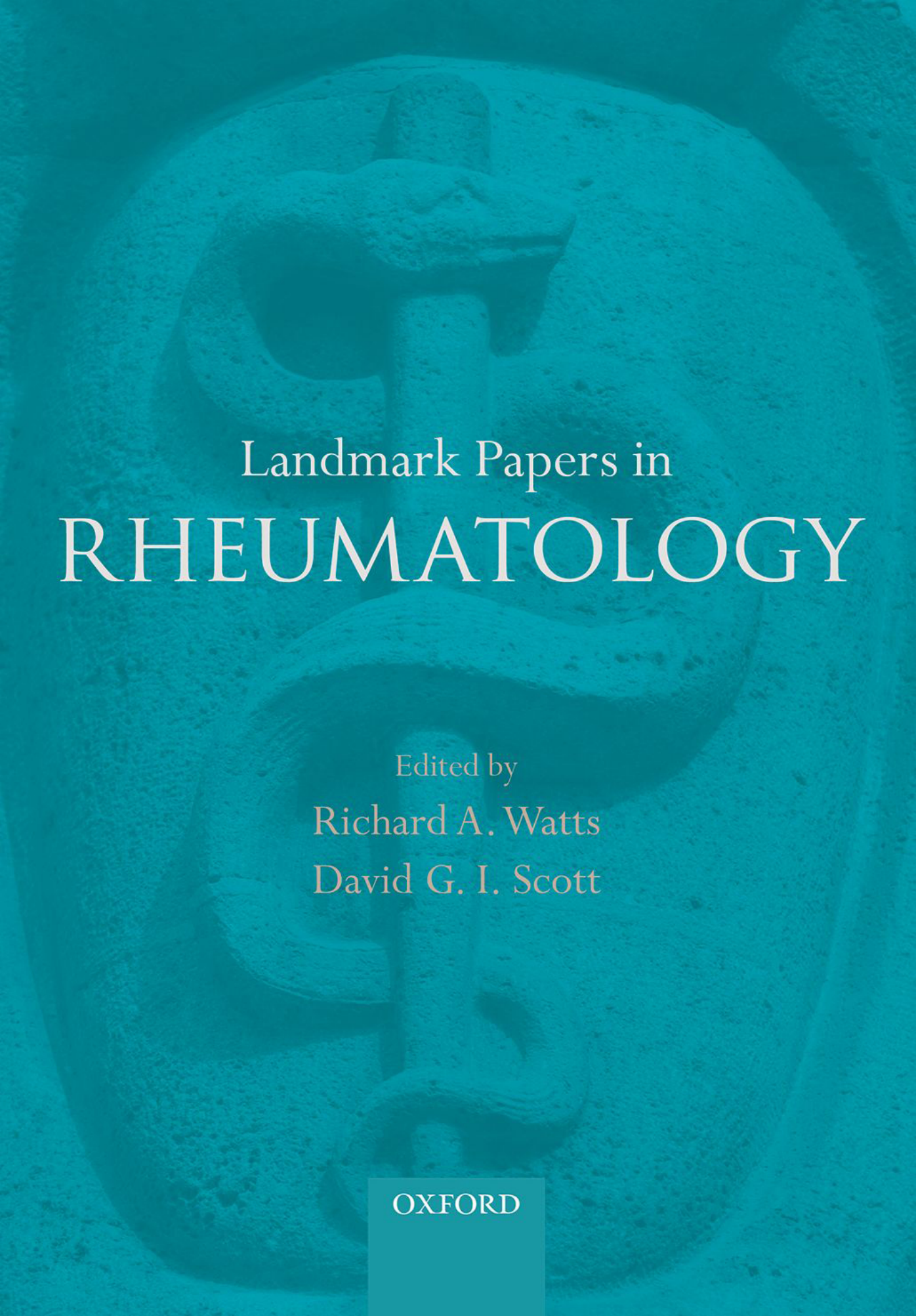
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Great Clarendon Street, Oxford, OX2 6DP,
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It furthers the University's objective of excellence in research, scholarship,
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First Edition published in 2015

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data
Data available

Library of Congress Control Number: 2015932388

ISBN 978–0–19–968837–1

Printed and bound by
CPI Group (UK) Ltd, Croydon, CR0 4YY

Preface

> The rheumatism is a common name for many aches and pains, which have yet got no peculiar appellation, though owing to very many different causes.
>
> (William Heberden (1710–1801) *Commentaries on the History and Cure of Disease*, Chapter 79 (1802)).

William Heberden in many respects summarized the state of rheumatic disease nomenclature and classification in 1802 with the statement quoted above. At that time, probably only gout was clearly distinguished from many types of aches and pains. In the commentaries he also gives the first description of the bony nodes over the distal interphalangeal joints—'What are those little hard knobs, about the size of a small pea, which are *frequently seen upon the fingers, particularly a little below the top, near the joint?*' He does not understand their aetiology but recognizes them not to be linked with psoriasis. During the late eighteenth and nineteenth centuries, descriptions of disease patterns that we now recognize began to be made. Sir Archibald Garrod in 1859 gave the name 'rheumatoid arthritis' to a disease that, although around for many years, had no nomenclature and up until that stage had been described as 'rheumatic gout', 'chronic rheumatism', and 'rheumalgia'. The first steps in the scientific investigation of arthritis were also made around this time; for example, Garrod differentiated gouty arthritis using the presence of serum hyperuricaemia. This process has continued up to the present day, with differentiation of further types of arthritis, using both traditional methods of clinical pattern recognition combined with improved investigative techniques, for example, the clear differentiation of inflammation due to synovitis from that due to enthesial inflammation using MRI, and better understanding of causation, for example, the recognition that a certain form of inflammatory arthritis of children is due to borrelia infection. As the study of rheumatic disease has become more scientific simple descriptions of disease patterns have become inadequate for clinical studies and this has led to the development of validated diagnostic and classification systems for many of the rheumatic diseases.

