ANIMAL models are an essential tool in the systematic dissection of immune and inflammatory pathways which contribute to the development and maintenance of arthritis. The majority of animal studies are carried out in rodents for historical and economic reasons. Here we discuss the contribution which studies of non-human primates can make to our understanding of arthritic processes in humans, together with an appraisal of their potential in evaluating therapies.

The aetiology of rheumatoid arthritis (RA) is regarded as being immune mediated with T lymphocytes having an important regulatory function [1]. The first step in an antigen-specific immune response is represented by the formation of a trimolecular complex, consisting of an antigentic peptide (epitope) complexed with an MHC molecule on the surface of an antigen-presenting cell (APC). This is in turn recognized by an antigen-specific receptor on the responding T cells (TCR) [2]. This antigen-specific interaction is stabilized by bridges between accessory molecules which may also transduce essential stimulatory signals, such as CD4 with MHC class II molecules, CD8 with MHC class I molecules, CD40 with CD40-ligand, CD28 with CD80/86, LFA-1 with ICAM-1, etc. [3].

How the T lymphocytes are activated in RA and by which antigen is not known. One possibility is that they respond to antigens derived from infectious pathogens which resemble antigens in the joint (molecular mimicry). In individuals with a certain genetic background, the autoreactive T cells may induce a cascade of reactions leading to RA. In genetic epidemiological studies, the risk for humans of developing RA has been linked to the possession of certain MHC alleles, in particular HLA-DR1 and -DR4 [4]. However, these associations are relatively weak and have been challenged by the observation that the actual risk element for RA may be a HLA-DQ8 molecule binding a conserved motif in one of the variable regions of the HLA-DR chain [5]. This motif is possibly closely associated with or identical to the ‘shared epitope’ [6].

Non-human primates are known to be susceptible to many of the arthritic diseases that affect the human population. They are the most closely related relatives of man and, therefore, of interest as models of human diseases. Spontaneous manifestation of spondyloarthropathies and osteoarthritis has been documented in apes and Old World monkey species [7–10]. Susceptibility to spondyloarthropathies shows considerable variation among primate species, namely 1–4% in humans, 2–3% in Old World monkeys and 20–30% in the great apes (chimpanzee and gorilla), with the exception of orang-utans. Remarkably, in two large outbred populations of chimpanzees (>100 individuals) and rhesus macaques (>1000 individuals), which are kept at the Biomedical Primate Research Centre in Rijswijk (The Netherlands), spontaneous manifestations of arthritis are only rarely observed. The animals are kept under much cleaner conditions than in the wild, reflecting the fact that strict veterinary care keeps them free of most pathogens. This supports the concept that the inciting event in RA may be associated with exposure of genetically susceptible individuals to infectious pathogens.

The evolutionary distance between the genomes of man and common laboratory primate species like the rhesus or cynomolgus macaques is estimated at 35 million years, whereas between humans and rodents it is ~80 million years. This has obvious implications for the similarity of the immune systems between primate species. Allelic lineages are related families of alleles which have maintained their genetic identity despite continued accumulation of mutations within a species. The presence of similar MHC-DR and MHC-DQ allelic lineages in humans and macaques has been well documented (reviewed in [11]) and is of interest because both loci have been implicated as major regulatory elements of susceptibility to RA in the human population [5].

In humans, three subgroups of class II MHC genes giving rise to functional products are recognized. These are DR, DQ and DP. The MHC-DQA1 and -DQB1 genes in primates exhibit extensive polymorphism. To date, 78 non-human primate MHC-DQA and 104 -DQB sequences have been documented. At least three lineages are common to humans, chimpanzees and macaques. In general, HLA-DQA2/DQB2 genes display only limited polymorphism.

In all primate species that have been investigated thus far, the MHC-DRA locus is invariant. Although humans, chimpanzees and macaques share many lineages at the MHC-DR loci, most alleles tend to be species specific. The MHC-DRB1*03, -DRB1*04 and -DRB1*10 lineages are at least 35 million years old. It has now been well established that some MHC-DR3 lineage members in humans, chimpanzees and macaques select the same epitopes from antigens like mycobacterial PPD or bovine myelin basic protein, and can even present them to T-cell clones of the other species [12–15]. This observation not only demonstrates the evolutionary conservation of certain allelic lineages and their peptide-binding capacities, but also points to the co-evolution of MHC and TCR gene repertoires. A comparative analysis of TCR β-chain structure and usage in humans, chimpanzees and macaques has revealed that their genomic and expressed repertoires do not differ substantially (reviewed in [11]).

