In 1802, William Heberden produced a treatise on the history and cure of diseases [1]. In this book, which enhanced his reputation as one of the major physicians of his time and led people like Sir William Osler to refer to Heberden as the English Celsius [2], he talked extensively of the treatment of rheumatic complaints with a range of concoctions from Portland powder to Peruvian bark. Heberden’s strength at that time was to rage against accepted (but unproven) therapies such as theriaca and ask that evidence be produced for their use. In short, he was one of the early proponents of evidence-based medicine.

Over the past 25 yr, we have seen enormous changes in our understanding of rheumatoid arthritis (RA). This has stemmed much from a careful dissection of the aetiopathogenesis of the disease, providing us with a relatively clear indication of how we might interfere in this inflammatory cascade to provide relief for our patients [3, 4] (Fig. 1). Although the exact aetiological factor(s) [5] causing RA remains elusive, we understand much more about the early events in cell activation, the interplay of a variety of cytokines and other substances, and the interaction of T and B cells. It is also likely that there is both an initiating event and a perpetuation of the inflammatory response probably dependent on different factors which are important for joint destruction. The genetic predisposition to RA and the roles that HLA DR3, 4 and the hypervariable region play in determining the severity of disease are also important [5].

In this oration, I wish to address a number of treatment issues and try to see what we can learn from the ‘therapeutic’ past to help us plan for the future. Our interventions, and in particular their potency, should be predicated to some extent on the impact that the disease has on the individual and on society because it is that which provides us with an indication of the risk and benefit.

OUTCOME OF RHEUMATOID ARTHRITIS

Over the last decade, it has been appreciated that RA is an extraordinarily aggressive disease. Not only does it cause significant disability, with 50% of patients being unable to hold down a full-time job within 10 yr of getting the disease, but it also causes significant mortality [6]. It has been estimated that between 3 and 7 yr are taken off the life of the person with RA, although the exact reason for this decrease in lifespan is not clear [7, 8]. In large part, this is due to an increase in renal and cardiovascular disease, which may well be a consequence of treatment rather than the disease itself. These data suggest that active RA has a similar mortality to diabetes, Hodgkin’s disease or to three-vessel coronary artery disease [9, 10].

Patients with RA become severely disabled over a period of 20 yr with out-patients having a 30% chance of disability and patients requiring in-patient care an 80% chance.

In terms of resource utilization, we know that RA is responsible for a significant number of visits to specialists, that patients with RA use an increased number of hospital bed days as well as community resources, and the cost of these is significant [11]. The total costs of musculoskeletal disease in the USA are estimated to be $150 billion, while in Britain £1.25 billion was estimated to be spent on RA in 1992–93 with a direct cost of £600 million [12]. Hospitalization made up 30% of this, nursing home help 25% and the cost of drugs was 15%. Pharmaceutical costs for RA are likely to escalate significantly with the increasing emphasis on relatively expensive therapies such as the
biologics and the more intensive monitoring of treatments [13].

There has been an appreciation over the last decade that the majority of patients with a definite diagnosis of RA will develop erosive disease over time and that if erosions are going to occur they will occur relatively early (within the first 2 yr) [14, 15]. This has been emphasized by people like Paul Emery promoting the concept that RA is 'an acute medical emergency' and needs to be treated aggressively right from the start [16].

The challenge for rheumatologists is to develop simple predictive models to indicate which patients with inflammatory arthritis will go on to develop severe erosive disease. To this end, the recent interest in the establishment of early arthritis clinics [16] and the development of cohorts of these patients [17, 18] will be very important. It does seem that few patients who have persisting synovitis after 3 months resolve spontaneously, and that the determinants of prognosis for disability and radiological progression may be different [19]. These determinants are likely to include clinical features and laboratory tests including genetic markers (see Table I). For example, Gough et al. [20] have shown that the possession of either rheumatoid factor or the genetically determined shared epitope provides a relative risk of 13.5 of developing erosions with a high sensitivity (95%) but a low specificity (40%). Functional assessments are also important in determining disability, although interactions with psychological and socioeconomic factors and other co-morbidities need to be explored [21]. Further studies need to be carried out to define predictors of poor prognosis and response to therapy.

