aetiopathogenesis of RA may be divided into three critical components summarised in Table 3: 1) what is known about the initiation of disease?; 2) what factors explain perpetuation and chronicity of RA; and 3) the molecular pathology of inflammation and tissue damage? For reviews see Harris 1990, Feldmann et al. 1996, Maini and Feldmann 1998a, Maini and Feldmann 1998b.

Diagnosis, assessment of disease activity and damage

Criteria for the diagnosis of RA combine a constellation of clinical, serological and radiological features. The first widely used criteria were formulated by the American Rheumatism Association (ARA) in 1956, and revised in 1958 (Ropes et al 1958). The American College of Rheumatology (ACR), the successor to ARA, responded to continuing criticism by a further set of revised criteria in 1987 (Arnett et al. 1988). Ten years on, these criteria still have critics, especially in the setting of diagnosing RA with a high degree of certainty within a few weeks of onset of symptoms. Moreover, since these criteria require a test for rheumatoid factor and radiological changes, they are not readily applicable on a large scale in epidemiological settings and do not permit inclusion of inactive disease. For these reasons other criteria were developed in the past e.g., Rome criteria and New York criteria—but these have not gained widespread usage.

The occurrence of autoantibodies in the serum of RA patients has encouraged the view that an autoantibody with a higher degree of sensitivity and specificity than obtained with rheumatoid factor, may prove to be a disease-specific marker. Anti-perinuclear antibody detected on a buccal epithelial smears and antikeratin antibodies reactive with keratinized cells of rat oesophagus may possess these characteristics and indeed, have been described in apparently healthy individuals who developed RA many years later on. However, the criteria substrates and tests are difficult to standardise and perform (van Venrooij and Maini 1993). Recently it has been shown the relevant antigen may be (pro-)fillagrin and that citrulline substitutions of its peptides in ELISA tests gave a promising degree of sensitivity and specificity (Schellekens et al. 1998)

A plethora of evaluations of disease activity, health status measurements and direct (by imaging) and indirect measurements of tissue damage (by laboratory tests) of connective tissue in cartilage and bone, have been described. Efforts are being made by ACR (Felson et al. 1995) and the European League Against Rheumatism (van Gestel et al. 1996) to develop a standardised 'core set' that is able to be used for serial measurements in monitoring the progress of patients predicting outcomes in clinical practise, and be applicable to clinical trials. It is desirable that such criteria should be able to *discriminate* deviations from the natural history of RA and *quantify* changes in disease activity, remission or progression of tissue damage and the health status of the individual. It is increasingly necessary to simultaneously evaluate iatrogenic

Table 3. Aetiopathogenesis of RA

I. Initiation

- *A disease of unknown aetiology* in which genetic and non-genetic (including environmental) factors interact.
- *A 'prodromal' (pre-symptomatic) phase* may be detectable by immunological tests (e.g. to autoantigens).
- *Genetic factors* strongly suggested by population, family, sibling and twin studies; account for ~ 30% of susceptibility; genetic mutations occur in B lymphocytes and in p53 tumor suppressor gene in synovium during evolution of disease process.
- *Environmental factors:* no clustering; length of incubation period unknown; bacterial and viral causes suspected; RA-like disease recorded in a few instances following rubella and parvovirus infection.

II. Perpetuation and chronicity

- *Immune response* regarded as pivotal in establishing chronicity; concept of 'molecular mimicry' between foreign (microbial) antigen and autoantigen reacting with CD4+ T cell as the basis of autoimmunity; loss of T cell tolerance; recognition of cryptogenic epitopes and epitope spreading may explain the observed oligoclonal/polyclonal response: Th1 responses dominate over Th2.
- *T cell autoantigens* not yet identified: candidates include collagen II, chrondrocyte glycoprotein 39, heat shock protein; antigen restricted to cartilage might explain localisation;
- *Autoantibodies* to IgG-Fc (rheumatoid factors), RA-33, anti-perinuclear, anti-fillagrin, anti-citrullinated peptides show diagnostic specificity - role in pathogenesis not certain.
- *Immune response drives inflammation.*

III. Inflammation and tissue damage

- *Chronic inflammation* characterized by angiogenesis; activation of lymphoid cells and macrophages in the synovium; pannus formation; and loss of cartilage and bone.
- *Increased cell mass* mainly a result of haematopoietic cell accumulation and a limited degree of mesenchymal cell proliferation.
- *Mesenchymal cells* intimately involved in tissue destruction.
- *Many pro-inflammatory and anti-inflammatory cytokines* are expressed; lack of balance between these favours disease process; evidence of 'hierarchy' with TNFα and IL-1 at apex; multiple cytokines regulate traffic of cells to joints, their activation, cell apoptosis, cellular and cell: matrix interactions, angiogenesis and production of mediators of tissue damage.
- *Other inflammatory molecules* include prostaglandins, matrix metalloproteinases, free radicals, nitric oxide.