Treatment in Heberden's day was limited and primarily consisted bleeding or purging, although the antipyretic properties of cinchona bark were recognized. The only specific therapy for a form of arthritis then was colchicine for gout, which had been used since the time of Hippocrates. Garrod suggested that hyperuricaemia could be controlled by limiting dietary intake of purines. The nineteenth century saw the development of aspirin and early analgesics. The twentieth century saw the introduction of corticosteroids—for which Hench won the Nobel prize—immunosuppressive drugs, and most recently the products of the biotechnology revolution, monoclonal antibodies and fusion proteins.

The aim of this book is to provide both practising and trainee rheumatologists with an overview of the history of their specialty by presenting some of the key papers, together with brief commentary as to why the paper is important. The authors were asked to select up to ten papers in their field covering in their opinion key developments. The papers range from initial descriptions of disease up to very recent innovations in our scientific understanding of aetiopathogenesis and therapy.

Richard A. Watts
David G. I. Scott

Acknowledgements

We are grateful to Eloise Moir-Ford and James Oates of Oxford University Press for all their unstinting help and enthusiasm during the production of this book. Without them, it would never have happened.

Our families, particularly Lesley and Dee, have been very supportive during the editing process and we are indebted to them.

Richard A. Watts
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Chapter 1

Epidemiology and genetics

James Bluett, Suzanne Verstappen, and Deborah Symmons

Introduction

Epidemiology

Epidemiology is the study of the distribution and determinants of disease in human populations. It is applied to describe the prevalence and incidence of a disease, to identify predictors (genetic and environmental) of the development of disease, and to describe the consequences of a disease. Understanding the distribution and the burden of diseases helps health policy makers and the general public to understand the impact of diseases and injuries across different regions of the world and the need for specific intervention programmes and better distribution of health care resources. We selected Paper 1.4 as an excellent example of the estimation of the occurrence/burden of rheumatic and musculoskeletal disorders (RMDs). It was published in *The Lancet* in 2012 as one of a number of papers on the global burden of disease, and possible risk factors. This paper showed that, over the last two decades, the disability-adjusted life years (DALYs) for rheumatoid arthritis, neck and back pain, and osteoarthritis have increased, whereas the death rate for rheumatoid arthritis has decreased by ~10%.

Although the Global Burden of Disease study provides the best available estimate of disease occurrence, these papers also illustrate the challenges epidemiologists face when estimating the impact of a disease in different countries, and amalgamating data from a variety of sources, often without case validation. Ideally, to determine prevalence and incidence of a disease, it is important to use validated tools for case definition. We selected two key papers (Papers 1.1 and 1.2) which demonstrate the development of case definitions for RMDs. The Kellgren and Lawrence radiological scoring system for osteoarthritis is one of the first examples of a validated tool in rheumatology. Although the scoring system has undergone a few minor changes since its introduction 50 years ago, it is often still used to estimate and compare prevalence rates for osteoarthritis and to assess radiographic damage over time in populations with osteoarthritis in different settings. For rheumatoid arthritis patients, a series of classification criteria sets have been developed by the American Rheumatism Association/American College of Rheumatology. The 1987 criteria set have been used extensively, not only to estimate the incidence and prevalence of rheumatoid

arthritis but also as part of the entry criteria to clinical trials and observational studies. In the last decade there has been a shift towards earlier classification and treatment of rheumatoid arthritis. Because of their increased specificity in early rheumatoid arthritis, the 2010 American College of Rheumatology/European League Against Rheumatism criteria for rheumatoid arthritis are beginning to replace the 1987 criteria in this setting.

Epidemiology studies are also suitable to describe the occurrence and predictors of long-term consequences of a disease (e.g. co-morbidities, disability, and mortality). Standardized mortality ratios (SMRs) or standardized incidence ratios (SIRs) are often calculated, using data from the general population as the reference, to quantify the excess risk of co-morbidities. Paper 1.3 illustrates one of the first examples of the use of population registers and record linkage in RMDs. It examined the risk of lymphoma, leukaemia, and myeloma in patients with rheumatoid arthritis compared to the general population. To date, this remains one of the largest observational studies showing an increased risk of lymphoproliferative malignancies in patients with rheumatoid arthritis.

Genetic epidemiology

A genetic basis underlying a number of RMDs has been established using twin and family studies. Using rheumatoid arthritis as an exemplar, we have selected and go on to discuss the milestones that have produced step changes in our knowledge of the genetics underlying the development of disease.

Paper 1.5, published in 1987 by Gregerson et al., described the shared epitope hypothesis to explain the association of the human leukocyte antigen (HLA) *DRB1* alleles as the major risk factor for rheumatoid arthritis; the paper is still widely cited and, until very recently, no other hypotheses could better explain the association observed. The next major milestone did not occur until 2004, when Begovich et al. (Paper 1.6) discovered the second-largest genetic risk for the development of rheumatoid arthritis: a protein-coding change in the PTPN22 gene. Their research not only identified this genetic variant but also investigated its biological impact and determined that there is a genetic difference between seropositive and seronegative rheumatoid arthritis, a potential clue in the disease pathogenesis.

As technological capabilities advanced, in 2007 a consortium of scientists from all over the UK came together to test genetic variants spanning the whole genome (a genome-wide association study) in order to establish which genetic markers are associated with a number of autoimmune diseases, including rheumatoid arthritis. The study (Paper 1.7) validated previous research findings and revealed nine new genetic variants associated with rheumatoid arthritis, greatly expanding our knowledge of the disease. The results from the Wellcome Trust Case Control Consortium represented a major advance in the genetic understanding of disease, confirmed the importance of large sample sizes to enhance power to detect modest genetic effects, and demonstrated how a large group of scientists and clinicians can work together to enhance our understanding of disease.