Data presented recently suggest that erosive change or cartilage damage may be present on MRI prior to any clinical evidence of synovitis [22]. Use of osteodensitometry (DEXA) clearly shows that bone loss occurs at an early stage in inflammatory arthritis, emphasizing the aggressiveness of the pathology and the need for early intervention [23].

PHARMACOLOGICAL INTERVENTION

Currently available medications for the treatment of RA are shown in Table II. The categorization of these drugs is arbitrary to a great extent and clear definitions do not exist. A more functional classification suggested by Edmonds et al. [24] has not been widely adopted, but does provide a better framework for testing these drugs (see Table III).

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Factors thought to determine prognosis in RA</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>Gender</td>
<td>Acute-phase reactants</td>
</tr>
<tr>
<td>Degree of joint involvement</td>
<td>Rheumatoid factor</td>
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<tr>
<td>Functional status</td>
<td>HLA-DRβ1 shared epitope</td>
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<tr>
<td>Type of onset</td>
<td></td>
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<td>Social and educational status</td>
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**TABLE II**

Currently available pharmacological interventions for RA

| Analgesics |
| Non-steroidal anti-inflammatory drugs (NSAIDs) |
| Anti-rheumatic drugs (SAARDs, DMARDs, TARTs) |
| Corticosteroids |
| Immunomodulatory drugs |

**TABLE III**

Proposed classification of anti-rheumatic therapies (from Edmonds et al. [24])

1. Symptom-modifying anti-rheumatic drugs (SMARDs)
   - These improve symptoms and clinical features of inflammatory synovitis
     - Non-steroidal anti-inflammatory drugs (NSAIDs)
     - Corticosteroids
     - Slower acting drugs, e.g. antimalarials, sulphasalazine, gold, d-penicillamine, cytotoxic agents (category 111 SMARDs)

2. Disease-controlling anti-rheumatic therapy (DC-ART)
   - These drugs change the course of RA, i.e. they both
     - improve and sustain function in association with decreased inflammatory synovitis, and
     - prevent or significantly decrease the rate of progression of structural joint damage.
   - These changes must be sustained for a minimum of 1 yr, the classification must include reference to the time period for which criteria have been satisfied, e.g. 2 yr DC-ART

Addendum: Most category 111 SMARDs also have a claim to be classified as DC-ART.

**NSAIDs**

Non-steroidal anti-inflammatory drugs (NSAIDs) still make up the most commonly prescribed group of drugs around the world. Some 300 million people take an NSAID each year, of whom 100 million obtain the medication on prescription and 200 million purchase it directly over the counter. The total cost of these preparations is in the order of US$13 billion per annum. Consumption of NSAIDs between countries still varies significantly, as demonstrated by McManus et al. [25] (Fig. 2), and there is no reason why this should occur. In some countries (Australia in particular) a significant decrease in NSAID use has occurred over the last 5 yr. This, in part, has been due to an aggressive campaign by the government to highlight adverse effects of NSAIDs, but also to some changes in the co-payment (government contribution) structure. NSAIDs still have a range of plasma half-lives and other pharmacokinetic differences, although the individual variability in response that is well known by rheumatologists does not seem to be clearly explained by dose or pharmacokinetic parameters alone [26]. An important aspect of NSAID pharmacokinetics is that the drug remains in the synovial fluid for a much longer period of time than it is found in the plasma, and this is important to reflect upon in terms of the development of so-called long-half-life drugs [27]. Emphasis on the plasma half-life was
longer half-life drugs are also more likely to produce GI toxicity [31, 32]. Of great interest is the recent suggestion that NSAIDs may also be associated with a significant incidence of congestive cardiac failure and renal impairment. Henry [33], in a case–control study, has demonstrated a relative risk of 2.3 for developing an episode of congestive cardiac failure requiring admission to hospital in those patients taking NSAIDs in the last 10 days, and this translates to a major public health problem. These data would suggest that in Australia each year some thousand patients die from congestive failure induced by NSAIDs, while in Great Britain this number may be of the order of 8000.

