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WHO Scientific Group



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Contents

1. Introduction	1
2. International cooperation in rheumatology	1
2.1 International League Against Rheumatism	1
2.1.1 Education and publications	2
2.1.2 Epidemiology	2
2.1.3 Clinical studies	3
2.1.4 National and international agencies	3
2.2 Recommendations for international cooperation	3
3. Educational programmes and opportunities for rheumatic diseases	3
3.1 Introduction	3
3.2 Public education	4
3.3 Undergraduate medical education	4
3.4 Postgraduate specialist education	5
3.5 Recommendations for training and research	6
4. Socioeconomic factors in rheumatic diseases	6
4.1 Introduction	6
4.2 International cooperation	8
4.3 Recommendations for research	8
5. Genetic factors in rheumatic diseases	9
5.1 Introduction	9
5.2 Recommendations for training and research	9
6. Rheumatoid arthritis	10
6.1 Introduction	10
6.1.1 Epidemiology	10
6.1.2 Clinical diagnosis	10
6.1.3 Pathogenesis	11
6.1.4 Rheumatoid factors and autoantibodies	11
6.2 Education	11
6.3 Cellular immunology	12
6.4 Lymphocyte trafficking and adherence	12
6.5 Regulation of the immune response	12
6.6 Recommendations for research	13
7. Systemic lupus erythematosus	14
7.1 Introduction	14
7.1.1 Clinical features	14
7.1.2 Diagnosis	14
7.1.3 Etiopathogenesis	15
7.1.4 Treatment	15
7.2 Education	16
7.3 Recommendations for research	16
8. Systemic sclerosis	17
8.1 Introduction	17
8.2 Pathophysiology	17
8.3 Treatment	19

8.4 Prognosis and disease monitoring	19
8.5 Recommendations for research	20
8.5.1 Epidemiology	20
8.5.2 Immunology	20
8.5.3 Pathophysiology	21
8.5.4 Experimental therapeutics	21
9. Sjögren syndrome	21
9.1 Introduction	21
9.2 Clinical spectrum	22
9.2.1 Diagnosis	22
9.2.2 Pathology	23
9.3 Education	24
9.4 Recommendations for research	24
9.4.1 Epidemiology	24
9.4.2 Immunopathology	24
9.4.3 Treatment	25
10. Lyme disease	25
10.1 Introduction	25
10.1.1 American history	25
10.1.2 European history	26
10.2 Clinical features	26
10.3 Diagnosis	27
10.4 Treatment	27
10.5 Education	28
10.6 Recommendations for research	28
10.6.1 Epidemiology	28
10.6.2 Clinical disease	29
10.6.3 Pathology	29
10.6.4 Prevention and treatment	29
11. Spondyloarthropathies	30
11.1 Introduction	30
11.2 Ankylosing spondylitis	31
11.3 Reiter syndrome	33
11.4 Psoriatic arthropathy	34
11.5 Education	34
11.6 Recommendations for research	35
12. Low back pain	36
12.1 Introduction	36
12.2 Treatment	37
12.3 Prevention	38
12.4 Recommendations for training and research	39
12.4.1 Etiology	39
12.4.2 Treatment	40
12.4.3 Long-term disability	40
13. Osteoarthritis	40
13.1 Introduction	40
13.1.1 Definition	41
13.1.2 Etiology	41
13.1.3 Pathology	42

13.1.4 Radiology	43
13.1.5 Clinical features	43
13.1.6 Treatment and outcome	44
13.2 Epidemiology	44
13.2.1 Prevalence	44
13.2.2 Risk-factors	45
13.2.3 The disease process	46
13.2.4 Impact and outcome	46
13.3 Education	46
13.4 Principal areas for research	48
13.4.1 Epidemiology	48
13.4.2 Clinical subsets	48
13.4.3 The role of trauma	48
13.4.4 The role of aging	49
13.4.5 The role of inflammation	49
13.4.6 The role of extracartilaginous structures	49
13.4.7 The role of the neuromuscular system	50
13.5 Recommendations for research	50
14. Soft-tissue rheumatism	52
14.1 Introduction	52
14.1.1 Fibromyalgia	52
14.1.2 Tendinitis, tenosynovitis, and bursitis	52
14.1.3 Polymyalgia rheumatica	53
14.1.4 Shoulder–hand syndrome	53
14.2 Education	54
14.3 Recommendations for research	54
14.3.1 General recommendations	54
14.3.2 Fibromyalgia	54
14.3.3 Tendinitis, tenosynovitis, and bursitis	55
14.3.4 Polymyalgia rheumatica	55
14.3.5 Shoulder–hand syndrome	55
15. Gout	55
15.1 Introduction	55
15.1.1 Hyperuricaemia	55
15.1.2 Crystal-induced inflammation	56
15.1.3 Population studies	56
15.1.4 Sustained hyperuricaemia	56
15.1.5 Juvenile familial gout	57
15.2 Treatment	57
15.3 Recommendations for research	58
Acknowledgements	59

WHO Scientific Group on Rheumatic Diseases

Geneva, 26–30 June 1989

Members*

Professor E. Allander, Department of Social Medicine, Huddinge University Hospital, Huddinge, Sweden

Professor L.I. Benevolenskaja, Institute of Rheumatology, Academy of Medical Sciences, Moscow, USSR

Professor J.C. Bennett, Chairman, Department of Medicine, University of Alabama, Birmingham, AL, USA

Professor K.D. Brandt, Head, Rheumatology Division, Indiana University School of Medicine, Indianapolis, IN, USA (*Co-Rapporteur*)

Professor W.H. Chahade, Director, Rheumatology Service, São Paulo State Public Hospital, São Paulo, Brazil

Professor Chang Nai-Cheng, Director of Rheumatology, Peking Union Medical College Hospital, Beijing, China

Professor P. Dieppe, Professor of Rheumatology, Department of Medicine, University of Bristol, Bristol, England

Professor L. Gordis, Chairman, Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, USA

Professor M. Homma, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

Professor A.N. Malaviya, Head, Clinical Immunology Service, Department of Medicine, All-India Institute of Medical Sciences, New Dehli, India

Professor C.J. Menkes, Department of Rheumatology, Cochin Hospital, Paris, France

Professor H.M. Moutsopoulos, Chairman, Department of Internal Medicine, University of Ioannina, Ioannina, Greece

Dr K.D. Muirden, Head, Rheumatology Unit, Department of Medicine, University of Melbourne, Victoria, Australia

Professor A.L. Nachemson, Chief, Department of Orthopaedics, Gothenburg University, Gothenburg, Sweden

Professor V.A. Nassonova, Director, Institute of Rheumatology, Academy of Medical Sciences of the USSR, Moscow, USSR

Professor C.M. Plotz, Department of Medicine, State University of New York, Downstate Medical Center, New York, NY, USA

Dr J.T. Scott, Consultant Physician, Department of Rheumatology, Charing Cross Hospital, London, England (*Co-Rapporteur*)

Dr L.E. Shulman, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA (*Chairman*)

Professor J. Villiaume, President, International League Against Rheumatism, Henri Mondor Hospital, Créteil, France (*Vice-Chairman*)

* Unable to attend: Professor E. Munthe, Medical Director, Oslo City Department of Rheumatology, Oslo, Norway, and Professor H.A. Valkenburg, Department of Epidemiology, Erasmus University, Rotterdam, Netherlands.

Secretariat

Dr E. Chigan, Director, Division of Noncommunicable Diseases, WHO, Geneva, Switzerland

Dr Hu Ching-Li, Assistant Director-General, WHO, Geneva, Switzerland

Dr N.G. Khaltayev, Medical Officer, Diabetes and other Noncommunicable Diseases, WHO, Geneva, Switzerland (*Secretary*)

1. **Introduction**

A WHO Scientific Group on Rheumatic Diseases met in Geneva from 26 to 30 June 1989. The meeting was opened by Dr Hu Ching-Li, Assistant Director-General, who welcomed participants on behalf of the Director-General.

The rheumatic diseases are a major cause of disability throughout the world. Chronic rheumatic conditions place a considerable social and economic burden on all societies, and not only on those with a high life expectancy. For example, the high prevalence of rheumatic complaints and disability in Indonesia, in both urban and rural areas, is similar to that in a more developed country such as Australia.

Much research is taking place into the causes and treatment of rheumatic disease. Significant advances that will result in more effective prophylaxis and treatment have been made in the areas of genetics, immunology, pharmacology and connective tissue biochemistry. In other areas, however, such as epidemiology, rehabilitation, risk-factor identification, education, and the social consequences of rheumatic diseases, there is an urgent need for more research. This need is all the greater owing to the changing morbidity and mortality patterns in both developed and developing countries as a result of increasing life expectancy, the rapid growth of urban populations, changes in lifestyle, and other factors.

In order to meet these new challenges effective rheumatological community control programmes are needed. These would encompass the education of professional staff and patients, community participation, early disease detection, and effective treatment and rehabilitation, and should be integrated into the existing primary health care system.

There are well over 100 rheumatic diseases, and it was not feasible to consider all of them. The Group therefore decided to consider in detail ten of the most important diseases. For each disease discussed, the principal objectives were as follows.

- To assess and review current knowledge and identify areas of deficiency.
- To select necessary information that should be made freely available.
- To make recommendations on education, prevention and treatment, and research.

2. **International cooperation in rheumatology**

2.1 **International League Against Rheumatism**

The International League Against Rheumatism (ILAR), founded in 1927, is a worldwide federation of national societies of rheumatology. National societies have now been set up in more than 70 countries throughout the

world, and are grouped by continent into regional Leagues Against Rheumatism.

The aims of ILAR are to increase awareness of the medical and social importance of rheumatic disorders and to foster knowledge of their prevention and treatment. It also promotes cooperation at all levels to combat the rheumatic diseases, and encourages and assists in the establishment of national societies of rheumatology. In order to achieve these goals, a World Congress is held every four years, which brings together rheumatologists from all parts of the world to share their experience.