From whole genome scanning, genetic studies have returned to focusing on particular sections of the genome. In 2012, technology and expanding cohort numbers enabled the investigation of the HLA region with fine mapping to determine the true disease-causing

variants. Raychaudhuri et al. (Paper 1.8) discovered three genetic variants within the *HLA DRB1* gene that increase the risk of rheumatoid arthritis independently of each other and together and explain the association observed better than the previous shared epitope hypothesis. The variants lie within the peptide-binding grove of the HLA molecule, giving a vital clue to the importance of antigen presentation in the development of seropositive rheumatoid arthritis. Outside the shared epitope region, researchers have fine-mapped areas of previous interest, and in 2012 Eyre et al. (Paper 1.9) characterized, by fine mapping, over 40% of the known susceptibility areas to rheumatoid arthritis in one analysis. This paper was among the first to demonstrate, in rheumatoid arthritis, how genetic studies can identify novel targets for disease treatment.

Gene–environment interaction

The paradigm for the development of RMDs is that one or more environmental risk factors act in a genetically predisposed host to produce the disease phenotype. This paper (Paper 1.10) was the first to illustrate, statistically, that a genetic risk factor (the shared epitope) and an environmental risk factor (smoking) interact to enhance disease susceptibility for rheumatoid arthritis.

Paper 1.1: Radiological assessment of osteoarthritis—the Kellgren and Lawrence score

Reference

Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16(4):494–502.

Purpose

To develop and validate a system for scoring X-rays for the presence and severity of osteoarthritis.

Study design

The authors selected standard radiographs to represent 5 grades of osteoarthritis: none (0), doubtful (1), mild (2), moderate (3), and severe (4) for 11 joint areas. The standard radiographs for Grades 1–4 for the distal interphalangeal (DIP) joints, proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, first carpometacarpal (CMC) joints, wrist, cervical spine, hip, and knee are reproduced in this paper—a forerunner of the much used Atlas of Standard Radiographs [1]. The other joint areas assessed were the dorsal and lumbar spine and the feet. Verbal definitions of the radiological features and the grading criteria are shown in Table 1.1.

Table 1.1 Kellgren and Lawrence grading system of osteoarthritis

Radiological features
- Formation of osteophytes on the joint margins or, in case of the knee joint, on the tibial spines.
- Periarticular ossicles; these are found chiefly in relation to the distal and proximal interpharangeal joints.
- Narrowing of joint cartilage associated with sclerosis of subchondral bone.
- Small pseudocystic areas with sclerotic walls situated usually in the subchondral bone.
- Altered shape of the bone ends, particular in the head of the femur.
Grading system:
- *Grade 0 (none):* No features of osteoarthritis.
- *Grade 1 (doubtful):* Minute osteophyte, doubtful significance.
- *Grade 2 (minimal):* Definite osteophyte, unimpaired joint space.
- *Grade 3 (moderate):* Moderate diminution of joint space.
- *Grade 4 (severe):* Joint space greatly impaired with sclerosis of subchondral bone.

Source data from Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957 Dec;16(4):494–502.

The inter-observer and intra-observer reliability of this scoring system was evaluated by Kellgren and Lawrence themselves using X-rays from a survey of rheumatic diseases in the Leigh, Lancashire, population, UK. X-rays of a random sample of 85 people aged 55–64 were read by the two observers by comparing these with the standard radiographs. Eleven joint areas were evaluated and the intervals between the combined and the independent readings were two months and one month, respectively, after the independent reading.

Results

Inter-observer agreement ranged from 0.10 for the wrist to 0.83 for the knee. Intra-observer agreement was higher and ranged from 0.42 for the dorso-lumbar spine to 0.88 for the MCP joints. Although, for most joints, the agreement was high, the estimated prevalence of the disease varied widely because of the cumulative effect of observer bias (±31%).

Critique of the Kellgren and Lawrence scoring system

Although the scoring system has been extensively used to define osteoarthritis, it has also been criticized. First, there are some inconsistencies in the description of the radiographic features leading to discrepancies in study results [2, 3]. Second, there is quite a large emphasis on osteophytes. Third, the scoring system is ordinal, and the lower end of the scale represents different pathological processes involving different tissues from those at the higher end of the scale. In more recent years, therefore, based on the Kellgren and Lawrence system, further subcategorization of specific features of individual joints (i.e. hand joints, knees, and hips) has been established. In addition, new atlases including standard radiographs and better descriptions of the radiographic features have increased the accuracy to grade osteoarthritis and have helped to improve the internal and external validity [4].

Significance and importance of the paper

After 50 years the Kellgren and Lawrence scoring system, albeit with some minor modifications, is still used to estimate incidence and prevalence rates and to assess radiographic progression in osteoarthritis. In the USA, incidence rates (Kellgren and Lawrence ≥2) of symptomatic hand, hip, and knee osteoarthritis were obtained among members of the Fallon Community Health Plan, a health maintenance organization in central Massachusetts [5]. Incident cases had joint symptoms at the time or up to one year before the radiographs and did not have a history of osteoarthritis. The age- and sex-standardized incidence rate of hand osteoarthritis was 100 per 100,000 person-years (95% confidence interval (CI), 86–115), for hip osteoarthritis, 88 per 100,000 person-years (95% CI, 75–101), and for knee osteoarthritis, 240 per 100,000 person-years (95% CI, 218–262). Prevalence rates of radiographic osteoarthritis have been reported in a few studies. In a Dutch study including 6,585 randomly selected inhabitants of Zoetermeer, gender- and age-specific osteoarthritis prevalence rates of 22 joints were calculated [6]. The prevalence of radiological osteoarthritis was highest for the cervical spine and increased from 0.3% in women aged

20–24 to 84.3% in women aged 75–79. In men a similar increase was observed, from 0.7% to 84.8%. Seventy-five per cent of the women had osteoarthritis (grade ≥2) of their DIP joints. Severe osteoarthritis was most common in those aged >45 years, and the prevalence rate exceeded the 20% for the cervical spine and lumbar spine, DIP joints of hands, and, in women only, MCP joints, first CMC joints, first metatarsophalangeal joints, and knees.