MHC-typed colonies of chimpanzees and macaques...
thus provide a unique setting to investigate in a controlled (laboratory) setting the activation of immunopathological pathways that lead to arthritis in a broadly similar genetic background as found in RA patients.

In the past decade, interest in valid non-human primate models of human diseases has grown. The main reason is that newly developed reagents for therapeutic application are often only reactive in humans and closely related non-human primate species. Examples include antibodies, cytokines, cytokine antagonists and viral vectors for gene therapy. Because the reactivity with the equivalent target molecules in rats and mice in most cases is poor, disease models in these species are usually invalid for efficacy evaluation of biological molecules. The considerable cross-reactivity of primate specific monoclonal antibodies with human, chimpanzee and macaque lymphocytes points to a high similarity of surface molecules between the three species [16–18]. With regard to safety assessment, the immunogenicity of recombinant human biological molecules, such as cytokines, should be considered in primates in particular, in view of the adverse effects of long-term neutralization of the natural cytokines [19].

Spontaneous arthritides in non-human primates are valuable for the study of pathophysiological pathways leading to RA, but are unsuitable for the testing of new therapies in view of their low incidence and unpredictability. For such studies, experimentally induced arthritides are more suitable. To our knowledge, the first report documenting experimentally induced arthritis in a rhesus macaque dates from 1965. This report documents the induction of arthritis in four rhesus monkeys using immunization with an emulsion of fibrin in complete Freund's adjuvant, followed by intra-articular challenge injection of fibrin 4 weeks later [20]. Collagen-induced arthritis (CIA) is a generally accepted model for human RA in rodents which can also be induced in Old World monkey species [21, 22]. CIA has also been successfully established in squirrel monkeys (Saimiri sciureus), while cebus monkeys (Cebus albifrons) were found to be resistant [23]. The two closely related macaque species cynomolgus monkeys (Macaca fascicularis) [24] and rhesus monkeys (Macaca mulatta) [25] are both susceptible to CIA. Surprisingly, a sex bias has only been found in M. fuscicularis [24, 26]. We have been unable to induce other forms of arthritis in rhesus monkeys, such as with bacterial antigens that have proved arthritogenic in susceptible rat strains [27]. Finally, it has been reported that intra-articular injection of methylated bovine serum albumin (BSA) into BSA-sensitized marmoset monkeys (Callithrix jacchus) induces a chronic synovitis [28].

Collagen-induced arthritis can be induced in rhesus monkeys by a single intradermal injection of heterologous type II collagen (C-II; usually bovine) in complete Freund's adjuvant. Susceptible monkeys develop a polyarthritis, which is mainly expressed as a symmetrical inflammatory swelling of the proximal interpha-

langeal and metacarpophalangeal joints of hands and feet and in wrists and ankles. In the more advanced stages of CIA, inflammation is also found in tarsal and carpal joints. The larger joints, such as knees, elbows and hips, become affected only in severe CIA. Reports on the histopathology of arthritic joints in CIA consistently mention hyperplasia of the synovium with dense infiltrations of mononuclear cells and pannus tissue covering the articular cartilage [26, 28, 29]. We have tested the suitability of various parameters for an objective assessment of the clinical signs in CIA [29, 30]. With such parameters established, the therapeutic effect of new experimental therapies can be described in quantitative terms and thus compared with existing ones. As well as being a semiquantitative score, body weight proved a good general disease marker. The serum C-reactive protein level was found to reflect the severity of inflammation and urinary excretion rates give an accurate reflection of the destruction of joint tissues. Since rhesus monkeys are relatively large animals, detailed information on inflammatory processes in individual joints can be obtained by arthrocentesis or arthroscopy, if relevant in combination with synovial biopsy. The technical feasibility of this procedure has been investigated in collaboration with Drs Tak and Kraan (Department of Rheumatology, Leiden University Hospital, Leiden, The Netherlands). This will enable us to phenotype the dynamic synovial changes during the course of CIA with immunohistology. At necropsy, dramatic erosion of the cartilage in affected synovial joints is found, whereas the cartilage of the nose and ears and the tracheal rings is usually spared. Deformations in the spinal column analogous to ankylosing spondylitis may occasionally develop.