Through its Standing Committees, which collaborate closely with WHO, ILAR's activities cover four main areas:

- education and publications
- epidemiology
- clinical studies
- national and international agencies.

2.1.1 ***Education and publications***

Apart from its role in publishing educational material and in organizing lectures and workshops, ILAR has established awards for young rheumatologists enabling them to travel abroad and obtain practical and theoretical training in rheumatology centres of their choice.

During the early 1980s, WHO and ILAR carried out a large-scale practical exercise, the Community Oriented Programme for the Control of Rheumatic Diseases (COPCORD), which originated within the geographical territory of the Asia/Pacific League Against Rheumatism. The study was based in Australia, Indonesia, Malaysia and the Philippines in order to assess the frequency of rheumatic pain and disability, and the natural history of rheumatic diseases, in more than ten thousand people in rural and urban areas.

COPCORD has been extremely useful, both in generating epidemiological data and as a model for teaching rheumatology to physicians and paramedical staff.

2.1.2 ***Epidemiology***

ILAR has instigated many epidemiological studies to explore the effects of race, climate, diet, economic factors, and environment on the development of the rheumatic diseases. Particularly for osteoarthritis and low back pain, which are important causes of morbidity, especially in the elderly, the recognition and correction of risk-factors, such as obesity, physical inactivity, stress and smoking, open the prospect of preventing these diseases.

ILAR and WHO are collaborating to produce an application of the Tenth Revision of the International Classification of Diseases (ICD-10) to

rheumatological and orthopaedic disorders as ICD-R & O (2nd edition). Such an expanded classification can lead to a greater understanding of the epidemiology of these diseases and to improved global statistical data.

2.1.3 ***Clinical studies***

Together with the International Union of Immunological Societies, ILAR has been involved in the development of reference reagents for antinuclear antibody testing and in the standardization of clinical laboratory tests. Work is also under way on the standardization of radiological criteria for the rheumatic diseases and on the post-marketing surveillance of anti-rheumatic drugs.

2.1.4 ***National and international agencies***

ILAR supports and encourages organizations throughout the world involved in the fight against rheumatic diseases. Recent efforts have been directed particularly towards China, where there is a great need for better prevention, diagnosis, and treatment of rheumatic diseases, and towards Africa, where rheumatic diseases are widespread and unusual in their etiology and natural history. Despite the more pressing needs of other diseases, national rheumatology societies have been established in many African countries in recognition of the importance of the physical and socioeconomic consequences of the rheumatic diseases.

2.2 **Recommendations for international cooperation**

- There should be increased international cooperation to educate doctors and other health workers in the importance of following a recognized disease classification for the consistent diagnosis of rheumatic disorders.
- The use by national data systems of ICD descriptors and codes should be encouraged.

3. **Educational programmes and opportunities for rheumatic diseases**

3.1 **Introduction**

Despite their recognized socioeconomic burden and the efforts of WHO and ILAR, the chronic rheumatic diseases continue to be largely neglected in the allocation of resources for education and health care.

In 1988, a population census in Australia showed that since 1981 there had been an 18% increase in the number of disabled and handicapped people, the most common causes of disability being musculoskeletal and connective tissue disorders. The increase may partly reflect the aging population and, perhaps, greater awareness and better diagnosis.

In developing countries, such as Indonesia, there is a high prevalence of rheumatic complaints and disability, surprisingly similar in both urban and rural settings to that seen in more developed countries, such as Australia.

Despite the large numbers of patients, figures from COPCORD show that even in very isolated rural areas almost all those with major rheumatic complaints were seen by a doctor, even though most patients were not happy with the outcome of their treatment. However, in Indonesia and the Philippines, many patients with less severe complaints did not see a doctor but were diagnosed and treated by relatively inexperienced community nurses. This finding raises doubts about the quality of care available and emphasizes the urgent need for better primary care education in the rheumatic diseases. This need is further illustrated by the high frequency of self-medication in many communities and the misuse and overuse of drugs such as corticosteroids.

3.2 Public education

The Australian Health Survey of 1981 revealed that about half the patients studied with rheumatic complaints had not recently consulted a doctor, mostly because they felt that doctors could not be of help.

The rheumatic diseases often do not receive the public attention that they merit. During the International Year of Disabled Persons in 1981, the rheumatic diseases were not even mentioned in a list of the ten diseases causing disability throughout the world and worthy of particular attention.

The popularity of folk remedies and special diets reflects the inadequacy of public education about the rheumatic diseases in many parts of the world, but much effort is now being put into combating this. In Indonesia, for example, a traditional type of puppet show, which is sometimes used in villages to convey a political message as well as for entertainment, has been successfully adapted to demonstrate simple measures for the prevention of rheumatic complaints. In some countries, television and public transport advertising are used to convey health messages about arthritis.

Many health departments run costly advertising campaigns warning the public about AIDS, smoking, alcohol, and drugs. Similar publicity should be given to ways of preventing osteoporosis and some other rheumatic conditions, including occupational diseases. Progress in this area has been slow, partly because many of the risk-factors for rheumatic diseases have not been clearly identified.

3.3 Undergraduate medical education

The needs of undergraduate rheumatology teaching were discussed in detail at a symposium of the European League Against Rheumatism (EULAR) held in 1987 and cosponsored by the WHO Regional Office for Europe. At that time, some medical schools in Europe still had no rheumatology teaching, but examination of the locomotor system was

included in the university medical curricula of all the participating countries.

In Australia, recent figures indicate that more than half of all medical students receive inadequate training in rheumatology, and very few medical schools teach about the role of allied health professionals.

In general, undergraduate teaching in family medicine gives insufficient emphasis to the importance of joint diseases, yet, in the United Kingdom, it is estimated that 20% of the average general practitioner's consulting time is devoted to rheumatic complaints.

3.4 Postgraduate specialist education

In many of the more developed countries, there are well-structured postgraduate training programmes in rheumatology, often as part of general training in internal medicine. The lack of specialists in developing countries could mean that shorter programmes with less emphasis on internal medicine might be more appropriate.

In many countries, teaching tends to be based in hospitals with emphasis on rheumatoid arthritis and connective tissue diseases. In practice, however, rheumatologists most often look after patients with osteoarthritis and soft-tissue rheumatic problems, which are also the commonest conditions seen in primary health care.

In some developed countries there are more than adequate numbers of trained rheumatologists in clinical practice, but too few teachers and research workers in the subject. This difference may partly be explained by the greater practical appeal and financial rewards of clinical rheumatology. However, research is becoming more attractive because of better communication and cooperation between people working in different disciplines.

Another important concern is how best to train rheumatologists in developing countries. The establishment of even limited personal contact with rheumatologists in more developed countries can have a beneficial effect in building up long-term relationships between developing countries and particular specialist units. Teachers may thus become more aware of the important diseases in a specific community and be able to visit the trainee's country and gain a better appreciation of its problems.

In 1985, the ILAR Post-Congress Education Workshop held in Sydney addressed the concern that it might be a mistake to take health workers from their own environment and send them overseas to train in sophisticated units in an entirely different society. It concluded that training should be flexible, depending on local needs and conditions, and that students should gain research experience. Moreover, it was agreed that, regardless of social and economic developments in different countries, the content and length of postgraduate core training in rheumatology should be similar. This consensus validated international

efforts to provide postgraduate training for students from developing countries in established units in developed countries where both funds and facilities were available. The Workshop concluded that such interchange, collaboration, and education would foster research and ultimately be of benefit to the treatment of all patients with rheumatic diseases.

Postgraduate training in specialist units for medical graduates from developing countries has proved extremely popular, and although it takes some months to acquire complex research skills, some clinical skills can be learnt in a much shorter time. Both the trainee and the host unit benefit from the interchange of ideas at a cultural as well as at a medical level.

ILAR helps in the setting up of educational projects and provides funding for postgraduate fellowships. WHO also offers fellowships in certain circumstances, for example in the clinical epidemiology of rheumatic diseases, and many countries have their own international fellowship programmes. Better coordination and integration of rheumatology teaching are necessary at all levels, as well as a source of reliable information on research and training opportunities for those who seek them.

3.5 **Recommendations for training and research**

More consideration should be given to methods of improving public education and to the possibility of using similar teaching methods and materials in different communities and cultures.

In order to train young rheumatologists from both developing and developed countries, fellowship programmes should be established or expanded in units where funds and expertise are available.

Reliable survey methods and questionnaires for use in both developed and developing countries are needed in order to acquire more information about the rheumatic diseases, including disability and methods of treatment.

The COPCORD database established for the Asia-Pacific region is an important international resource that could be used for case-control and incidence studies as well as for the assessment of risk-factors and educational initiatives.

4. **Socioeconomic factors in rheumatic diseases**

4.1 **Introduction**

In developed countries the rheumatic diseases cause greater morbidity than any other group of conditions. Data from many countries show an increase in the number of people affected, even allowing for the aging of the population.

Pain and disability, often with fatigue, depression and loss of employment, are associated with the major groups of rheumatic conditions that affect the lives of so many people. Pain is the clinical symptom common to all rheumatic conditions, yet knowledge and understanding of it, especially in relation to depression, fatigue and social factors, are poor.

The rheumatic diseases have a major impact on the work and personal lives of individuals, and the magnitude of this impact seems to be linked to a country's level of industrial development. Health expenditure for rheumatic conditions has also been increasing significantly, and will continue to do so as people live longer and treatment, particularly surgery, becomes more expensive.

The few studies from developing countries on the above aspects have shown strikingly similar results, but for most countries there are few reliable data on rheumatic disorders.

Risk-factors can be modified by preventive measures. For example, in postmenopausal women estrogens are beneficial in the prevention of osteoporosis, but this protection lasts only as long as administration of the hormone continues. The effect of such treatment on fracture rates is not yet clear. However, falls among the elderly can be prevented by advice on home safety, the wearing of correct footwear, and consideration of other factors. The question of whether or not oral contraceptives prevent rheumatoid arthritis remains unanswered.