Since the Kellgren and Lawrence score is based on an ordinal scoring system, it is more difficult to determine annual progression than to assess changes in joint space narrowing over time. In a systematic review, the annual radiographic progression was calculated as percentage with change of at least one grade [7]. Including both data from observational studies and clinical trials, the overall mean risk of Kellgren and Lawrence annual progression of at least one grade was 5.6 ± 4.9%, with a higher risk associated with shorter disease duration, and with cohorts that included both incident and prevalent cases. This overview also showed that patients with a Kellgren and Lawrence score ≥2 at inclusion into a study have a higher risk of progression than those recruited with a Kellgren and Lawrence score ≥1 (6.2% vs 3.3%).

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Paper 1.2: The association between rheumatoid arthritis and lymphoma

Reference

Isomäki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J Chron Dis* 1978;**31**(2):691–6.

Purpose

To compare the incidence of malignancy in patients entitled to free medication for rheumatoid arthritis in Finland with that in the general Finnish population matched for age and gender.

Population studied

The population studied comprised patients on the Finnish Social Insurance Institution's Population Data Register (started in 1965) as being entitled to reimbursable medication for 'rheumatoid arthritis'. The term 'rheumatoid arthritis' included systemic connective tissue disease until 1970 (1.7% of cases) and ankylosing spondylitis since 1970 (2.2% of all cases).

Study design

This paper describes a longitudinal observational study using population registers. Details of patients entitled to reimbursable medication for 'rheumatoid arthritis' from 1967–1973 were linked to the Finnish Cancer Registry in order to identify all new cancer cases diagnosed from 1 January 1967 or the date of the first rheumatoid arthritis prescription until 31 December 1967 or death. The numbers of various types of malignancy observed were compared with those expected in the general Finnish population matched for age and sex.

Results

The study follows 11,483 men and 34,618 women with 'rheumatoid arthritis' for 213,911 years. The authors report 1,202 incident malignancies as compared to the 1,137.89 expected.

The authors report that the incidence of cancer of the respiratory organs, lymphoma, myeloma, and leukaemia was increased in men with rheumatoid arthritis (Table 1.2). Although the overall incidence of malignancy was not increased in women, the incidence of Hodgkin's disease, lymphoma, and myeloma was increased.

Critique of the paper

There are two weaknesses in the composition of the rheumatoid arthritis cohort: (i) no case definition was used beyond the requirement of medication for a condition labelled as rheumatoid arthritis by the physician in charge of the case, and (ii) there was 'contamination' of the cohort with cases of connective tissue disorder and ankylosing spondylitis.

Table 1.2 Occurrence of malignancies by site

Sex	Primary site	Observed number	Expected number	P value	SIR (95% CI)*
Male	All	407	354.11	<0.01	1.14 (1.04–1.27)
	Respiratory organs	171	132.75	<0.01	1.28 (1.10–1.50)
	Hodgkin's disease	5	2.28	NS	2.10 (0.71–5.12)
	Lymphoma	13	4.84	<0.01	2.69 (1.43–4.59)
	Myeloma	7	3.26	<0.05	2.15 (0.86–4.42)
	Leukaemia	18	7.10	<0.01	2.54 (1.50–4.01)
Female	All	795	783.78	NS	1.01 (0.94–1.09)
	Hodgkin's disease	14	4.54	<0.01	3.08 (1.69–5.17)
	Lymphoma	25	9.34	<0.01	2.68 (1.73–3.95)
	Myeloma	21	9.49	<0.01	2.21 (1.37–3.38)
	Leukaemia	27	18.74	NS	1.44 (0.95–2.10)

* CI, confidence interval; SIR, standardized incidence ratio. Calculated using a Poisson distribution around the observed number. Not presented in the original paper.

In addition, the paper was published before the widespread calculation of relative risk and 95% CI. We have included these in Table 1.2 for completeness. In addition the authors do not address the possible reasons for the link beyond speculating that in some way patients are susceptible to both rheumatoid arthritis and lymphoproliferative malignancies.

Significance and importance of the paper

This is one of the earliest examples in rheumatology of the use of population registers and record linkage to address an important epidemiological question. The Scandinavian countries are ideally placed to conduct such studies as the use of a unique identification number, and the existence of a large number of population-based registers makes linkage relatively straightforward. This was the first study to use this design to address the hypothesis of an increased risk of lymphoproliferative malignancies in patients with rheumatoid arthritis and remains the second largest study conducted to date [1]. A meta-analysis published in 2008 of 14 studies published between 1990 and 2007 found an overall twofold increase risk of lymphoma in rheumatoid arthritis (SIR: 2.08; 95% CI, 1.80 –2.39)—very similar to that reported by Isomäki [2]. In recent years we have seen an elegant demonstration that the risk of lymphoma in rheumatoid arthritis is associated with cumulative disease activity and exposure to immunosuppressive medications such as azathioprine [3, 4]. There was considerable concern at the time of their introduction that anti-tumour necrosis factor therapy might further increase the risk of lymphoma—but this has not been borne out with time. The Isomäki paper continues to provide a useful benchmark with which to compare more recent studies conducted in an era when treatment of rheumatoid arthritis has improved dramatically and one might therefore expect the excess risk of lymphoma to diminish.

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Paper 1.3: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis

Reference

Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31(3):315–24.

