 *Clinical Medicine* 2010, Vol 10, No 2: 156–63

# Career lifetime advances in rheumatology

David L Scott

## Background

My first rheumatology clinic was undertaken as a senior house officer working under the direction of the late Professor Verna Wright in Leeds. My most recent clinic was undertaken as a senior academic rheumatologist in London. Over the years I have changed significantly but the overall tenor of the clinics has stayed remarkably similar. I see about the same number of patients, their problems are much the same and the good and bad things about clinics themselves have not greatly altered. On a very superficial level it seems as if not much is different.

Yet the whole ethos and practice of rheumatology has been revolutionised during my professional lifetime. My formative years were spent looking after patients in spa hospitals such as the Royal Bath Hospital in Harrogate and the two specialist rheumatology hospitals at Droitwich Spa. I cannot recall the last time I needed to admit anyone for inpatient treatment and the idea of bed rest of six weeks for rheumatoid arthritis (RA), which was a standard regimen during my training, seems antediluvian.

Not all changes are advances. The way care is organised reflects many tensions within the medical profession and is not influenced by technical advances alone. The concept of rheumatology being practised outside the mainstream of medicine, which was part of the spa hospital approach, has certainly vanished. However, I have practised as a general physician, a specialist rheumatologist and a pure rheumatologist, and the relative merits of each approach seem to be finely balanced. Changes in division between primary and secondary care sectors and pressures to involve a broader range of experts in looking after musculoskeletal disease, including more active roles for physiotherapists, are likely to impact on the next few years of clinical practice in rheumatology. At present, it is difficult to know what impact these will have at an individual or global level. However, changes are inevitable.

The main advances can be divided into four broad spheres. Firstly, there are new investigations. Secondly, there are new treatments. Thirdly, there are new diseases, or perhaps new names for old diseases. Finally, as a consequence of these, there have been some differences in the patients referred for specialist advice.

## Musculoskeletal imaging

Without doubt the largest change that can be directly attributed to advances is access to new imaging modalities. Plain X-rays, which are now fully digitised and never come as films, remain the mainstay of musculoskeletal imaging. However, access to magnetic resonance imaging (MRI) and, more recently, the ready availability of musculoskeletal ultrasound has had major effects on clinical rheumatology. The importance of MRI was recognised by the award of a Nobel prize; ultrasound, though equally important, is unlikely to attract such scientific accolades.[1]

Many patients with serious back problems expect to have an MRI and the ability to image disc disease and identify a range of soft tissue problems involving the spine remains a remarkable achievement. Spinal MRI shows a range of pathologies. Rarely a month goes by without it revealing an important and often unsuspected finding. Yet its many advantages must be carefully weighed against the problems in defining normality; it is well known that not all disc protrusions are clinically relevant and in many patients with chronic back pain MRI results do not change their management.[2–4] As a consequence, despite the remarkable diagnostic power of MRI, its role in everyday care must remain a topic of ongoing evaluation.

Musculoskeletal ultrasound is likely to have comparable advances in defining the severity of synovitis in RA and for showing the underlying structural changes in patients with unilateral shoulder pain.[5] New entrants to rheumatology are likely to press to be trained in these exciting imaging modalities.

## Immunological investigations

A far more extensive range of immunological tests that have known associations with better defined rheumatic disorders can now be ordered. In RA class-specific IgM and IgA rheumatoid factors are often used and more specific tests for anti-cyclic citrullinated peptide antibodies (CCP) are available.[6] In connective tissue diseases there have been even more developments including the introduction of more specific tests for DNA antibodies, for a range of extractable nuclear antigens and for anti-neutrophil cytoplasmic antibodies (ANCA) and cardiolipin antibodies.[7,8] The increased numbers of immunological tests has allowed far more accurate classification of patients' disorders. Some syndromes, such as anti-cardiolipin antibody syndrome often affectionately termed Hughes syndrome after its greatest advocate, have had marked popularity. Other syndromes, particularly mixed connective tissue disease, are now rarely diagnosed and appear unfashionable. There remains some doubt about the value of too many subdivisions as the evidence base supporting different treatment strategies is either incomplete or absent.

Some investigations that seemed of critical importance when I was training, such as identifying immune complexes, have vanished; they are rarely, if ever, requested. Other tests, such as the routine assessment of serum amyloid A protein, which seemed to

**David L Scott,** professor of clinical rheumatology, Department of Rheumatology, King's College London School of Medicine

 

offer advantages over more established investigations like C-reactive protein levels, have fallen out of favour and their benefits ultimately proved to be illusory.[9]

## Disease modifying drugs

The main focus of rheumatologists remains inflammatory arthritis and its treatment has dramatically improved in the last decade.[10] One change has been the introduction of new disease modifying anti-rheumatic drugs. Historically, gold and penicillamine were the dominant treatments for RA. Both had modest benefits, caused many unpleasant side effects and were called slow-acting drugs.