Methods for measuring the effectiveness and outcome of health care, including rheumatological and orthopaedic care, are now available for feasibility studies. Such studies would help to explain the increasing mortality seen in some countries for rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and other related diseases.

Among the lower social classes there is a higher percentage of more severe complaints, and many rheumatic diseases – with a few exceptions such as ankylosing spondylitis and gout – are more prevalent. The higher prevalence of some rheumatic diseases in rural areas may be explained to some degree by social class differences. However, there is evidence that rheumatoid arthritis and gout are more prevalent in urban than in comparable rural populations.

Differences in incidence and prevalence between the sexes have been found for most rheumatic disorders, but hormonal differences do not appear to be a sufficient explanation. Data of good quality on the role of diet, stress and climate on the incidence of rheumatic diseases are relatively few and difficult to interpret. This lack of data reflects the complexity of assessing these three components and also the high cost of carrying out appropriate studies.

4.2 International cooperation

If the worldwide demographic trend towards urbanization continues there will be an unprecedented increase in morbidity from rheumatic diseases, with serious socioeconomic consequences, unless action is taken at national and international levels to disseminate information and provide expertise to fight these diseases. Such information should be available to those working in medical and health education at all levels and should be communicated to the general public and patients as well as to rheumatologists and orthopaedic surgeons.

The rheumatic diseases account for a significant and increasing number of working days lost through illness. The economic impact of these diseases is therefore considerable, but their causes and how they might be prevented are poorly understood. There is a need for demographic projections relating to the planning and utilization of health services to take account of morbidity from rheumatic disease.

4.3 Recommendations for research

Studies comparing different national systems and their response to rheumatic disease morbidity are few and incomplete, whereas reliable socioeconomic data from well-designed studies based on large populations are underused.

In order to plan realistically for future needs, accurate and reliable data are essential. Future studies on the socioeconomic impact of the rheumatic diseases will need to consider carefully how different health care policies and economic circumstances will influence the acceptability and relevance of the results.

A multidisciplinary approach to research, incorporating knowledge from the medical and biological sciences, sociology, biostatistics, health economics and health sciences research, is necessary to measure the impact of demographic changes on the rheumatic diseases. It is also important that such studies have clearly formulated hypotheses and specific aims, and thus yield practicable results.

Criteria for specific diseases should be developed, applicable not only to diagnosis, classification and treatment, but also to disease screening and natural history and to the planning and management of health services.

The different degrees of morbidity caused by rheumatic diseases require careful definition according to validated criteria and an appropriate use of WHO's ICD coding. This coding is currently handled unsatisfactorily in many countries.

Projections of disease frequency and of disease-related events should be made, using short- and long-term estimates of population growth and age and sex composition. Distinction should be made between processes related to aging and those related to disease.

Clearer identification of subsets of diseases and syndromes with common features should be supported to identify similarities in natural history, manifestations and response to treatment, and in order to discover their causes.

The significance and context of sex differences in disease frequencies, as in systemic lupus erythematosus, ankylosing spondylitis, rheumatoid arthritis and others, unexplained by hormonal factors, should be explored.

An international comparative study of the contribution of rheumatic and orthopaedic conditions to work disability should be initiated. The first step could be a comparative study of the content, validity, and other parameters of disability registers.

Existing questionnaires relating to rheumatic diseases should be translated into other languages and tested and evaluated in different sociocultural settings.

The processes should be studied, using international comparisons, by which uncommon rheumatic diseases are identified in order to discover methods that can be used for the early detection of these conditions.

5. Genetic factors in rheumatic diseases

5.1 Introduction

The significance of genetic factors in the pathogenesis of rheumatic diseases is well recognized. The non-random distribution of genetic markers, especially in the human leukocyte antigen (HLA) system, among patients with certain rheumatic diseases, as well as the clustering of cases within families, are strong evidence for the existence of genetic predisposition to rheumatic diseases.

It is important to identify genetic risk-factors so that those affected may have the opportunity to protect themselves, for example by changing their lifestyle and behaviour.

There is little information about the genetic predisposition of different communities to rheumatic diseases, and available data are often insufficient or unsuitable for cross-national studies.

5.2 Recommendations for training and research

Through training courses, general practitioners and other health workers should be educated about the genetic factors related to rheumatic diseases, and more information and educational tools should be provided for this purpose.

The genetic classification of the rheumatic diseases needs to be developed further.

The molecular mechanisms of genetic predisposition to rheumatic

diseases should be studied using the methods of molecular biology and genetic engineering; the responsible genes should be identified, mapped, and isolated for different populations and cultures.

The genetic and environmental risk-factors interacting in the pathogenesis of rheumatic diseases at the patient, family and population levels should be studied and high-risk groups identified for specific diseases.

The relationship between genetic heterogeneity and the clinical polymorphism of nosological forms of rheumatic diseases should be investigated.

6. **Rheumatoid arthritis**

6.1 **Introduction**

Rheumatoid arthritis (RA) is a chronic systemic disorder of unknown cause. It results in debilitating musculoskeletal deformities due to destruction of articular tissues and erosions of bone, and in severe mechanical abnormalities of the joints. Although there are many clues as to the initiating event or events in the development of RA, their precise nature is not completely understood. Research suggests that its pathogenesis involves both humoral and cellular immune processes, and that genetic and environmental factors may also play a part.

6.1.1 ***Epidemiology***

The prevalence of RA in different populations has been shown to vary from less than 1% to almost 5%. It is not known whether this variability reflects the true pattern of disease or simply differing survey methods and diagnostic sensitivity. Some experienced rheumatologists have the clinical impression that the incidence of new cases of RA in Europe and North America is slowly declining, but there are no epidemiological data to confirm this.

Epidemiological studies of RA will lead to a better understanding of its etiopathogenesis only if the clinical definition of the disease in the study population is unambiguous and if objective standards of disease severity are employed.

6.1.2 ***Clinical diagnosis***

RA covers an enormous spectrum of clinical presentations, and this can sometimes result in difficulties with diagnosis and classification for epidemiological purposes. However, systematic clinical descriptions of RA have been developed, and most doctors and research workers would agree on the definition of “classical” and “definite” RA, but would not be unanimous about the definition of “probable” and “possible” disease. RA can thus vary from being a severe destructive symmetrical polyarthritis with systemic manifestations, such as vasculitis, to a mild chronic and

fluctuating seronegative polyarthritis. Many cases of the latter condition could perhaps better be labelled chronic inflammatory polyarthritis.

6.1.3 ***Pathogenesis***

Research into the pathogenesis of RA has suffered for want of an appropriate animal model. The adjuvant arthritis and collagen-induced arthritis models have been useful, but many features of their pathogenic mechanisms do not parallel those found in human rheumatoid disease. Another animal model, the autoimmune MRL/Mp-lpr/lpr mouse strain, spontaneously develops a destructive arthropathy with several features in common with RA. These include synovial cell proliferation, the formation of pannus, the presence of rheumatoid factors, bone erosions, and joint inflammation similar to that seen in RA. Studies of this model suggest that non-immunological mechanisms may be involved. Furthermore, it has been shown that the earliest pathological change in RA is synovial proliferation without a significant inflammatory reaction. This finding is consistent with the view that one of the initiating events in RA may be the production of endogenous growth factors that have specific effects on synovial tissue, but further research is required to define the precise pathogenic mechanisms involved.

6.1.4 ***Rheumatoid factors and autoantibodies***

Autoantibodies against several types of collagen, including non-cartilaginous collagen, have been found in the sera of patients with RA. The historical development of research into RA parallels the discovery of rheumatoid factors, which are antibodies directed against the Fc portion of immunoglobulin (Ig) G. About 80% of patients with RA have raised serum concentrations of rheumatoid factor and it is believed that this molecule plays some role in tissue injury in RA. However, such a role has never been demonstrated. Furthermore, rheumatoid factors are found in many inflammatory diseases, such as sarcoidosis, tuberculosis, leprosy and systemic lupus erythematosus, but they do not appear to cause tissue destruction as seen in RA. The presence of rheumatoid factors may be an incidental phenomenon and has yet to be explained. In order to elucidate possible mechanisms of tissue injury due to immunoglobulins, their genetics, structure and degree of galactosylation have been studied extensively, as well as the activity of galactosyltransferase in B cells and the proliferation of certain subsets of B cells. However, there is no experimental evidence from these studies that rheumatoid factors initiate the events leading to RA.

6.2 **Education**

Perhaps the greatest need worldwide in the rheumatic diseases, and particularly in RA, is for adequate public and professional education. The general public needs to know what RA is, its treatment and prognosis, the role of rehabilitation, and the importance of family support. Doctors and

allied health personnel must gain more experience in making differential diagnoses and become familiar with newer treatments. They should also understand the importance of socioeconomic and psychological factors in disease outcome. The possibility must also be recognized that the disease process and clinical picture may be modified by other disorders, such as AIDS.

Research should be carried out into ways of improving professional and public education about RA, with initial emphasis on developing countries.

6.3 Cellular immunology

There is evidence of increased numbers of activated T lymphocytes in chronically inflamed rheumatoid synovial tissue. Associated with this is a reduction in the suppressor cell activity of certain T-cell subsets. In the synovial fluid of patients with RA, a significant increase has been found in the number of T cells bearing the CD4+, 4B4+ helper-inducer receptor phenotype, and a significant decrease in the number of cells bearing the CD4+, 2H4+ suppressor-inducer receptor phenotype, compared with levels in the peripheral blood of both RA patients and normal controls. There is recent evidence that the 2H4+ receptor (CD4 5R) is a marker for undifferentiated CD4+ T cells, whereas 2H4- cells are memory cells. In addition, studies of the clonal diversity of the T-cell response in rheumatoid synovium, using restriction fragment length polymorphisms, have failed to confirm the presence of T-cell receptor rearrangement of the B gene, even though other studies had suggested that this might be present. The T-cell response in RA therefore appears to be polyclonal rather than oligoclonal. There is also some evidence that, in activated T cells in rheumatoid synovial tissue, the DR antigen/anti-DR/anti-idiotypic network may be of importance in regulating disease activity.