Purpose

The 1987 American Rheumatism Association/American College of Rheumatology criteria for rheumatoid arthritis were developed in order to improve specificity and sensitivity and additionally to improve simplicity, as compared to the 1958 American Rheumatism Association criteria. [1–4]

Participants and patients

In this study, 262 consecutive patients with rheumatoid arthritis and 262 control patients with a rheumatic disease other than rheumatoid arthritis (e.g. osteoarthritis, systemic lupus erythematosus, psoriatic arthritis, or other), including both new and established patients, were selected by the nine rheumatologist members of a subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology and 32 other rheumatologists. The certainty of the patient having rheumatoid arthritis was estimated by the rheumatologist on a 10 cm visual analogue scale.

Study design

The evaluated criteria set included the individual items of the old American Rheumatism Association and New York criteria (Table 1.3) for rheumatoid arthritis and items considered to be important by the committee following a Delphi method procedure. Two statistical approaches were applied to develop the classification criteria. First, combinations of variables which were most sensitive and specific to the classification of rheumatoid arthritis were selected by means of Boolean algebra; for example, a patient would be classified as having rheumatoid arthritis if at least X out of Y criteria were present. The second method involved selecting variables which best discriminated rheumatoid arthritis patients from controls using a 'classification tree'. All analyses were repeated for patients with 'new' disease and for patients with established disease. Finally, the specificity of the two methods was tested against 137 consecutive subjects enrolled in a USA prospective study.

Results

Items selected by the committee included morning stiffness, pain on motion in joints, swelling in ≥3 joint areas, symmetric swelling, subcutaneous nodules, abnormal rheumatoid factor, and radiological findings. The accuracy, calculated as the mean of sensitivity and specificity, of these individual items varied from 50.3 for pain on motion of the distal interphalangeal joint to 87.4 for swelling of ≥3 joint areas upon physical examination. The

Table 1.3 Comparison of items included in the American Rheumatism Association criteria and the New York criteria

Item	American Rheumatism Association criteria	New York criteria
Morning stiffness	X	
Joint pain	X	X
One joint swollen	X	
Two joints swollen	X	
Symmetric swelling	X	
Joint swelling		X
Rheumatoid nodules	X	
Serum rheumatoid factor	X	X
Mucin clot	X	
Synovial biopsy	X	
Nodule biopsy	X	
Radiographic findings	X	X

Table 1.4 The 1987 revised criteria for the classification of rheumatoid arthritis (list format)*

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least one hour before maximal improvement.
2. Arthritis of three or more joint areas	At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP < wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least one area swollen in a wrist, MCP, or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in Criterion 2) on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal mounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal controls.
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posterior/anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

* For classification purpose, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with Criterion 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made; DIP, distal interphalangeal; PIP, proximal interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal.

Source data from Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988 Mar;31(3):315–24.

final seven criteria and their definitions included in the 1987 criteria for rheumatoid arthritis are shown in Table 1.4. To be classified as having rheumatoid arthritis, patients had to satisfy at least four out of these seven criteria. The criteria included in the classification tree were slightly different and did not include morning stiffness or rheumatoid nodules (Figure 1.1) [5]. Compared to the 1958 American Rheumatism Association and New York criteria, the sensitivity and specificity improved for the revised classification criteria and classification tree to 91.2% and 93.5%, respectively, for sensitivity and to 89.3% and 89.3%, respectively, for specificity.

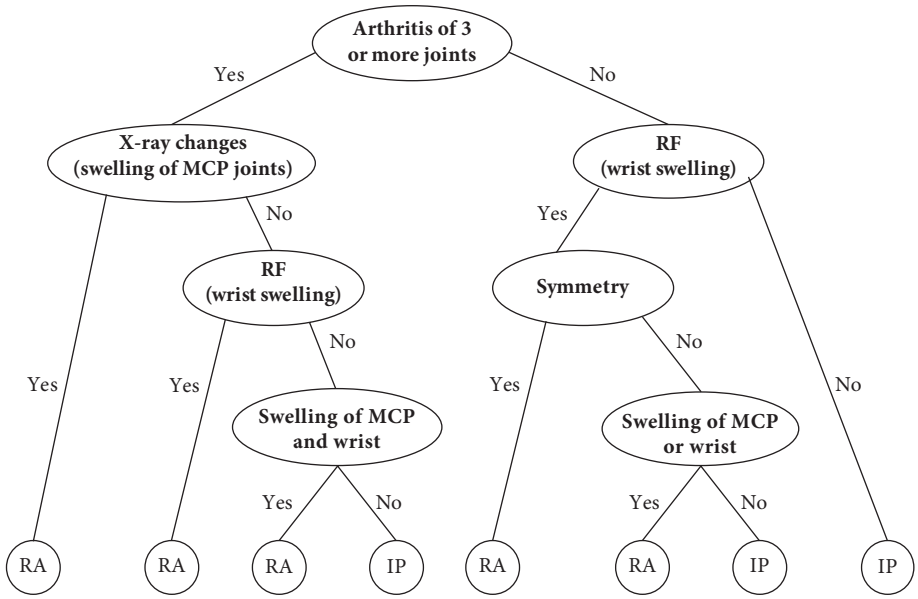

Fig. 1.1 Tree format of the American College of Rheumatology 1987 criteria for the classification of rheumatoid arthritis, as applied to patients with inflammatory polyarthritis; IP, inflammatory polyarthritis; MCP, metacarpophalangeal; RA, rheumatoid arthritis; RF, rheumatoid factor.