The first change, and probably the most important innovation of all, has been the widespread use of methotrexate at higher doses with more intensive treatment regimens favoured.[11] Methotrexate reduces joint inflammation, decreases overall disease activity and even lessens the risks of extra-articular disease and comorbidities.[12] Early methotrexate treatment is now the mainstay of managing inflammatory arthritis. It is not a new drug, as it has been used for over 50 years, but its increased use represents a new approach with an established agent.

A second change has been the introduction of new disease modifying drugs. Leflunomide is the best example. It has been used since the late 1990s and is effective and well tolerated.[13] It is probably less effective and less widely used than methotrexate but it is nonetheless a significant advance.

Finally, there has been the rise of combination therapy using two or more disease modifying drugs at the same time.[14] Many different combinations are effective, though a widely used approach is to use methotrexate with sulfasalazine and hydroxychloroquine, which is often termed 'triple therapy'.

The greater intensity of current treatments with disease modifying drugs and their use earlier in the course of RA has greatly improved the overall outcome of the disease. Patients live longer and have less extra-articular disease.

## Biologics

The advances with disease modifying drugs have been relatively slow and low key. By contrast the impact of biologics has been dramatic and very high profile. Tumour necrosis factor (TNF) inhibitors, which were developed on the basis of very innovative work from Maini and colleagues at the Kennedy Institute of Rheumatology in London, have set the pace over the last decade.[15] It is difficult to recall the problems for severe RA prior to the introduction of these new approaches. They are highly effective, rapidly active and improve both arthritis and overall health. Patients and clinicians have been given a clear sense that treatment has genuinely advanced and the tenor of clinical practice has moved forward.

Other biologics have followed in the steps of TNF inhibitors. One alternative treatment is B-cell inhibition with rituximab.[16] Other approaches interfere with T-cell function and inhibit other cytokines such as interleukin-6.[17]

It would be naive to assume biologics were the answer to inflammatory arthritis or that they were without problems. These are very expensive treatments that can have equally dramatic adverse effects, particularly the risk of severe infection. Not all biologics have been so effective in RA; for example, interleukin-1 inhibition appears to have very limited benefits.[18] However, the overall impact of these agents has been dramatic.

## Anti-inflammatory drugs

Compared with disease modifying drugs and biologics the development of anti-inflammatory drugs has been less straightforward. The identification of their mode of action by Sir John Vane, which was one of the few rheumatological advances to lead directly to a Nobel prize, revolutionised our understanding of how these drugs work.[19]

Over the years many non-steroidal anti-inflammatory drugs have been developed; indomethacin, naproxen, diclofenac and celecoxib exemplify drugs I and many other rheumatologists have widely used. They all reduce pain and stiffness, though their benefits are incomplete; all also have a range of adverse events. Patients naturally seek drugs that are highly effective and can be taken infrequently. However, they also want drugs that are safe, and these two requirements are somewhat contradictory.[20]

For many years gastrointestinal ulcers were the Achilles heel of these drugs. Understanding COX-1 and COX-2, which was a direct result of the Vane hypothesis, led to the development of theoretically safer COXIBs like celecoxib. For a while these safer anti-inflammatory drugs dominated rheumatology. However, cardiovascular toxicity with some COXIBs, particularly the risks of cardiac infarctions, and liver toxicity with other COXIBs has dulled their earlier lustre.[21] Though they are still widely used their limitations are now more readily appreciated and patients are less enthusiastic.

## Fibromyalgia

Changing views on how best to classify rheumatic diseases never create the same scientific excitement as understanding pathogenesis. Yet it can have major impacts on how we practice and the way we deal with our patients. Over the last 10 to 20 years there has been a growing interest and focus on chronic pain and the emergence of fibromyalgia as a common rheumatic disease. Although chronic widespread pain and terms such as fibrositis have a long history it was only in the 1990s, with the publication of classification criteria, that the diagnosis of fibromyalgia came into its own.[22] Whether it is a disease in the true sense of the word or simply a constellation of symptoms remains debatable. Nevertheless I now frequently diagnose fibromyalgia and it has entered the lexicon of established diseases.

In very recent times the rise of new imaging techniques, particularly functional MRI, has enabled the central processing of pain to be captured digitally.[23] So far this technique remains within the boundaries of clinical research, but it is likely to spill over into routine practice in the near future. It shows that fibromyalgic pain

is a genuine and readily identifiable problem and indicates how it responds to a range of treatments.

Not all new diseases stand the test of time, and many vanish into obscurity after an initial flourish. Though fibromyalgia is here to stay other musculoskeletal disorders that first came to attention at about the same time have lost credibility. A good example is repetitive strain injury (RSI). This was a 'fashionable' diagnosis in the 1990s and for a while reached almost epidemic proportions before sinking out of sight. Workplace problems affecting the musculoskeletal system still occur but they are not merely a reflection of RSI. Hence new diagnostic classifications only last if they have a credible clinical base.