6.4 Lymphocyte trafficking and adherence

Some studies have suggested that lymphocyte trafficking and homing are very important mechanisms for the adherence of lymphocytes to specific vascular endothelial cells. Small venules and capillaries proliferate greatly in rheumatoid tissue, and some undergo conversion to high endothelial venules (HEV) during active inflammation. This phenomenon is associated with increases in the amounts of adhesion-related endothelial glycoproteins, which seem to be important in binding T cells to various endothelial structures in synovial tissue during the inflammatory response. The molecular and genetic mechanisms of receptor-directed lymphocyte homing remain to be clarified.

6.5 Regulation of the immune response

An important development has been the recognition of specific epitopes present in the class II major histocompatibility (MHC-II) molecules of patients with RA, which suggests that certain amino acid residues are

found in association with the disease. Residues in the third hypervariable region of the first domain of the B chain may be associated with cross-reactivity with certain antigens, perhaps of viral origin. This knowledge is significant because of the MHC-II molecule's important role in antigen presentation to T lymphocytes by way of the T-cell receptor. These genetic and immunological phenomena are particularly relevant in the light of growing evidence that cytokines may play a pivotal role in the regulation of immune responses in rheumatoid synovitis. Interleukin-1 is synthesized by macrophages during inflammation and together with interferon gamma brings about the formation of HEV. Samples from synovial cells in RA have raised concentrations of messenger RNA for the synthesis of interleukin-1 and for tumour necrosis factor B. It is also known that interleukin-1B induces increased secretion of prostaglandin (PG) E₂, thromboxane, and 6-keto-PGF_{1α} by chondrocytes. These immunological events have yet to be integrated into a clear pathogenetic mechanism.

6.6 Recommendations for research

The greatest recent advances in our understanding of RA have been in the areas of the molecular biology of the immunoglobulin and the T-cell receptor genes, the X-ray crystallographic structure of the MHC-I molecules and the presumptive evidence that the MHC-II molecules have a similar structure, and the production and regulation of growth factors. Further research in these areas will increase our knowledge of the pathogenesis of RA.

International concern over the AIDS epidemic has focused enormous activity on retroviral research, and major advances have been made in our understanding of the structural regulation and propagation of these viruses. Retroviral-like antigens have recently been discovered in the cerebrospinal fluid of patients with multiple sclerosis and in the synovial tissue of patients with RA. Much research is now going on into their possible significance.

Valuable information could be gained from familial and geographical studies of inflammatory joint diseases resembling RA, as well as from microbiological, genetic and immunological studies of those affected.

Reliable and accessible data are required on patients who would be ready and willing to participate in clinical trials of new treatments, enabling results to be evaluated as quickly as possible.

More research is needed on cartilage breakdown, the effects of synovial growth and proliferation, the immunopathology of matrix components, the healing process, and the structural mechanisms underlying joint deformities.

A deeper knowledge and understanding of the events surrounding inflammation are required. These include lymphocyte trafficking, cell

adhesion, the release of proteases and other enzymes, and gene activation and control for the synthesis of immunoglobulins, including rheumatoid factors.

Studies should be performed to elucidate further the structure of MHC-II molecules and T-cell receptors and to determine antigenic similarities between selected MHC epitopes. T-cell receptor antigenicity should be studied with a view to vaccine development.

More research should be conducted on regulators of the immune system such as lymphokines and other cytokines and arachidonic acid metabolites. Gene activation and the intracellular message transfer system should also be studied.

The role of retroviruses and other slow viruses in the etiology of some rheumatic conditions needs to be further elucidated using viral probes and the latest techniques in serology, culture and *in vitro* hybridization.

7. **Systemic lupus erythematosus**

7.1 **Introduction**

Systemic lupus erythematosus (SLE) is a chronic, progressive, multisystem disease, and occurs ten times as frequently in women as in men. Patients may present within a number of different specialties including rheumatology, haematology, nephrology, neurology, general medicine, and paediatrics. SLE is characterized by the genetically determined development of autoimmunity; this is reflected by the presence in serum of a wide variety of antinuclear antibodies, including antibodies directed against native DNA.

SLE is seen throughout the world and in all climatic zones, but is not a common disease. However, it tends to cluster in families and has a higher prevalence in certain ethnic groups, for example black female Americans and Mexican mestizo families.

7.1.1 **Clinical features**

The commonest clinical features of SLE are a (butterfly) rash on the bridge of the nose and cheeks, capillaritis in the hands, non-erosive polyarthritis, exudative polyserositis and lymphadenopathy. Other systemic findings may include glomerulonephritis (which may lead to nephrotic syndrome), central and peripheral nervous system involvement, pneumonitis, myositis, Raynaud phenomenon, systemic vasculitis and autoimmune cytopenias.

7.1.2 **Diagnosis**

Because of its varied clinical presentation, the diagnosis of SLE is based on certain laboratory findings. Those most commonly employed are the

criteria of the American College of Rheumatology for the classification of SLE, developed in 1982. These criteria include:

- Haematological abnormalities, such as leukopenia, anaemia and thrombocytopenia.
- The presence of LE cells.
- A positive antinuclear antibody test, reflecting the presence of autoantibodies to nuclear components such as native (double-stranded) DNA.
- The detection of Sm antigen.
- The presence of histones in serum.
- The detection of Ro/SSA and La/SSB antigens.

7.1.3 *Etiopathogenesis*

SLE appears to be caused by the interaction of environmental, genetic, hormonal and social factors, and has many features in common with AIDS. It has thus been suggested that a slow virus, possibly a retrovirus or other related virus, may contribute to the pathogenesis of the disease. A hereditary predisposition to SLE is evident from the familial aggregation of cases and the occurrence of SLE in identical twins. There is evidence of an association between the presence of HLA-DR2 or DR3 and deficiency of C4 in some patients with SLE. In addition, patients with SLE have abnormal estrogen metabolism and hyperprolactinaemia, suggesting the involvement of hormonal factors in its pathogenesis. Exposure to ultraviolet light, stress, nutritional imbalance and smoking may be precipitating or aggravating factors.

Immune dysregulation appears to underlie the development of SLE, where T cells and products of mononuclear cells (lymphokines and monokines) participate in the activation and differentiation of B cells into autoantibody-producing cells. The abnormal immune response produces autoantibodies to normally inaccessible antigens. Circulating immune complexes are associated with, and may cause, local and systemic inflammation.

7.1.4 *Treatment*

The main principle of treatment of SLE is to suppress the patient's inflammatory and immune responses by means of nonsteroidal anti-inflammatory drugs, corticosteroids and, when necessary, immunosuppressive agents such as cyclophosphamide and azathioprine. Immunosuppressive treatment is used when corticosteroids fail and if unfavourable prognostic factors, such as adolescence, nephritis (especially nephrotic syndrome), and central nervous system (CNS) and pulmonary involvement are present. In severe SLE, treatment is by pulsed intravenous methylprednisolone or cyclophosphamide. Extracorporeal plasmapheresis may be used in patients with nephrotic syndrome, hyperviscosity syndrome and involvement of the CNS, and in other serious clinical situations such as rapidly progressive disease.

In less serious cases, immunosuppressive doses of corticosteroids are given at the onset of exacerbations of the disease, and follow-up maintenance therapy is with low doses of corticosteroids or nonsteroidal anti-inflammatory drugs, under constant medical supervision.

7.2 Education

Educational programmes aimed at the general public and at patients with SLE and their families are needed in order to dispel the unwarranted pessimism attached to the disease. Such programmes should provide information about SLE and emphasize the effectiveness of treatment in reducing disability and improving quality of life. Support groups for patients with SLE and their families should also be developed.

Educational programmes about SLE are also required for doctors and other health professionals. Such programmes must stress the fact that patients with SLE may present to any one of a number of medical specialists, e.g. ophthalmologist, chest physician, haematologist, nephrologist, or orthopaedic surgeon. These programmes should also provide information about the significance of laboratory findings and about recent advances in treatment and rehabilitation.

Where clinical laboratories do not exist, they should be developed for the diagnosis of SLE and related diseases. In addition, hospitals and medical centres should have the facilities and expertise to treat and rehabilitate patients with SLE and other autoimmune rheumatic diseases.

7.3 Recommendations for research

Worldwide studies of the prevalence of SLE and of patient survival are necessary. In view of improvements in diagnosis and treatment, such studies should take into account the year in which the patient first presented and the year in which the diagnosis was established.

The committee established with the support of ILAR for the purpose of standardizing antinuclear antibody tests and other serological studies in European laboratories should be maintained. Further research is needed to identify autoantibodies in SLE and their clinical significance.

The correlation of serological abnormalities with clinical features should improve our understanding, for example, of the relationships between anti-DNA antibodies and renal lupus, and between anti-Ro antibodies and neonatal lupus.

Studies should be initiated to ascertain whether there are national differences in the prevalence and manifestations of drug-induced SLE.

Statistical analysis of the risk-factors for various clinical manifestations of SLE and for disease progression is necessary. The results should be related to the presence or absence of proteinuria, nephrotic syndrome, and serum antibodies at presentation. The indications for and outcome of renal transplantation and dialysis of patients with SLE require further study.

Prospective studies of family members of patients with SLE should be performed to determine the immunological risk-factors for clinical disease in people who have no such disease, but in whom immunological abnormalities can be demonstrated.