Critique of the 1987 criteria

The main criticism of the 1987 criteria for rheumatoid arthritis is that they were developed in a cohort of patients with established rheumatoid arthritis. The specificity of the criteria was especially low in patients with early rheumatoid arthritis. The pooled sensitivity and specificity of the 1987 criteria in early rheumatoid arthritis (<1 year disease duration) were 77% (68%–84%) and 77% (68%–84%), respectively, for the list format and 80% (72%–88%) and 33% (24%–43%), respectively, for the tree format [6]. In established rheumatoid arthritis, the pooled sensitivity and specificity were respectively 79% (71%–85%) and 90% (84%–94%), respectively, versus 80% (71%–85%) and 93% (86%–97%), respectively. In the

last decade it has been shown that early and aggressive treatment of inflammatory arthritis is clinically more beneficial, resulting in less accrual joint damage and long-term disability [7–9]. If the 1987 criteria for rheumatoid arthritis are used to determine which patients should be included in treatment studies, or even as a guide in clinic for treatment decisions, those who might benefit most from early intensive treatment would be excluded. For these reasons, new criteria showing better specificity were developed and published in 2010 [10–12].

A further criticism is in the selection of the comparison cohort. Many of the patients included in the comparison cohort had non-inflammatory conditions which are easily distinguishable from rheumatoid arthritis. In studies of criteria development, the comparison group should have diseases which have features in common with the disease under study.

Finally, unlike the 1958 criteria, there are no exclusions included in the 1987 criteria. Thus it is possible, for example, for someone with classical gout to also be classified as having rheumatoid arthritis if they happen to fulfil the 1987 criteria.

Significance and importance of the paper

In the 30 years following the publication of the 1987 criteria for rheumatoid arthritis, the criteria have been used extensively as entry criteria in clinical trials and for observational studies. This has facilitated generalisability of the results of such studies. Due to a lack of diagnostic criteria for rheumatoid arthritis, the criteria have also been widely used in practice for diagnosis. Furthermore, incidence rates, based on the 1987 criteria, have been reported among different populations, ranging from 0.1 cases per 1,000 for France to 0.5 cases per 1,000 for the USA [13]. Prevalence rates range from 1.8 cases (crude rate) per 1,000 in Yugoslavia to 10.7 cases per 1,000 in the USA.

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Paper 1.4: The global burden of disease

Reference

The Global Burden of Disease Study 2010. *Lancet* 2012:380(9859): 2053–260.

Background

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) was launched in 2007 and is a collaboration of 486 scientists from 302 institutes in 50 countries. In 2012 a summary of the methods and findings of the GBD 2010 was published in the Lancet [1–3].

Purpose

1. To assess diseases, injuries, and causes of death, including musculoskeletal disorders (MSD), across the world, and their risk factors.
2. To describe changes in the burden of disease between 1990 and 2010.

Study design

Review of all the relevant data (published and unpublished) concerning the incidence, prevalence, and burden of MSDs.

Methods

The GBD study group, with the help of experts in the field, gathered information on causes of death, diseases, and injuries and their risk factors by age, sex, and geography at specific points in time [4]. Countries were divided into 21 regions, or 7 super-regions, based on 2 criteria: epidemiological homogeneity and geographical contiguity. The burden of disease was estimated for 20 age–sex groups. The group analysed causes of death, years of life lost due to premature mortality (YLLs), years lived with disability (YLDs), and disability adjusted life years DALYs. The construct of DALYs was originally developed by the 1990 GBD group to capture both the prevalence and burden of disease and injury and premature mortality. DALYs were calculated as the sum of YLLs and YLDs. In addition, risk factors for specific diseases and causes of death were evaluated. For each analysis, a major effort was made to define the outcome and introduce a replicable scientific approach to global epidemiological research. Advanced statistical models were used to estimate DALYs, YLLs, and YLDs, and 95% uncertainty intervals were calculated to take into account the heterogeneity in empirical data, and uncertainty in the direct estimation models used when source data were scarce.

Results

Between 1970 and 2010, average life expectancy for both men and women increased from 56.4 years (55.5–57.2) to 67.5 years (66.9–68.1) for men and from 61.2 years (60.2–62.0) to 73.3 years (72.8–73.8) for women [5]. Changes in global and regional mortality rates between 1990 and 2010 from 235 causes of death were estimated for 187 countries. In 2010, there were 52.8 million deaths globally with an age-standardized death rate of 784.5

(756.3–801.6) per 100,000 [6]. The age-standardized death rate for MSDs was estimated to be 1.7 (1.1–2.2) per 100,000 in 1990 and 2.3 (1.7–3.2) per 100,000 in 2010, an increase of 37.8%. This increase was mainly attributable to MSDs other than rheumatoid arthritis, as the age-standardized death rate for rheumatoid arthritis decreased by 9.9% between 1990 and 2010 (respectively, 0.8 (0.6–1.1) vs 0.7 (0.6–1.0) per 100,000).

In addition to death rates and causes of death, it is also important to raise awareness of the prevalence and severity of non-fatal health outcomes from diseases and injuries in the general population in different regions [7]. Among 291 diseases and injuries, MSDs were very common with an estimated global prevalence for men and women of, respectively, low back pain (9.64% vs 8.70%), osteoarthritis of the knee (2.56% vs 4.74%), and other MSDs (7.56% vs 8.73%). Although all cause YLDs remained relatively stable between 1990 and 2010 (%Δ 2.5%), there was a steep increase in YLDs for all investigated MSDs: rheumatoid arthritis (%Δ 13.2%), osteoarthritis (%Δ 26.2%), low back and neck pain (%Δ 9.4%), gout (%Δ 14.9%), and other MSDs (%Δ 11.3%).