The discovery over the last decade of a second enzyme system involved in cyclooxygenase (COX 2) [34] has led to a resurgence of interest within the pharmaceutical industry in NSAIDs. The COX 1 enzyme system is found in the stomach and the kidney, and functions as the ‘housekeeping’ enzyme, while the COX 2 system is induced by inflammation and is also found in the brain. Tantalizing data suggest that the COX 2 inhibitors may be useful in reducing the incidence of toxicity due to the fact that the physiological prostaglandins in the stomach and kidney do not have a chance to recover during a dosing interval. Side-effects of NSAIDs are significant, as demonstrated by a number of studies [28]. Over the last 5 yr, it has become apparent from some of these large epidemiological databases that differences do exist in the propensity for individual NSAIDs to cause side-effects, particularly in the gastrointestinal (GI) tract [29]. Using ibuprofen as a marker, it can be seen from Fig. 3 that there are significant differences in the relative risks for peptic ulcer production by NSAIDs [30]. Patients with a risk of GI toxicity can now be identified and are those who have had a previous history of gastric ulcer, have significant co-morbidities such as cardiac or renal disease, have severe RA or are also on corticosteroids. There is also a significant dose effect with NSAIDs and some data suggesting that

**ANTI-RHEUMATIC DRUGS**

It is now standard practice amongst rheumatologists to commence anti-rheumatic drug therapy at or within 3 months of the time of diagnosis of RA. The majority of anti-rheumatic drugs have been shown to slow erosion rates, but there are few patients in these trials or in practice who go into full remission according to the ACR criteria [41]. Large databases of patients taking anti-rheumatic drugs also reveal that a significant majority cease their anti-rheumatic drug within 3–5 yr because of lack of efficacy or the development of side-effects [42, 43]. Use of oral methotrexate has
made a significant difference to the way we treat RA, but even with this medication few patients go into a full remission [44]. Studies from Möttönen et al. [45], in following a cohort of patients with non-erosive disease, show that after a mean of 6 yr of therapy with anti-rheumatic drugs, 98% have erosions even though up to 25% of patients will have fulfilled ACR criteria for remission at least once during that period. The ARAMIS database also suggests that treatment with anti-rheumatic drugs significantly slows progression of disability measured by the Health Assessment Questionnaire, while NSAID and steroid therapy is associated with an increase in disability [46].

The choice of anti-rheumatic drug can only be determined on an individual basis with patient preferences often relating to potential side-effects being a significant determinant. Side-effects of anti-rheumatic drugs are many and varied, but the risk is not significantly different from that seen with NSAIDs [47]. With careful monitoring, adverse drug reactions, or at least the serious ones, can be kept to a minimum, and although standard monitoring practices are published [48], there are little cost-effectiveness data to support these regular blood tests. This is even so for the ophthalmological monitoring of hydroxychloroquine where it has been recently suggested that, based on evidence (or lack of it), a good case for continuing routine monitoring cannot be sustained [49].

Combination of anti-rheumatic drugs is now the norm rather than the exception, with low doses of corticosteroids often being added to that combination. Prednisolone in doses up to 7.5 mg daily has been shown to reduce the erosion rates in patients with early RA, although the magnitude of the reduction is not large [50]. A major concern regarding corticosteroids is evidence from case-control studies that their prescription is associated with a significant incidence of adverse events including infections [51]. More recent data on the use of corticosteroid preparations in other conditions, such as asthma, would suggest a significant increase in cataract formation [52], although this has never been investigated in RA and should be evaluated. Many combinations of anti-rheumatic drugs have now been tested with some studies showing an increased efficacy of the combination, while others show no difference or an increased incidence of side-effects [53]. Combinations such as salazopyrin, methotrexate and hydroxychloroquine have been shown to be of particular benefit, but, even with this combination, the changes over methotrexate or sulphalazine alone are relatively small [54]. Cyclosporin plus methotrexate has been shown to be better than methotrexate alone, but again the size of the difference was not all that great [55]. Great care should be taken in interpreting combination drug trials because in many situations the pharmacokinetic interactions are not discussed. Cyclosporin and methotrexate combination is now being suggested as a useful way of treating RA, and yet no data have been published on the possibility of a pharmacokinetic interaction. Given the known effect of cyclosporin on renal function [56], it would not be surprising if the excretion or metabolism of methotrexate was interfered with in some way by cyclosporin. This might not be a problem except for the cost of cyclosporin, but if cyclosporin does increase methotrexate levels, then a more appropriate trial design would be to test methotrexate vs cyclosporin plus methotrexate vs twice the dose of methotrexate and evaluate the cost effectiveness of that study.