Other areas for research include:

- SLE in the elderly.
- The factors leading to polyclonal activation of B cells.
- The early immunological abnormalities in SLE, e.g. the interactions of T cells, B cells and macrophages.
- The comparison of the amino acid sequences of autoantigens found in SLE with those of known viruses.
- The modifying effect of factors such as smoking, diet and medication, particularly oral contraceptives, on the disease process.
- The effects of pregnancy on the progress of the disease.
- The long-term effects of cytotoxic drug treatment (immunosuppression) on the outcome of nephritis and disease of the central nervous system.

8. **Systemic sclerosis**

8.1 **Introduction**

Systemic sclerosis is a disease of connective tissue that most often affects the skin, gastrointestinal tract, lungs, kidneys, and cardiovascular system. If there is widespread skin involvement the disease may be referred to as scleroderma. In patients with the CREST syndrome (C=calcinosis; R=Raynaud phenomenon; E=(o)esophageal involvement; S=sclerodactyly; and T=telangiectasia), skin fibrosis is usually restricted to the fingers and the face, and renal and pulmonary involvement is mild or absent. In contrast, patients with diffuse scleroderma have extensive skin fibrosis and frequent involvement of the kidneys, lungs and heart, and thus have a worse prognosis.

In most patients with the CREST syndrome, a highly sensitive and specific anticentromere antibody is present in plasma. In patients with diffuse scleroderma, the presence of antitopoisomerase I antibody (SCL-70) is specific for the disease, but is found in less than one-third of cases and is therefore of low diagnostic sensitivity.

8.2 **Pathophysiology**

Systemic sclerosis is characterized by extensive fibrosis, vascular and microvascular abnormalities, and numerous immunological defects. Fibrosis probably represents the end stage of the disease. In the skin, marked deposition of glycosaminoglycans and of type I and type III collagen is seen. Electron microscopy reveals disorganization of collagen fibrils, with many being thin and immature. Fibronectin is found in the

lower dermis and subcutaneous tissue, and its presence appears to identify areas in which active collagen synthesis is occurring.

Cultured fibroblasts from patients with systemic sclerosis have high levels of messenger RNA for *c-myc* proto-oncogene and for collagen, and they produce more collagen and fibronectin than normal controls. Clones of fibroblasts can be identified from patients with the disease that produce large amounts of glycosaminoglycans and collagen, suggesting that skin affected by scleroderma is composed of cells that are heterogeneous with respect to the synthesis of connective tissue components *in vivo*.

The early phase of skin involvement is characterized by inflammation and oedema. The inflammation most often occurs in the lower dermis and subcutaneous tissue, with a cellular infiltrate of lymphocytes, plasma cells, and histiocytic-type cells.

An increased density of dermal mast cells may be seen in patients with systemic sclerosis and in the tight-skin mouse model of scleroderma. In the mouse model, dermal mast cells show massive degranulation, and treatment with disodium cromoglicate, an inhibitor of mast cell degranulation, has been shown to reduce dermal fibrosis.

Vascular abnormalities

Vascular and microvascular abnormalities are prominent features of systemic sclerosis. Major capillary abnormalities are visible by wide-field nailfold microscopy. The most abnormal capillary patterns, with dilated, distorted capillaries adjacent to regions of absent capillaries, are seen in those patients with the largest number of organ systems involved.

Raynaud phenomenon occurs in 90% of patients with systemic sclerosis, and is due to vasospasm of the small digital arteries. Structural abnormalities of the vessel wall may or may not be present. Spontaneous or cold-induced vasoconstriction may be an important cause of dysfunction in all the target organs in systemic sclerosis. For example, renal cortical blood flow drops strikingly after a cold-pressor test. Similar vasoconstriction may account for some of the pulmonary function abnormalities seen in this disorder.

The capacity of the coronary arteries to vasodilate is dramatically impaired in patients with systemic sclerosis, presumably because of structural abnormalities of the small coronary vessels. Thallium-201 studies have demonstrated myocardial perfusion defects at rest or after induction by cold or exercise in patients with the disease. These defects are presumably due to vasospasm since they may improve after coronary artery vasodilation with intravenous dipyridamole or calcium channel blockers, such as nifedipine or nicardipine.

A common pathogenesis, such as endothelial cell injury, would seem a reasonable hypothesis to explain both the vascular and the microvascular lesions of systemic sclerosis. Increases in von Willebrand factor activity and in the concentration of VIII/von Willebrand factor antigen in the

plasma of patients with systemic sclerosis may reflect endothelial cell injury. Raised levels of circulating platelet aggregates and of plasma β -thromboglobulin are evidence of *in vivo* platelet activation in these patients.

Circulating factors that are selectively cytotoxic for endothelial cells are present in the plasma of patients with scleroderma, but their precise nature remains unclear. Endothelial cell injury in small arteries may lead to platelet aggregation, myo-intimal cell proliferation, and narrowing of the vascular lumen. Platelet factors may then activate interstitial fibroblasts to synthesize collagen. The sclerotic disease is due to this excessive collagen synthesis by fibroblasts, the cause of which is unknown. In addition, an endothelial cell lesion has been identified that causes obstruction of blood vessels, especially in the microvascular circulation, and is probably induced by immunological abnormalities.

Dyspnoea during exercise or at rest in patients with systemic sclerosis is indicative of either pulmonary interstitial fibrosis with impaired gas exchange or ischaemia. Pulmonary hypertension is rare and has a very bad prognosis.

8.3 Treatment

Identification of the immunological, vascular, and fibroblast abnormalities in systemic sclerosis has led to several new therapeutic approaches. Captopril, an orally active angiotensin-converting-enzyme inhibitor, is effective in reducing the severe hypertension in patients with renal involvement. With prompt treatment, the prognosis for patients with malignant renal hypertension, which is the most serious complication of the disease, has been greatly improved.

Some calcium channel blockers, such as nifedipine, reduce the frequency and severity of digital vasospastic attacks and mitigate thallium-201 myocardial perfusion abnormalities in patients with systemic sclerosis.

Gastrointestinal malabsorption, another serious complication of the disease, can now be reversed by drug treatment.

Physiotherapy is important in allowing patients to retain function, particularly of the hands.

8.4 Prognosis and disease monitoring

Although there is no cure for systemic sclerosis, much can be done to improve the patient's quality of life. The perception of systemic sclerosis as a rapidly progressive disease is often incorrect; many patients have prolonged periods of remission, sometimes lasting for years.

Systemic sclerosis is predominantly a disease of middle-age and is three times commoner in women. The skin is most often involved and most patients also have symptoms of Raynaud phenomenon – a vasospastic syndrome of the digital arteries. However, in some patients the clinical

findings may indicate the presence of progressive systemic sclerosis. Such findings include sclerodactyly, oesophageal dysfunction, capillary dystrophy, and disease-specific antinuclear antibodies in plasma.

Studies are needed of predictors of the development of diffuse connective tissue disease in patients presenting with Raynaud phenomenon.

It is important that the patient is cared for by a physician who has experience with this disease and is aware of the need to assess visceral involvement, particularly of the gastrointestinal tract, lungs, heart and kidneys. It is essential that the patient gives up smoking, since nicotine is a potent vasoconstrictor and will exacerbate the symptoms and signs of the disease.

The blood pressure of patients with systemic sclerosis must be monitored frequently since hypertension is a manifestation of renal involvement, and malignant hypertension, which may have an abrupt onset, is the main cause of death in this disease. Prompt treatment to control hypertension can therefore be life-saving.

8.5 Recommendations for research

8.5.1 *Epidemiology*

Little is known about the incidence and clinical manifestations of systemic sclerosis in relation to geography, climate, race and other environmental and host factors. The role of these factors, particularly with regard to disease severity, needs further study.

8.5.2 *Immunology*

Several immunological abnormalities have been described in systemic sclerosis. These include the finding of antinuclear antibodies and immune complexes; decreased numbers of circulating T lymphocytes; an increased CD4+/CD8+ ratio with reduced numbers of CD8+ cells; a decreased proliferative response of lymphocytes after exposure to mitogens; impairment of antibody-dependent cell-mediated cytotoxicity; increased production of interleukin-2; defective Epstein-Barr virus-specific suppressor T-cell function; and increased proto-oncogene expression in peripheral T lymphocytes. These findings are consistent with an immunological mechanism causing recurrent episodes of endothelial injury and, eventually, widespread fibrosis.

Studies should be conducted to identify possible environmental factors and defects in regulation of the immune system responsible for systemic sclerosis. There is a particular need for better serological markers for the disease and its subsets.

Research needs to be conducted to increase knowledge about defective T-cell regulation, B-cell activity, antibody-dependent cell-mediated cytotoxicity, cell-mediated immunity to skin extracts and collagen, and interleukin-2 production.

8.5.3 **Pathophysiology**

The pathophysiology of systemic sclerosis is unclear. A variety of plasma factors, lymphokines, and monokines have been proposed as effectors of fibrosis.

A mutant gene for the synthesis of fibronectin has recently been identified in skin fibroblasts from sclerotic lesions of patients with systemic sclerosis, but the role of fibronectin in the disease process is uncertain.

Research on vascular and microvascular abnormalities should include pharmacological studies of vasomotor reactivity, studies of endothelial cell injury by circulating factors, the elucidation of factors selectively cytotoxic for endothelial cells, and the investigation of platelet factors that activate interstitial fibroblasts.

Studies of fibroblasts in culture should be undertaken to investigate the action of growth factors, the regulation of collagen synthesis, the role of procollagen in feedback mechanisms, and the role of fibronectin.

Particular emphasis should be given to elucidating the interplay between the vasculopathy and immunopathological processes and to determining whether connective tissue proliferation in CREST is different from that in systemic sclerosis.

8.5.4 **Experimental therapeutics**

Penicillamine may be effective in some patients with skin involvement, but controlled studies are lacking and there is no clearly effective treatment for the disease. Some encouraging preliminary reports have recently appeared describing the beneficial effects of recombinant interferon gamma in patients with scleroderma.