Table 4. Current drugs used in the treatment of RA

I. *Analgesics:* e.g., paracetamol and rarely opiates. Used as adjunctive therapy, especially in the later phases of RA when mechanical derangement significantly contributes to pain and discomfort.
II. *Non-steroidal anti-inflammatory drugs (NSAIDs):* Extensively used; gastropathy, renal and other side-effects contribute to significant morbidity and mortality, especially in the elderly. Proton-pump inhibitors, H2-blocking agents, prostaglandin analogues increasingly used to counteract side effects - add to costs. Cox-II inhibitors in development may reduce toxicity but increase cost without gains in efficacy.
III. *Corticosteroids:* Effective anti-inflammatory effect, in low dose appear to retard cartilage and bone destruction in affected joints; side-effects such as osteoporosis, hypertension, diabetes, severely limit long-term use.
IV. *Disease-modifying drugs (DMARDs):* (Syn. slow acting anti-rheumatoid drug; second-line anti-rheumatic drugs). Examples include methotrexate, sulphasalazine, injectable gold, auranofin, D-penicillamine, azathioprine, cyclosporin, hydroxychloroquine.

risk and value for money of all management strategies of the present and future.

Current therapies

The traditional approach to treating RA (the pyramid), relied on the premise that no drug therapy cured the disease. Thus treatment was centred on the use of NSAIDs and, in the most serious cases, a cautious and judicious use of corticosteroids and disease modifying anti-rheumatic drugs (DMARDs). A list of the category drugs is shown in Table 4. The radical change in outlook over the past decade has instead emphasized the philosophy that aggressive control of disease activity as early as possible using monotherapy with a DMARD (and possibly low dose corticosteroids), achieves better control of the disease with a better short and long term result with a drug toxicity profile comparable to, or even better than, that obtained with the traditional approach. However, it is uncertain whether early intervention prevents the ultimate course of joint damage and loss of response to one DMARD after another usually follows in 1 to 5 years, even with methotrexate, the drug with the best record (Felson et al. 1992, van de Putte and van Riel 1997). Current trials are seeking to examine the benefit and toxicity of *combinations* of 2 or more DMARDs usually combined with corticosteroids with the aim of demonstrating better results than obtained with the inevitable progression of using one DMARD followed by another (Tugwell et al. 1995, O'Dell et al 1996, Boers et al. 1997). The trials do suggest that a greater proportion of patients with continuing disease activity respond to such measures in the short-term. Whether such combinations will offer a better long-term outcome for all patients if introduced early in the course of disease is unknown at present. Combinations are increasingly being used in the management of refractory cases of RA.

New therapeutic modalities—the rational biological approach

The advances in knowledge of the aetiopathogenesis of RA has led to an expectation that rational new treatments and preventative strategies will become available. The past 6 to 7 years have indeed demonstrated a great deal of enthusiasm for the application of biological therapies, and they are providing powerful means for testing the proof of biological principles based on *in vitro* observations and experience in animal models of RA. Thus far, most of the experience has been in Phase I/II trials and the most impressive results have been with anti-TNF agents (monoclonal antibodies and soluble TNF-receptors (both p55 and p75) fused to the constant region of IgG). Topical reviews are readily accessible in the literature. A summary is given in Table 5 (Harris 1990, Feldmann et al. 1997, Maini and Feldmann 1998a)

Future perspectives

- The key goal of the next decade in regard to RA must be to arrest the disease, restore health and develop preventive measures.
- The most promising and rewarding areas of research need to be highlighted and given priority for research and development.
- Talented researchers and health care providers need to be attracted to the field of work.
- A much greater investment in basic research is required, coupled with long-term funding of epidemiological and clinical research. Much of this funding is likely to arise from governmental and charitable sources. However, since the translation of research into clinical practice is also driven by the biotechnology and pharmaceutical industry, the roles of each of the constituencies has to be better understood and partnership fostered.