By combining YLL and YLD data, DALYs were calculated to assess the overall burden of diseases [8]. For both men and women, the impact of MSDs compared to other diseases is especially noticeable in the population aged over 40 years (Figure 1.2). MSDs accounted for 6.8 of DALYs, with low back pain accounting for about 50%, neck pain 20%, osteoarthritis 10%, and rheumatoid arthritis for approximately 3% of MSD DALYs. In the last two decades, among 291 diseases, MSDs ranked higher in 2010 compared to 1990, and the percentage increases in DALYs are as follows: low back pain (%Δ 9.7%), neck pain (%Δ 8.5%), osteoarthritis (%Δ 26.2%), and rheumatoid arthritis (%Δ 11.1%). The ranking varies by region, and MSDs are ranked higher in high-income Asia Pacific, Western Europe, Australasia, high-income North America, Central Europe, Southern Latin America, Eastern Europe, East Asia, and Central America compared to Central and East Asia and Africa.

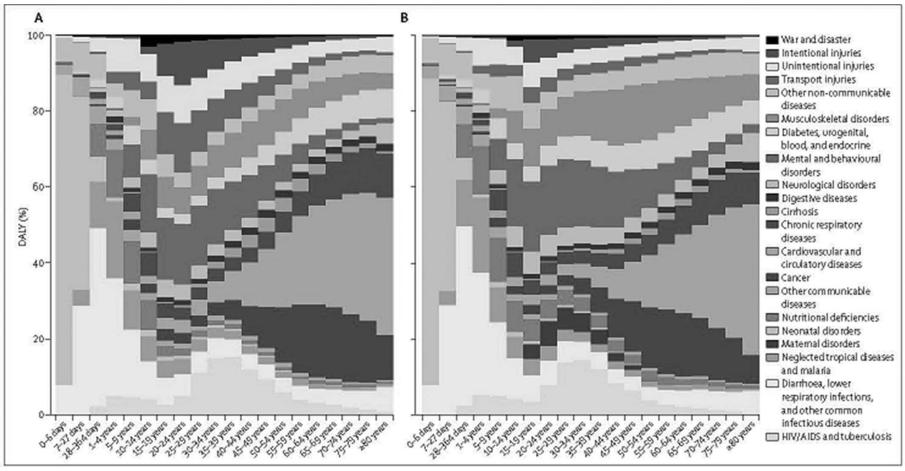

Fig. 1.2 Percentage of global disability-adjusted life years by age, sex, and cause in 2010. Distribution of disability-adjusted life years for male individuals (A) and female individuals (B); DALY, disability-adjusted life years.

Identification of risk factors for diseases will help in the development of prevention programmes [9]. In general, the most common risk factors for diseases and injuries are those associated with poverty and those that affect children. Risk factors related to MSDs were limited and included high body mass index and a diet high in sugar-sweetened beverages, both associated with osteoarthritis and low back pain. Interestingly, smoking, one of the major risk factors for developing rheumatoid arthritis, was not reported [10, 11].

Critique of the study

These estimates represent a tremendous amount of work for the scientists involved. They will have been hampered by the lack of contemporary data for many regions, and by contradictory results from studies from the same region. Then there is the challenge of developing and implementing a measure of disability and disease burden which is applicable across the whole range of human disease, the whole age span, and regions with very different health systems. This is especially challenging for diseases which are slowly progressive, as opposed to conditions which are life changing (e.g. limb trauma) but then stable.

Significance and importance of the study

The papers included in this special issue of *The Lancet* are a major contribution to researchers, health policy makers, world health organizations, and the general public in understanding the global burden of disease, injury, and its risk factors. These findings will help us to understand the impact of diseases and injuries across different regions in the world and the need of specific intervention programmes. These papers also emphasize the growing burden of MSDs. Although the death rate for rheumatoid arthritis has decreased by ~10% over the last two decades, DALYs have increased. There is also a considerable increase in DALYs for neck and back pain and osteoarthritis. The latter may partly be explained by an aging population and an increase in body mass index, especially in high-income regions.

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Paper 1.5: The shared epitope hypothesis

Reference

Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987;30(11):1205–13.

The major histocompatibility complex

The molecules of the human leukocyte antigen (HLA) interact with the immune system to discriminate self from non-self. The HLA molecules bind peptide antigens and present them to T-lymphocytes. Crucial to this role is the three-dimensional structure of the HLA molecules, as it determines peptide and T-cell binding (Figure 1.3).

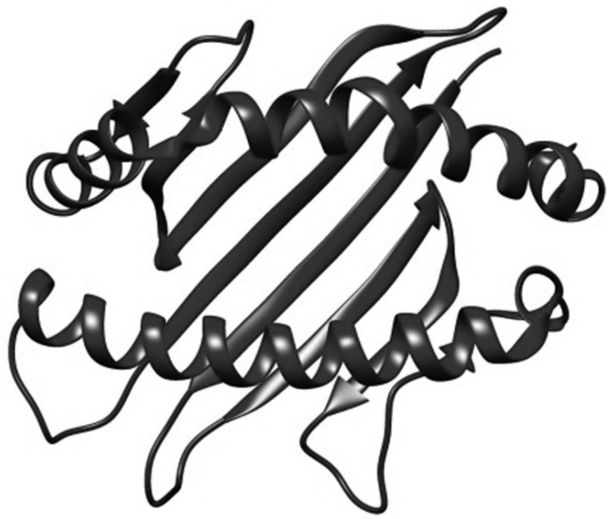

Fig. 1.3 Three-dimensional diagram of human leukocyte antigen B. This structure is based on Protein Data Bank entry 3bvp. This figure was prepared using UCSF Chimera.

The HLA molecules are encoded in a gene-rich region of chromosome 6 known as the major histocompatibility complex (MHC). There is a vast amount of genetic variation (polymorphism) within the MHC, enabling the HLA molecules to bind to a variety of peptides; the *MHC* genes are among the most polymorphic human genes.