New therapeutic approaches should focus both on substances that inhibit the formation of collagen or promote its degradation, and on drugs that may be effective in correcting immunological abnormalities and endothelial cell injury in systemic sclerosis. Controlled clinical trials are needed on the efficacy of penicillamine and other agents currently in use.

9. **Sjögren syndrome**

9.1 **Introduction**

Sjögren syndrome (Ss) is a chronic autoimmune disorder of the exocrine glands, affecting nine females to every male. The prevalence of Ss among the elderly is from 3 to 4%, but its prevalence in the general population is unknown. It occurs either alone (primary) or in association with other autoimmune rheumatic diseases, such as RA, SLE, systemic sclerosis, or mixed connective tissue disease. Ss may mimic many other diseases, including primary amyloidosis, sarcoidosis, some lymphoproliferative

disorders, the hyperlipoproteinaemias types IV and V, chronic graft-versus-host disease, and HIV infection.

9.2 Clinical spectrum

The clinical spectrum of primary Ss is very diverse. It expands from an autoimmune exocrinopathy (keratoconjunctivitis sicca, xerostomia, major salivary gland enlargement, xerotrachea, subclinical pancreatitis, and atrophic gastritis) to a systemic disorder (Raynaud phenomenon, interstitial nephritis, glomerulonephritis, interstitial lung disease, chronic persistent hepatitis, myositis, and systemic vasculitis) and to B-lymphocyte malignancy (Waldenström macroglobulinaemia and lymphoma). Some of the systemic manifestations may precede the sicca symptoms by many years (e.g. Raynaud phenomenon), while others, such as vasculitis and lymphoma, may develop many years after the appearance of local autoimmune exocrinopathy.

Studies of unselected patients with RA, scleroderma and SLE have shown histological evidence of Ss in 30% of patients with RA, in 20% of patients with scleroderma, and in about 10% of patients with SLE. Most patients with RA and histopathological lesions of Ss do not complain of sicca symptoms; if they do, dryness of the eye is much commoner than dryness of the mouth or parotid gland enlargement. In contrast, patients with systemic sclerosis and SLE have the same sicca complaints as patients with primary Ss. Patients with RA and Ss, when compared with patients with primary Ss, less frequently show enlargement of the major salivary glands and extraglandular manifestations (Raynaud phenomenon, lymphadenopathy, splenomegaly, myositis, and interstitial nephritis).

9.2.1 *Diagnosis*

The diagnosis of Ss is still based on the definition proposed by Bloch et al. in 1965: "Sjögren's syndrome consists of a triad: keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis or other connective tissue syndrome. Salivary or lacrimal gland enlargement may or may not be present."

Recently, other groups have proposed different criteria.

Tests to document keratoconjunctivitis sicca include:

- Lacrimal flow rate (Schirmer I and II tests).
- Lacrimal composition (tear break-up time and lysozyme content).
- Rose bengal staining and slit-lamp examination of the eye to detect damage resulting from abnormal tear flow and composition.

Xerostomia may be assessed by using:

- Parotid flow rate (stimulated or unstimulated) and total salivary flow rate.
- Parotid sialography.
- Salivary scintigraphy.

Tissue biopsies for histological diagnosis may be taken from the labial minor salivary glands or the superficial parotid lobe.

9.2.2 **Pathology**

The histopathological hallmark of Ss in the exocrine gland biopsy is focal lymphocytic infiltrates and myoepithelial islands (particularly in the major salivary glands). Lymphocytic infiltrates consist primarily of activated T lymphocytes bearing the helper-inducer phenotype CD4+, 4B4+. B cells are also activated. Epithelial cells of ducts and acini express, inappropriately, HLA class II molecules.

Positive laboratory findings include:

- Leukopenia (10% of patients).
- Thrombocytopenia (infrequently).
- Raised erythrocyte sedimentation rate (80% of patients).
- Hypergammaglobulinaemia (80% of patients).
- Antibodies to immunoglobulins (rheumatoid factors, 70% of patients).
- Antibodies to Ro/SAA and La/SSB autoantigens (patients with primary Ss).
- Monoclonal type II cryoglobulins with rheumatoid factor activity (30% of patients with primary Ss).

Primary Ss is associated with HLA-B8, DR3 and DRw52, except in Greeks, where the association is with HLA-DR5, and in Japanese, with HLA-DRw53.

Characteristic immunopathological findings include B-cell hyperactivity, which proceeds through the following steps:

1. Polyclonal activation; autoantibody production against immunoglobulins and Ro/SSA and La/SSB cellular antigens (glandular disease).
2. Polyclonal/oligoclonal/monoclonal activation as evidenced by the presence of monoclonal type II cryoglobulins circulating in plasma or monoclonal light chains excreted in the urine (systemic Ss).
3. Monoclonal activation (lymphoma).

B-cell hyperactivity is localized in the affected tissues and cannot be explained solely on the basis of T-cell immunoregulatory aberrations, since the number and function of T suppressor cells are intact. T cells are activated and B cells produce autocrine factors supporting activation and proliferation of B cells. Natural killer cell function is impaired; Fc-receptor clearance is impaired primarily in patients with the systemic form of the disease; and the autologous mixed lymphocyte response is impaired.

Treatment consists of stimulation of exocrine glands or replacement of their secretions. There are anecdotal accounts suggesting that bromhexine helps dry eyes and dry mouth. Prednisone, a cytotoxic agent, and plasmapheresis are indicated in the systemic vasculitis of Ss.

9.3 Education

Sjögren syndrome is a much more common condition than is generally appreciated, and doctors should be better educated to recognize it. National societies for patients with Sjögren syndrome are also useful. As with other autoimmune diseases, diagnosis and treatment are greatly aided by national and international immunology reference laboratories.

9.4 Recommendations for research

9.4.1 *Epidemiology*

The classification criteria currently applied for Ss are largely empirical, representing the biased opinion of the investigator(s), and are not based on critical, statistical analysis of their sensitivity, specificity and predictive value. There is considerable variability in the tests applied for the evaluation of keratoconjunctivitis sicca and xerostomia, and the lack of uniformly accepted classification criteria prevents accurate comparisons of results between studies. Thus, it is most important that the international scientific community develops classification criteria for Ss to facilitate collaborative studies among different countries. The natural history of primary Ss, its differences from Ss in SLE and systemic sclerosis, and its HLA associations will be better understood as a result of such efforts.

Studies of the incidence and prevalence of Ss using validated epidemiological methods should be carried out.

The specificity and sensitivity of the diagnostic tests for the documentation of keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) need to be evaluated.

Internationally accepted criteria for the classification of Ss need to be developed.

Further studies are needed of the similarities and differences between primary Ss and Ss associated with other connective tissue diseases, such as RA, SLE and systemic sclerosis.

9.4.2 *Immunopathology*

In order to elucidate further the immunopathology of Ss, the main thrust of research should be to:

- Study and compare the anti-Ro/SSA response in Ss patients and SLE patients.
- Evaluate the role of glandular epithelial cells in the inflammatory process.
- Study homing patterns of lymphocytes to exocrine glands.
- Study the cytokine cascade in Ss patients.
- Determine the novel agent(s) that participate in the polyclonal/oligoclonal/monoclonal B-cell activation.

9.4.3 **Treatment**

Double-blind therapeutic studies should be carried out using anti-CD4 monoclonal antibodies and high doses of intravenous immunoglobulins.

10. **Lyme disease**

10.1 **Introduction**

10.1.1 **American history**

From 1972 to 1975 two mothers observed an “epidemic” of arthritis in children in the small coastal town of Lyme, Connecticut, USA. The mothers reported this juvenile arthritis to the state health department and to a rheumatologist. In 1975, an epidemiological study was carried out in the geographical area concerned. The survey, carried out in three contiguous small towns, revealed arthritis in 39 children and 12 adults. The cases were found to be clustered in wooded areas, which suggested transmission of the disease by an arthropod vector.

A spreading rash preceding the arthritis was reported in 25% of the patients. Subsequently, the rash was observed and diagnosed as erythema chronicum migrans (ECM). The rash, in turn, was found to be a reaction to the bite of a tick. The responsible tick was identified as a deer tick, *Ixodes dammini*.

During the next three years (1976-1979), 512 cases of “Lyme arthritis” were identified in the United States, largely in three geographical areas. Neurological and cardiac complications were also discovered as late manifestations, along with chronic, at times destructive, arthritis. Presuming that the disease was caused by an infectious agent, doctors gave antibiotics, such as penicillin, to patients with early Lyme disease. The antibiotics seemed to shorten the duration of the skin lesions and attenuated the early subacute arthritis.

It was not until 1981 that the cause of the disease – a spirochaetal bacterium – was discovered by Burgdorfer, at the National Institutes of Health (NIH). Burgdorfer, an expert in tick-borne diseases, discovered the spirochaete while examining the mid-gut of an infected tick removed from a patient in an area endemic for Lyme disease. The spirochaete turned out to belong to the genus *Borrelia* (not *Treponema*) and was named in 1983 after its discoverer as *Borrelia burgdorferi*. In 1982, another scientist at NIH succeeded in isolating the spirochaete and growing it in culture, using a special medium.

Spirochaetes were subsequently identified in the blood, skin lesions, and spinal fluid of a small number of patients with Lyme disease. During the next two years, 1983-1984, serological tests for Lyme disease, measuring antibodies to *Borrelia burgdorferi*, were developed. There were also reports of “effective” antibiotic treatment for both the early and the late features of Lyme disease.