The individual susceptibilities to CIA of randomly selected rhesus monkeys from an outbred population vary considerably. Importantly, the different manifestations of CIA could be associated with genetic and immunological parameters. To date, no association between CIA susceptibility and any MHC class II allele has been found. However, monkeys in which CIA cannot be induced share the same serologically defined MHC class I allele Mamu-A26 [31], which is actually an HLA-B locus equivalent. The resistance defined by Mamu-A26 is specific for CIA, segregates as a dominant trait in families, and seems to be independent of the MHC class II background of the monkey. The resistance to CIA may be associated with the reduced capacity of Mamu-A26-positive monkeys to produce anti-C-II antibodies of the IgM isotype. The production of IgG autoantibodies was comparable in responder and non-responder monkeys [32]. More recently, the critical role of IgM autoantibodies in the induction of CIA was confirmed [33]. Analysis of the reactivity of sera from arthritic monkeys showed no consistent recognition patterns with cyanogen bromide fragments of the collagen molecule [24] or with overlapping 15mer peptides from the major arthritogenic CB11 fragment [34].

The protection of monkeys from CIA by cyclosporin
A treatment points to involvement of T cells in the induction of the disease [35]. Interestingly, in monkeys in which a relapse of the arthritis could be induced, a higher proliferative response to C-II was found in the first disease phase than in monkeys with a monophasic disease pattern [33]. The fine specificity analysis of collagen-reactive T cells is technically difficult because even in severely arthritic monkeys the proliferative response of peripheral blood T cells to C-II is usually very poor. To resolve this problem, alternative approaches have been exploited to obtain enriched populations of C-II-reactive T cells [36].

A valid arthritis model in non-human primates is relevant for the safety and efficacy evaluation of new therapies such as biological molecules or gene therapy vectors which react only with components of a primate immune system. Obviously, the costs of research in non-human primates are high and for ethical reasons a highly regulated approach is demanded. Disease models in transgenic rodent strains have been developed as an alternative for non-human primates. Transgenic rodent models are useful for efficacy evaluation of an experimental therapy, but are less effective for the assessment of side-effects, which may not occur in a mouse background. Moreover, the genetic manipulation of animals has also raised public objections and the costs of creating them are also very high. Knowledge of the activation and genetic regulation of pathophysiological pathways leading to RA is still incomplete. We propose that advantage can be taken of the close genetic and immunological similarities between non-human primates and man in studying these complex processes under controlled laboratory conditions. Second, a score of new and promising therapeutic strategies have been developed for the treatment of RA. We have discussed above that for the pre-clinical evaluation of the safety and efficacy of biological molecules or viral vectors for gene therapy, the use of non-human primates is often the only option. The same may hold true for bone marrow transplantation as an optional cure for severe RA.

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REFERENCES

STANDARDS OF CARE FOR ARTHRITIS: POINTING THE WAY FORWARD

Last November, the British League Against Rheumatism (BLAR) [1] introduced the UK’s first ever nationally agreed standards of care for arthritis with the launch of its report ‘Standards of care—towards meeting people’s needs’ [2]. The launch was the culmination of a lengthy project, funded by the Department of Health and involving input from a range of professional and patient groups.

THE NEED FOR NATIONALLY AGREED STANDARDS

In 1994, BLAR published ‘Disability and arthritis’ [3], which reported the results of a survey of almost 500 people with arthritis across the UK. Although it is universally recognized that a high quality arthritis service requires input from a multi-disciplinary team, the report showed that most people surveyed received care wholly from their GP or a hospital-based rheumatologist; only a small proportion received input from other health professionals [3].

The Patient’s Charter [4] promotes standards of care for the general UK population and national standards of care exist for other conditions such as diabetes [5] and back pain [6]. In the absence of nationally agreed standards of care for arthritis, commissioning authorities use different benchmarks for their quality specifications for rheumatology services, resulting in regional differences in the quality they require [7].

SETTING THE STANDARDS

A multi-disciplinary advisory group was set up, comprising representatives from all the major organizations whose area of interest lay in each of the categories that the standards would cover, namely: Arthritis Care, the British Society for Rheumatology, the British Society for Rehabilitation Medicine, British Health Professionals in Rheumatology, the British Orthopaedic Association, the Disability Living Allowance Advisory Board, the Primary Care Rheumatology Society and the Royal College of Nursing Rheumatology Nursing Forum. The standards were set by the advisory group using a modified Delphi method [8] to achieve consensus views. ‘Essential’ and ‘desirable’ standards were set for both osteo- and rheumatoid arthritis; the essential standards representing the minimum service provision, whilst the desirable represent an ideal level.