There are two subgroups of HLA molecules: Class I includes HLA-A, B, and C. They bind to the membrane of all nucleated cells. Class II molecules include HLA-DR, DQ, and DP and are present on the cell surface of antigen-presenting cells predominantly (including B lymphocytes, macrophages, and dendritic cells). Class II molecule expression can also be

induced during inflammation on cell types that normally have little or no expression. A Class II molecule is composed of an α chain and a β chain. Class I molecules contain an α chain encoded within the MHC and a β_2 microglobulin which is encoded elsewhere (Figure 1.4). Class II molecules present processed peptide fragments to CD4 T-lymphocytes, a process which, in health, causes both activation and proliferation of T-lymphocytes if non-self is presented, or anergy, whereby the T-lymphocyte is functionally inactivated if self is presented.

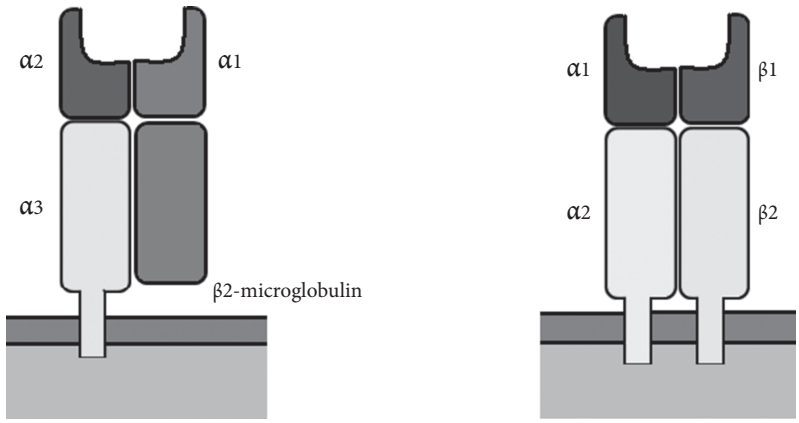

Fig. 1.4 Two-dimensional image of human leukocyte antigen Class I and II molecules.

HLA Class II genetics

Genes (such as *HLA-DRA* and *HLA-DRB*) within the MHC code for both the α (heavy) and β (light) chains. The DQ and DP antigens have highly variable (polymorphic) α and β chains which can unite in numerous combinations. The DR antigens share an essentially non-polymorphic α chain, while the β chain remains highly polymorphic. The number of *DR* genes that are expressed can also vary between individuals. In some cases, two DR molecules are expressed; both will express the same non-polymorphic DR-α chain but one will express the β chain encoded by the *DRB1* gene and the other will express a β chain encoded by a second *DR* locus, called *DRB3*, *DRB4*, *DRB5*, etc.

As the technology used to classify *HLA* genes has evolved over the years, so has the nomenclature for the different alleles at individual *HLA* genes. The original nomenclature was based upon immunological techniques. With the advent of gene sequencing methods, it was possible to further classify *HLA* genes into subtypes which required revision of the nomenclature.

HLA association with rheumatoid arthritis

With respect to HLA and rheumatoid arthritis, much focus has been on the *HLA-DR* locus. Astorga et al. first suggested that HLA subtypes may be associated with rheumatoid arthritis

in 1969 [1]. They established that the lymphocytes from two different individuals with rheumatoid arthritis were frequently nonstimulatory and therefore expressed similar HLA Class II molecules. Further work established that *HLA-DR4* alleles are associated with rheumatoid arthritis [2, 3]. Within the HLA-DRβ chain, there are three highly variable regions (hypervariable regions) which distinguish between the DR subtypes. The third hypervariable region is located between amino acids 68–77 and is a major site of variation defining the *DR4* allele (Figure 1.5), and sequence differences in this region affect T-cell function [4].

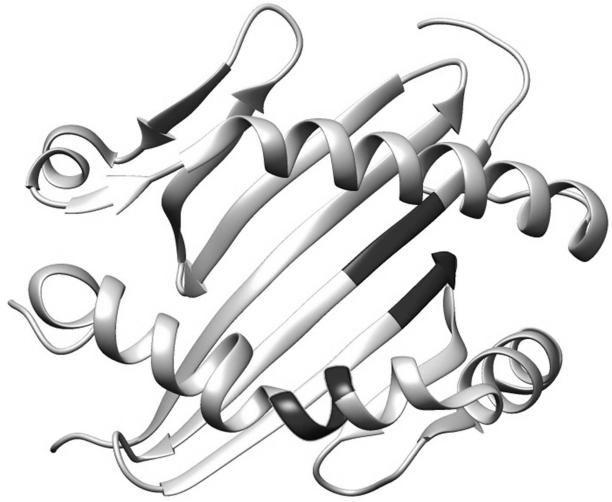

Fig. 1.5 Three-dimensional diagram of the human leukocyte antigen DRB chain illustrating the three hypervariable regions (dark coloured). This structure is based on Protein Data Bank entry 3pdo. This figure was prepared using UCSF Chimera.

However, *HLA-DR4* is neither necessary nor sufficient for the development of rheumatoid arthritis. Other alleles such as *HLA-DR1* also confer an increased susceptibility to rheumatoid arthritis. This has led to the shared epitope hypothesis [5].

Significance and importance of this paper

The shared epitope hypothesis aims to explain the association of multiple *HLA* alleles with rheumatoid arthritis. Gregersen et al. described the results of previous research as evidence for their shared epitope hypothesis. Three subtypes of *HLA-DR4* (historically named *Dw4*, *Dw6*, and *Dw14*) were strongly associated with rheumatoid arthritis, whereas a fourth subtype (*Dw10*) was not. Gregersen et al. compared the sequences of HLA alleles associated with rheumatoid arthritis and discovered a region of shared amino acid sequence in the third hypervariable region (Figure 1.5). This led to the shared epitope hypothesis, which proposed that this shared amino acid sequence conferred a proportion of risk for the development of rheumatoid arthritis.