10.1.2 *European history*

As early as 1909, Afzelius in Sweden described a spreading rash that he named “erythema migrans”, subsequently called erythema chronicum migrans (ECM). Erythema migrans was later thought to be caused by the bite of a tick that was transmitting a toxin. A chronic neurological disease, characterized by meningitis and known as Bannwarth syndrome, was then found to be associated with antecedent tick bites and a spreading erythematous eruption. A chronic distinctive skin disease, acrodermatitis continua atrophicans, was also first described in Europe, and later found to be associated with previous tick bites and ECM, and, still later, with chronic neurological disease. In fact, in 1949, Hellerström proposed that a tick bite caused both the ECM and the neurological disease; he also reported that treatment with penicillin was beneficial. However, the latter observation received little attention since the disease was thought to be caused by an as yet unidentified virus. Although arthritis has recently been described in European cases, there is less rheumatic involvement seen in Europe than in the United States.

10.2 **Clinical features**

As more cases of Lyme disease were recorded in academic centres in the United States, the frequencies of the main clinical features of the disease were reported as follows:

- Erythema chronicum migrans; 80%.
- Joint disease; 60%.
- Neurological disease; 15%.
- Cardiac disease; 8%.

Reports in the literature and at international meetings suggest that Lyme disease develops in stages, as do other spirochaetal diseases such as syphilis. Many investigators divide Lyme disease into three stages. The stages, however, often overlap, and not all patients go through all three stages. The disease usually begins with a slowly expanding red skin lesion, erythema migrans, that starts at the site of the tick bite. The lesion grows in a circular pattern with a red border, and may look like a bull’s-eye. The lesion varies in size, but may be several centimetres in diameter. In addition, early signs and symptoms may include low-grade fever, fatigue, muscular aching, joint stiffness, headache, and lymphadenopathy. Thus, the early phase of the illness may resemble an influenza virus infection.

In the second stage of the disease, occurring within weeks or months of the tick bite, patients may develop arthritis or neurological or cardiac abnormalities. The arthritis is intermittent, and tends to affect only one or a few joints. Neurological involvement may cause paralysis or weakness in the muscles of the face or the extremities. Heart problems may include palpitations, syncope, or shortness of breath.

The third stage of Lyme disease occurs several months later with chronic involvement of the joints, the nervous system, or the skin. The chronic

arthritis may be destructive and usually affects only a few joints. There may be chronic meningitis or neuropathy. The chronic skin disease is acrodermatitis continua atrophicans, a penetrating and disfiguring condition.

10.3 **Diagnosis**

The diagnosis of the arthritis of Lyme disease can be difficult since the pattern differs for each stage of the disease. In the early stage it may resemble viral arthritis or fibromyalgia. In the second stage it may mimic juvenile arthritis, reactive arthritis, rheumatic fever, or incomplete Reiter syndrome. In the later stage, Lyme disease may resemble chronic reactive arthritis or seronegative rheumatoid arthritis.

Several techniques have been developed for the laboratory confirmation of the diagnosis of Lyme disease. These include various serological tests for the disease, the measurement of cellular immune responses (B cells and T cells) to the spirochaete, and detection of the bacterial antigen in body fluids, such as blood or urine, and in tissues, such as synovium. Reliable laboratory tests are needed for the numerous patients who present without a history of tick bite or characteristic ECM. Several commercial tests, some packaged as kits, are now available, but their sensitivity and specificity vary greatly.

IgM antibodies do not become detectable in serum until one month after the onset of ECM. These persist for one or two months when IgG antibodies begin to appear. Thereafter, IgM antibodies decrease or disappear, and IgG antibodies increase and persist for months or years. They may or may not decline after successful treatment of the clinical features of the disease.

The sensitivity of both the indirect fluorescent antibody (IFA) technique and the enzyme-linked immunosorbent assay (ELISA) is, therefore, usually low during the first few weeks of the disease.

The specificity of the serological tests for Lyme disease may be poor, especially in the later stages of the disease. False-positive reactions may occur due to cross-reactivity with other spirochaetal diseases, such as relapsing fever and other borrelioses. Caution in interpretation of laboratory results is especially important in areas highly endemic for Lyme disease, where the population is exposed to infected ticks throughout the spring and summer. Symptoms may be caused by one of several disorders other than Lyme disease.

10.4 **Treatment**

The mainstay of treatment for Lyme disease is antimicrobial drugs. Results vary greatly with the stage of the disease, and, in general, treatment is much more successful when given early. For the first stage of Lyme disease, the objectives of treatment are to eradicate the ECM and other symptoms and to prevent the development of the second and third stages of the disease.

The antimicrobial drugs of choice are tetracycline, doxycycline, penicillin, and amoxicillin, given for 10 to 21 days. Penicillin is recommended for pregnant and lactating women, and some advise intravenous administration to ensure a sufficiently high plasma concentration, since transplacental transmission of the disease may occur. Treatment for three weeks is advisable for patients with more severe early disease.

Such treatment may not be successful for the subacute and especially for the chronic phases of Lyme disease. In such cases, large doses of intravenous penicillin or cephalosporins, ceftriaxone in particular, have been given, often with good results. Nevertheless, the later manifestations of Lyme disease, such as arthritis, meningitis and cardiopathy, may not respond to such treatment. The efficacy of anti-inflammatory or immunosuppressive drugs for the treatment of such late manifestations remains uncertain.

10.5 **Education**

The number of cases of Lyme disease being reported in many countries is rising rapidly, and it is known to occur worldwide in countries with temperate climates.

Particularly in endemic areas, the general public need to know about the risk of contracting Lyme disease and how they may protect themselves, for example by wearing suitable protective clothing.

People living in tick-infested areas should be familiar with the early signs and symptoms of the disease and aware of the need for early diagnosis and treatment in order to avoid later complications.

Doctors must also be better educated to recognize and treat the disease as early as possible.

10.6 **Recommendations for research**

10.6.1 ***Epidemiology***

Prevalence and incidence rates for Lyme disease in different countries should be determined, since it is important to find out whether the disease is just being increasingly recognized or is truly spreading. Epidemiological research is also needed to ascertain whether the clinical picture varies geographically (e.g. less arthritis and more neuropathy in Europe than in the United States) or if the suggested differences are more apparent than real because of different methods of assessment.

In order to accomplish the above and other studies, there is a compelling need for the setting up of national registries for Lyme disease, as well as a library of well-characterized reference sera for the development of standards for evaluating diagnostic tests.

More research into the risk-factors for Lyme disease, both in humans and in animals, needs to be carried out in different parts of the world. The

ecology of *Borrelia burgdorferi* also requires further study. In addition to deer and mice as important hosts, we need to know how important other animals, such as rabbits, horses, dogs and cats, are as reservoirs of the disease. We also need to know whether birds transport the disease to distant sites and if non-tick transmission, perhaps by mosquitos and fleas, plays a significant role in the spread of the disease.

10.6.2 **Clinical disease**

Standardized clinical definitions of Lyme disease are needed for clinical, laboratory, and epidemiological investigations.

We need to know more about the involvement of organs such as the eye, liver, or kidney. But above all, more intensive research is needed to develop sensitive and specific diagnostic laboratory tests for the early and late stages of the disease. These tests must be rapid, practical and inexpensive.

10.6.3 **Pathology**

The histopathological findings in early and late Lyme disease need to be described and documented more fully, and more needs to be known about the nature of the inflammatory reactions and immune responses, both humoral and cellular, occurring in the disease.

Finally, it is important to establish whether some patients are genetically predisposed to developing the late manifestations of the disease affecting the joints, the nervous system and the skin.

10.6.4 **Prevention and treatment**

More effective antimicrobial treatment regimens are needed, especially for late disease, and long-term clinical trials of both antimicrobial and immunosuppressive agents should be carried out.

National and international attention should be directed to research and education on diverse preventive strategies, including:

- deer control (fences, culling)
- tick control (insecticides)
- control of other reservoirs
- avoidance of low-lying bushes at forest edge
- protective and impregnated clothing
- public and professional education
- vaccine development.

11. **Spondyloarthropathies**

11.1 **Introduction**

The spondyloarthropathies, also known as seronegative arthritis, spondylitic syndrome, the spondyloarthritis or the seronegative spondyloarthropathies, are a group of closely related inflammatory diseases involving axial diarthrodial and/or the sacroiliac joints. These conditions include:

- Idiopathic ankylosing spondylitis.
- Juvenile ankylosing spondylitis.
- Reiter syndrome.
- Reactive arthropathy – associated with infection due to *Campylobacter*, *Yersinia*, *Shigella* and *Salmonella* spp.
- Enteropathic spondylitis – associated with Crohn disease or ulcerative colitis.
- Seronegative enthesopathic arthropathy (SEA) syndrome.
- Undifferentiated spondylitis – subsets of patients who have features of spondyloarthropathy that do not meet the criteria for ankylosing spondylitis, Reiter syndrome or other well-recognized conditions; frequently, some features of SEA syndrome and unilateral sacroiliitis may be present.

Some conditions, such as uveitis and pustulotic arthro-osteitis, overlap with the spondylitic syndromes.

The spondyloarthropathies have several features in common:

- absence of rheumatoid factors
- asymmetrical peripheral joint involvement
- presence of the HLA-B27 marker
- familial aggregation
- mucocutaneous and sometimes vascular lesions.

Immunogenetics

Immunogenetic studies have demonstrated that susceptibility to the development of spondyloarthropathy is related to the major histocompatibility complex (MHC). In 1973, a strong correlation was demonstrated between the possession of HLA-B27 and the likelihood of developing ankylosing spondylitis and Reiter syndrome.

In an investigation of Brazilian male Caucasians, 82.5% of patients with ankylosing spondylitis and 6.3% of a control group were HLA-B27 positive. In Reiter disease that frequency was 67.5%, and in psoriatic arthropathy 45%. In several studies in different countries, the figures for Reiter disease have been 60-80%, and for psoriatic arthropathy 20-50%.