The standards do not concern issues such as waiting times (which are covered in the Patient’s Charter [4]), nor do they deal with how an individual’s arthritis
should be managed medically, as appropriate guidelines also exist [9, 10]. They do, however, reflect the philosophy of meeting the growing demand by patients for information about illness and the services that can play a part in care [11]. The full list of standards and the condition to which they apply are shown in the appendix.

AUDITING THE STANDARDS

The project also aimed to discover how well care for people with arthritis in the UK measured up to the standards. A nationwide questionnaire audit was conducted involving 18 regions in the UK and over 1000 people with arthritis. In brief, the main findings are as listed below.

Primary care

Almost all respondents said they had discussed the nature of their arthritis with their GP, and over three-quarters said that their GP had examined their joints. Primary care also fared well in providing explanations concerning certain medication. However, in terms of providing explanations about other possible treatments and services, and in providing written information, the situation was less flattering.

Rheumatology secondary care

Rheumatology departments had discussed the kind of arthritis people had with over three-quarters of respondents. As in primary care, they also fared relatively well in providing discussions of the various arthritic medication. However, like primary care there also existed a shortfall in providing information, both verbal and written, about other aspects of treatment and care.

Orthopaedic secondary care

It seems that orthopaedic departments fared much better in providing the recommended verbal explanations, and in providing advice about returning home after an operation, but the provision of written information was another area of concern, particularly for the respondents with osteoarthritis. Of those respondents requiring an orthopaedic operation, over a quarter had not received any relevant literature.

In-patient care and X-rays

The findings regarding standards for in-patient care, including orthopaedic in-patient care, are very encouraging. Very high proportions of respondents reported that all of the relevant standards had been met. Also encouraging was the finding that only a small percentage of those having an X-ray experienced discomfort in joints other than those being X-rayed.

WHAT THE STANDARDS CAN ACHIEVE

The purpose of the audit was not to criticize, but to highlight where improvements could and should be made. The standards should be considered a challenge to the services involved rather than a threat. BLAR is not calling for widespread increases in referrals to a range of multi-disciplinary services, but for a greater awareness among people with arthritis of how these services are involved in the care of the disease. Critics may claim that such measures will raise patient expectations unfairly, but BLAR takes the view that it is only through discussion and explanation that people will come to understand what can and cannot be achieved in relation to their arthritis. Evidence suggests that people with arthritis have different views as to the cause and nature of their illnesses than their doctors [12, 13], and BLAR hopes the provision of information called for in the standards of care will help address this problem.

Whilst BLAR has no specific evidence that meeting these standards will improve the medical outcome of people with arthritis, there is an increasing body of evidence to suggest that information about, and greater understanding of, chronic illness can improve outcome. Within rheumatology, a great deal of evidence has been compiled suggesting a complex relationship between information/education and outcomes such as pain reduction, increased exercise behaviour, improved psychological status and coping skills, improved doctor–patient communication and reduced use of health services [14]. Most of the standards of care reflect this philosophy of supporting people with arthritis through education and awareness, and BLAR believes that through meeting the standards, the lives of people with arthritis will be improved irrespective of medical advances.

POINTING THE WAY FORWARD

In today’s health care climate of audit, clinical effectiveness and increased public accountability, the aim of ensuring the quality of the entire care experience has never been more explicitly stated and there has been a trend towards developing national standards of care and good practice in many different specialities across the globe [15–18]. We hope that the multi-disciplinary approach to developing standards that has been outlined above will be utilized internationally, and we look forward to the development of standards for arthritis from the wider rheumatology community.

As for the UK, BLAR believes that the way forward in the care of arthritis is for its standards to become the benchmark of the level of quality required by commissioners of rheumatology services. To this end, BLAR is attempting to persuade health authorities/commissioners to incorporate the BLAR standards into their contract or service specifications for rheumatology services: commissioners who already have specific quality standards for rheumatology services could do this quite easily. Ultimately, however, the only way such standards will be implemented is through the cooperation of rheumatology service staff and therefore over the last 4 months, the ‘Standards of care’ report has been distributed to every rheumatology department in the UK.

The standards are comprehensive, yet flexible enough to allow the multitude of individual care approaches to flourish. A unique feature of the BLAR...
standards is that they were devised through patient and multi-disciplinary professional group collaboration. In the UK in particular, it seems likely that such a philosophy will have a major role in the future of the health service [19, 20]. Therefore, as we approach the next millennium the importance of these standards for rheumatology should be recognized, and accordingly, they should be truly considered to point the way forward in the care of people with arthritis.