An agenda for the next decade might include some of the following:

1. In the epidemiological area, to obtain a definitive data on the incidence and prevalence of RA in different regions and countries in the world. Such information will highlight whether marked differences exist and whether there are indeed any trends in reduction of the incidence of RA. Emphasis on data

Table 5. Biologicals in trials in RA

Target	Biological	Company	Comment
T cells: Monoclonal antibodies (Mab)			
CD5	Anti-CD5-Ricin Mab	Xoma	Promising Phase I; unconvincing RCT; discontinued
CD7	Anti-CD7 Mab	Sandoz	No therapeutic effect, T cell reduction; discontinued
CD4	Anti-CD4 Mab	Centocor	Depleting antibody; no convincing effect in RCT
CD4	Anti-CD4 Mab	Johnson & Johnson	Efficacy in dose-ranging study
CD4	Anti-CD4 Mab	SmithKline Beecham	Non-depleting in early RCT, later found to be depleting; efficacy trials continue
CD4	Anti-CD4 Mab	GlaxoWellcome	Non-depleting; efficacy in Phase I/II trial. Trials continue
T cells: Non-antibody			
CD25	IL2-DAB	Seragen	Toxic, discontinued
TCR	Peptides of Vß3, 14, 17	Immune Response Corp	Continuing
T cells	Oral collagen II	Autoimmune	Efficacy in phase II; continuing trials
Cytokines: Proinflammatory			
TNFα	Anti-TNFα Mab (cA2, Avakine)	Centocor	Effective in single and multiple dosing in RCT (Phase II) Phase III ongoing
TNFα	Anti-TNFα Mab (CDP571)	Celltech	Dose-ranging Phase I/II effective; ?continuing trials
TNFα/β	p75-TNF-R-IgG (Enbrel)	Immunex	Effective in RCT Phase II/III trials; continuing
TNFα/β	p55-TNF-R-IgG (Lenercept)	Roche	Phase I/II efficacy in some (not other) trials, discontinued
IL-6R	Anti-IL-6R Mab	Chugai	Phase I in progress
IL-1	IL-1ra	Amgen	Phase II, III, efficacy in RCT; continuing
Cytokines: Anti-inflammatory			
IL-10	rhuIL-10	Schering Plough	Efficacy in Phase I/II; Phase II RCT continuing
IL-4	rhuIL-4	Schering Plough	Phase I/II study in progress
IL-11	rhuIL-11	Genetics Institue	Early Phase I/II trials

to illuminate the part played by genetic and non-genetic factors may yield important clues on disease causation and, hence, on preventive strategies.

2. There is a need for more extensive studies on the quality of life of RA patients at different stages of disease and over the lifetime of the disease. It is still necessary to ascertain the degree to which access to specialist care impacts on both short-term and long-term outcome. It is to be expected that such information is the baseline which permits comparisons to be made of the efficacy of different management strategies.
3. Having identified the determinants of the cumulative costs of RA over the lifetime of RA patients - i.e., direct, indirect and intangible costs - data is required of the current cost. Such information is necessary to support a case for improved health care not only for these communities in regions of one nation currently receiving sub-optimal care, but also for nations where insufficient resources directed towards rheumatic diseases. Such data is also necessary to evaluate the relative cost benefit of new therapeutic modalities (e.g., biological therapies) which might be introduced in the near future and are potentially very expensive.
4. Utilizing the new biotechnological advances is a key area of research and development. Thus it can be confidently predicted that information from the human genome project, the application of genechip technology for identifying the products of multiple genes, as well as technology of defining proteins expressed by cells and tissues from joints, blood and other organs from RA patients, will provide insight into the genetics and pathophysiology of RA at the molecular level. However, to be successful in yielding meaningful results, these studies require systematic collection and study of tissues from clinically well characterized sources, including that from families and twins of RA patients. It may be safely assumed that preventive and therapeutic advances are likely to result from such initiatives.
5. Hypothesis testing by specific biological therapy - e.g., anti-cytokine and anti-T-cell therapy is already with us. By understanding the role of the immune system and cytokines in model systems and in patients, it should be possible to aim to not only use antagonists and agonists to block an excess or correct a deficiency of a putative molecule, but to restore homeostasis by reprogramming inter- or intracellular signals.
6. Hitherto therapeutic biologicals have been delivered as proteins. 'Gene therapy', by delivery of DNA to tissues where tissue specific transcription may be regulated at will, is on the threshold of dis-

covery (Chernajovsky et al. 1995). This should enable the delivery of the therapeutic molecules to the site of the disease process such as the joint or lymphoid system.

7. Stem cell therapy (Tyndall and Gratwohl 1996) and tissue engineering are developing in the wake of accumulating knowledge on the factors involved in growth and differentiation of cells and their organisation into specific tissues. Repopulation of damaged cartilage and bone depleted of chondrocytes and bone cells (i.e., tissue repair) may prove feasible in the foreseeable future.

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