These combination treatments are now being trialled in RA patients with early disease with emphasis on the way in which the drugs are prescribed as well as the drugs themselves. The 'stepdown bridge' approach of Wilske et al. [57] and the 'sawtooth' approach of Fries [58] are both appropriate strategies and need to be tested in appropriate trials [45]. Boers et al. [59] have recently demonstrated significant benefit from a combination of sulphasalazine (2 g daily), methotrexate (7.5 mg weekly) and prednisolone (initially 60 mg/day tapering to 7.5 mg at week 6) vs sulphasalazine alone (2 g daily). Prednisolone was stopped at 28 weeks and methotrexate at 40 weeks. The significant clinical differences in favour of the combination therapy which existed between the groups at week 28 disappeared when steroids were ceased. However, significant differences in radiographic damage score in favour of the combination persisted up to 80 weeks (Fig. 4).

These data shed new hope on the efficacy of combination therapies, but do emphasize the importance of careful trial design, particularly as regards the type of patient studied (early disease), and the particular drug combination and strategy employed, and explain some of the negative results of previously studied combinations [60].

**BIOLOGICALS**

A greater understanding of the pathobiology of RA has allowed the development of more targeted therapies.
based on new technologies of monoclonal antibody and cytokine production. This has led to the development and trialling of a range of so-called biological agents [61] (Table IV). The most dramatic responses have thus been seen with anti-tumour necrosis factor alpha (TNF-α) [62], although recent studies with interleukin (IL)-1 receptor antagonist [63] demonstrate for the first time an effect of a biological in reducing erosion rates. Conceptually, the direct targeting of the apy with stem cell rescue—a protocol with a mortality of <1%—in attempting to suppress RA activity [71]. Studies on animal models of autoimmune disease [72] demonstrate the benefit of pursuing autologous stem cell transplantation as an experimental procedure in an effort to achieve better, if not permanent, disease control. Protocols for priming and conditioning regimens have now been developed through international consensus, and a number of groups are exploring these procedures. Carefully controlled studies need to be carried out to assess the usefulness of manipulations such as T-cell depletion and all patients should be entered into a register with long-term follow-up to assess outcome [73].

RA may not be a ‘killer’ disease like myocardial infarction or cancer, but it is common and it does cause very significant morbidity and some mortality. As we look back at RA ‘therapeusis’ over the past three decades, the agenda has often been driven by the pharmaceutical industry rather than ourselves. This was particularly so in the 1970s–80s, with a focus on NSAIDs—drugs which do not alter the course of RA at all. Are we in danger of repeating the same mistakes with anti-rheumatic drugs—researching combinations of often expensive drugs to achieve minor goals. We need perhaps to alter the goal posts (or at least the goal) from control to cure and to pursue that outcome vigorously. It will not be easy and there will always be that balance between risk and benefit. I suspect, however, that we could do better by taking greater risks without compromising patient care.

The road ahead will not be easy, but we do need to learn from our haematology/oncology colleagues—RA does behave like a locally invasive tumour [74] and should be approached as such. As rheumatologists, we have always espoused the team approach; now is the time to extend that team and involve other groups, particularly with an expertise in chemo- and immunotherapy. As we move ahead, we must continue to provide for our patients support, advice and respect for their wishes in what are going to be difficult therapeutic decisions.

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