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REFERENCES
10. Guidelines and audit measures for the specialist super-weight control as a possible treatment OA & RA

APPENDIX: THE BLAR STANDARDS OF CARE FOR OSTEOARTHRITIS (OA) AND RHEUMATOID ARTHRITIS (RA)

ESSENTIAL STANDARDS

<table>
<thead>
<tr>
<th>Standard</th>
<th>Applicable to</th>
</tr>
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<tbody>
<tr>
<td>1. In primary care, a general practitioner should discuss the nature of arthritis (at an early stage)</td>
<td>OA &amp; RA</td>
</tr>
<tr>
<td>2. In primary care, a general practitioner should examine the joints (at an early stage)</td>
<td>OA &amp; RA</td>
</tr>
<tr>
<td>3. In hospital out-patients, a rheumatology department should explain and discuss the kind of arthritis</td>
<td>OA &amp; RA</td>
</tr>
<tr>
<td>4. In hospital out-patients, a rheumatology department should explain the role of</td>
<td>OA &amp; RA</td>
</tr>
<tr>
<td>5. In hospital out-patients, a rheumatology department should provide written information on</td>
<td>OA &amp; RA</td>
</tr>
<tr>
<td>6. If admitted to hospital because of arthritis, the hospital should ensure people are admitted to wards with easily accessible facilities (chairs, taps etc.)</td>
<td>OA &amp; RA</td>
</tr>
<tr>
<td>7. If admitted to hospital because of arthritis, the hospital should ensure the patient has the name and number of a contact if further problems arise (in relation to their admission)</td>
<td>OA &amp; RA</td>
</tr>
<tr>
<td>8. If admitted to hospital because of arthritis, the hospital should ensure the patient’s GP is made aware of their discharge</td>
<td>OA &amp; RA</td>
</tr>
</tbody>
</table>


7. If an orthopaedic operation is required, the orthopaedic department should explain exactly which joint or joints the operation will affect. 
explain any complications that may arise from the operation.

8. If an orthopaedic operation is required, the orthopaedic department should explain the role of a physiotherapist, an occupational therapist and a social worker.

9. If an orthopaedic operation is required, the orthopaedic department should provide written information on the operation itself, exercises that can be done after the operation, things that shouldn’t be done after the operation, pain that may occur after the operation and dealing with that pain.

10. If an orthopaedic in-patient, the orthopaedic department should ensure people are admitted to wards with easily accessible facilities (chairs, taps etc.) state the probable length of hospital stay for an operation.

11. In the community, the local pharmacist should be able to offer clients the choice of not having child resistant caps put on their medication containers.

12. In the hospital pharmacy patients should be offered the choice of not having child resistant caps put on their medication containers.

13. In the hospital X-ray department staff should take account of the possibility that patients have pain in joints other than those being X-rayed.

14. For patients attending hospital ambulance or other accessible transport organized by the health service should be made available (if the patient’s circumstances require).

15. Additionally, information/advice should be made available about Social Security benefits (including Disability Living Allowance, Attendance Allowance, Disability Working Allowance, Incapacity Benefit etc.) social or leisure activities.

16. Physical access in the following environments should be ensured:
- GPs’ surgeries
- local/community pharmacist
- people’s homes
- hospital premises
- all public buildings
- all public transport vehicles

17. In primary care, a general practitioner should explain the role of:
- the hospital (rheumatology or orthopaedic department) in the treatment/care of arthritis
- physiotherapy as a possible treatment
- steroid injection as a possible treatment
- someone able to discuss personal and/or sexual relationships
- footwear/chiropody as a possible treatment

18. In primary care, a general practitioner should provide written information on:
- arthritis in general
- medication being taken for arthritis
- exercise
- voluntary self-help/support groups
- self-management courses

19. In hospital out-patients, a rheumatology department should explain the role of:
- someone able to discuss personal and/or sexual relationships
- oral steroids as a possible treatment

20. If an orthopaedic operation is required, the orthopaedic department should offer the patient the chance to talk to other people who have had the operation.

21. If an orthopaedic operation is required, the orthopaedic department should explain the role of:
- someone able to discuss personal and/or sexual relationships

22. Additionally, information/advice should be made available about:
- arthritis and the workplace
- PACT and the Access To Work scheme
- Arthritis Care/Young Arthritis Care
- the Arthritis and Rheumatism Council for Research
- Disabled Living Centres
- social or leisure activities