## The disappearance of secondary amyloidosis

When I was training secondary amyloidosis was a dreaded consequence of longstanding severe arthritis. It was not common but it was devastating. Yet in the last decade I do not think I have seen a single case. I have no doubt that this change reflects the impact of treating RA and other forms of inflammatory joint disease more intensively with disease modifying drugs. There may be other less obvious reasons but as the reasons why a problem has vanished are of less interest than the reasons for a new disease developing, the issue is not much researched.

## Moving polymyalgia rheumatica into primary care

Twenty years ago a substantial number of new referrals had previously undiagnosed polymyalgia rheumatica. These patients were easy to identify clinically and responded well to low dose steroids. Today I rarely see them, not because the disease has vanished but in the main on account of the disorder being recognised and treated in primary care. This is a substantial advance from the perspective of good patient care. As polymyalgia is a circumscribed clinical syndrome that usually responds rapidly and completely to treatment, its adoption by general practitioners seems highly appropriate. The extent to which other diseases will mainly be dealt with in primary care is uncertain at present but it is bound to be a key issue in determining the future of the specialty.

## Looking forward

It is always harder to know what is coming than to describe what has passed. White coats have long gone from my practice and I anticipate jackets and ties will soon follow. Fountain pens and notes have also been replaced by a digital world of email, electronic patient records and computer images of X-rays. I cannot, however, envisage tête-à-tête discussions with patients being lost as the basis for consultation.

One great uncertainty is the impact of predictive markers in general and genetic markers in particular. Though many genes can be rapidly analysed using chip technology I have never heard of this approach being used in routine care. Despite many future visions focusing on using genomics to guide treatment decisions, I doubt it will happen anytime soon.

Until now most rheumatologists have been generalists, albeit with some areas of interest. This contrasts with the orthopaedic surgeons who over the last decade have focused on individual joints or specific treatment areas, with a significant rise in standards appearing as an apparent consequence. I think the concept of the general rheumatologist may be reaching a crossroads and the rise of the super specialist seems inevitable.

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**Address for correspondence: Professor DL Scott, Department of Rheumatology, King's College London School of Medicine, Weston Education Centre, King's College, 10 Cutcombe Road, London SE5 9RS.**
**Email: d.scott1@nhs.net**

## CURRENT KEY DEVELOPMENTS

# Revitalising glucocorticoids for (rheumatoid) arthritis

**John R Kirwan,** *professor of rheumatic diseases, University of Bristol, Academic Rheumatology Unit, Bristol Royal Infirmary*

Email: John.Kirwan@Bristol.ac.uk

Glucocorticoids (also called corticosteroids or steroids) have been used to treat rheumatoid arthritis (RA) ever since they were discovered in 1948.[1] They have a potent anti-inflammatory effect, and even in low doses (7.5 mg daily prednisolone or equivalent) they can control the symptoms of inflammation more effectively than non-steroidal anti-inflammatory drugs for a few weeks or a few months.[2,3] This makes them a useful treatment in the short to medium term, but it is likely that the benefit wears off after a year or so.[4] Concerns about potential adverse effects (which are widespread when high doses are used) meant that for many years in the 1970s and 1980s they were advocated only for short courses to treat severe exacerbations or 'flares' of inflammation. The position was unsatisfactory – publicly rheumatologists declared their intention to avoid glucocorticoids, but in practice many patients were being treated with them.[5]

In the last 15 years strong evidence has emerged for an additional, fundamental effect of glucocorticoids on the disease process in RA, while in the last five years novel formulations of glucocorticoids have revitalised interest in their wider potential:

- there is now incontrovertible evidence that they are disease modifying agents with the power to halt the destructive changes of RA
- short exposure to high dose glucocorticoid (followed by low dose) can control the overall clinical picture just as effectively as modern (and very expensive) anti-tumour necrosis factor (TNF) 'biologic' drugs
- this positive effect on arthritis may persist even several years after the treatment has been stopped, leading to the exciting possibility that there is an opportunity to have a long-lasting effect on the disease process following an early intervention
- new formulations of glucocorticoids are being tested for their ability to enhance therapeutic effects while avoiding adverse effects
- the potential for selective glucocorticoid agonists is emerging from a greater understanding of cellular mechanisms of action.

Although a number of early trials in the 1950s and 1960s had hinted at the ability of glucocorticoids to control joint destruction, this was not established with confidence until 1995 by the ARC Low Dose Glucocorticoid study and the 1997 COBRA study.[5,6] In the first, adding 7.5 mg prednisolone daily to standard treatment with disease modifying drugs substantially