In contrast to the above, in females with psoriatic arthropathy in Brazil, a correlation was found with Bw38 but not with B27 (relative risk =12). The frequency of HLA-B27 varies widely from one geographical area to

another and between different racial and ethnic groups. The association between ankylosing spondylitis and HLA-B27 in blacks (40–50%) and in Japanese (the data are conflicting) is not as striking as that in Caucasians, in whom B27 and ankylosing spondylitis are both uncommon. The Pima and Haida American Indians, with a high frequency of HLA-B27 and sacroiliitis, develop Reiter syndrome only rarely.

With the development of immunology and molecular biology, many biochemical and immunological differences were observed within the B27 group. Cross-reactivity with other antigens has also been noted. To date, more than 8 subtypes of HLA-B27 have been identified. However, no specific association with a subtype has been established for ankylosing spondylitis.

Another finding has been the association of ankylosing spondylitis with intestinal infections caused by Gram-negative microorganisms. The circulation of Batson's plexus has been suggested as a basis for spinal involvement and ocular manifestations. Studies have shown cross-reactivity between B27 and antibodies against *Klebsiella* spp, leading to the concepts of "reactive" arthritis and molecular mimicry.

Although HLA determinations may be useful in facilitating diagnosis in patients with undifferentiated spondyloarthropathy, it is important to pursue the identification of a possible infectious agent. Since reactive environmental microbial factors, such as enteric infections, seem important, investigations will require the collaboration of epidemiologists and immunologists.

In undifferentiated spondyloarthropathy and in the SEA syndrome, the following features are frequently associated with B27 positivity:

- Sausage digits (representing juxta-articular disease).
- Insertional tendinitis (Achilles tendon, intercostal muscles).
- Asymmetrical sacroiliitis.
- Periostitis, spurs.
- Peri-insertional osteoporosis and erosions.

11.2 Ankylosing spondylitis

Ankylosing spondylitis presents most commonly in males in the third or fourth decade of life, and differences exist between patients with ankylosing spondylitis who are B27 positive and those who are B27 negative (Table 1).

The back pain of ankylosing spondylitis is characterized by the following features:

- Insidious onset under the age of 40 years.
- Higher incidence in males.
- Lasts longer than 3 months.
- Associated with morning stiffness.
- Improves with exercise.

Table 1

Characteristics of ankylosing spondylitis in patients with and without HLA-B27

Characteristic	B 27 +	B 27 –
Race	all races	especially non-Caucasians
Age	younger	older
Family history	present	absent
Uveitis	++	+
Skeletal changes	++	++

Table 2

Sex differences in ankylosing spondylitis

Clinical features	Males	Females
Interval (yr), onset of symptoms to diagnosis	3	10
Progression	+++	+
Severity	+++	+
Spinal ankylosis	+	++
Osteitis pubis	+	+++

Major differences exist between ankylosing spondylitis in men and in women (Table 2).

No satisfactory test exists for the diagnosis of ankylosing spondylitis. Laboratory studies, such as the erythrocyte sedimentation rate and other measures of the acute-phase reaction, are insensitive markers in ankylosing spondylitis, but may allow spondylitis to be distinguished from degenerative and mechanical causes of back pain. Positive tests to detect an acute-phase reaction correlate poorly with disease activity. Scintigraphy can be helpful in diagnosis during the early stages of the disease.

There is no specific cure for ankylosing spondylitis. Medication may sometimes arrest the inflammatory process. It should be emphasized, however, that early diagnosis is required to obtain maximum benefit from treatment and rehabilitation programmes.

Good management includes an active physical therapy programme, with exercise aimed at maintaining good posture and range of movement and preserving respiratory capacity. Rehabilitation is often best accomplished with the help of a physiotherapist. An individual exercise programme should be outlined for each patient. Swimming is often excellent for patients with spondylitis. Because of the likelihood of restrictive pulmonary disease, every effort should be made to help patients to stop smoking.

Nonsteroidal anti-inflammatory drugs are useful for reducing pain and improving mobility. In rare situations, steroid treatment may be indicated.

11.3 Reiter syndrome

The diagnosis of Reiter syndrome requires the presence of a seronegative asymmetrical arthropathy, predominantly affecting the lower limbs, plus one or more of the following:

- Urethritis or cervicitis.
- Inflammatory eye disease.
- Dysentery.
- Mucocutaneous disease (balanitis, oral ulceration and keratoderma blenorrhagica).

There is a lack of good prognostic data for Reiter syndrome. The prevalence of this disease seems to be underestimated, and several factors may account for this:

1. There is no diagnostic test.
2. The disease affects chiefly young adults who are a socially mobile group.
3. The venereal history is often suppressed and enteric features, such as an episode of diarrhoea, may be readily forgotten.
4. A number of the “diagnostic features” are clinically unapparent: the mouth ulcers are painless, and balanitis, urethritis and cervicitis are often silent and unrecognized by the patient, as is the conjunctivitis (Table 3).
5. Extra-articular involvement, such as eye disease and skin disease, may be seen as nonspecific and its significance go unrecognized.
6. Reiter syndrome is commonly misdiagnosed as “seronegative rheumatoid arthritis”.
7. Because Reiter syndrome is a multisystem disorder, health care may be fragmented among specialists (e.g. ophthalmologists, dermatologists, urologists, and gynaecologists), none of whom may see the complete picture.

Reiter syndrome and gonococcal arthropathy share some features. For example, both are characterized by oligoarthritis, tenosynovitis, conjunctivitis, urethritis, skin lesions, fever and a history of sexual activity. However, Reiter syndrome affects predominantly white males while gonococcal arthritis affects mostly females. A positive culture for *Neisseria gonorrhoeae*, obtained from synovial fluid, skin, pharynx, rectum or blood, makes a definitive diagnosis, but *N. gonorrhoeae* is a fastidious organism and, even in clear-cut cases, positive cultures may be difficult to obtain. About 25-30% of patients with Reiter syndrome have a chronic course of recurrent attacks; recurrent episodes of gonococcal arthritis are rare, so that a previous attack points to a diagnosis of Reiter syndrome. A history of back pain, and the presence of plantar fasciitis, stomatitis, and keratoderma blenorrhagica are additional features that characterize Reiter syndrome.

Table 3

Clinical features of Reiter syndrome at presentation

Clinical feature	Found at presentation (%)
Arthritis:	
monoarthritis	4
polyarthritis	96
Urethritis / cervicitis	90
Diarrhoea	18
Eye disease	63
Back pain	72
Heel pain	56
Tendinitis	52
Balanitis	46
Stomatitis	27
Keratoderma	22
Nail lesions	6

Gonococcal arthritis and Reiter syndrome may coexist in the same individual, and this possibility should be considered whenever the arthritis does not respond well to treatment with penicillin.

11.4 Psoriatic arthropathy

About 5–7% of patients with psoriasis have some joint involvement. In 70% this is pauciarticular, but in 5% the joint disease is more severe and debilitating. Distal interphalangeal joint involvement is often present and axial involvement (sacroiliitis and/or spondylitis) is present in 5–10% of cases. A small proportion of patients with psoriasis have a form of symmetrical arthritis resembling RA. More commonly it is a bilateral, asymmetrical arthritis. Of patients with psoriasis who do not have joint symptoms, 20% have radiological sacroiliac changes. It will be valuable to study the evolution of these forms in different countries and to assess the effects of treatment with non-steroidal anti-inflammatory drugs, methotrexate and etretinate.

There are a number of similarities between Reiter syndrome and psoriatic arthropathy (Table 4). There are, however, many differences between the two conditions (Table 5).

11.5 Education

Education programmes should aim to increase public awareness of the various forms of these spondylitic (spinal inflammatory) diseases, of the value of physiotherapy in preventing deformity, and of treatments that provide symptomatic relief.

Table 4

Similarities between Reiter syndrome and psoriatic arthropathy

Clinical features	Reiter syndrome	Psoriatic arthropathy
Peripheral joint disease	+	+
Axial disease	25%	25%
Association with:		
eye disease	+	rare
skin disease	+	+
Nail involvement	+	+
HLA-B 27 positive	80%	20–50%

Table 5

Differences between Reiter syndrome and psoriatic arthropathy

Clinical features	Reiter syndrome	Psoriatic arthropathy
Sex ration (M:F)	10:1	3:2
Age at onset (yr)	20–30	all ages
Type of onset	acute	insidious
HLA association	B 27	B 27, B 13, Bw 17, Bw 38
Mouth ulcers	+	—
Urethritis	+	—
Joint predisposition	lower limb	upper and lower limb
Relation of joint disease to severity of skin lesion	+	±

Education programmes on the spondyloarthropathies are also needed for doctors and other health professionals. Gynaecologists and urologists are appropriate target groups for this education. These specialists need to be able to distinguish Reiter syndrome from gonococcal arthritis. Similarly, the orthopaedic surgeon, dermatologist, and paediatrician need to be able to recognize the juvenile forms and incomplete forms (SEA syndrome) of these diseases. Ophthalmologists must be constantly aware that ocular manifestations may present as part of a multisystem disease.

11.6 Recommendations for research

International studies are needed on the incidence and prevalence of the spondyloarthropathies, differences in genetic markers, secondary complications of the spondyloarthropathies, and diagnostic and classification criteria.

National or regional studies are needed in order to identify infectious agents and to investigate the socioeconomic implications and clinical aspects of the spondyloarthropathies. Clinical trials both of drug treatment and of physiotherapy are needed, as are studies on survival and prognosis.

Epidemiological studies are needed on the incidence and prevalence of the different features of the spondyloarthropathies, including urban and rural geographical distribution and ethnic and familial groups affected. Regional differences in the frequency of HLA-B27 subtypes and other genetic markers in these diseases should also be determined and improved criteria established for the diagnosis and classification of the spondylitic syndromes.

The prevalence of renal, pulmonary, ocular, vascular, and cardiac involvement in various types of spondyloarthropathy should be ascertained.

12. **Low back pain**

12.1 **Introduction**

Low back pain, with or without sciatica, has reached epidemic proportions in most industrialized countries. This same trend, however, is not seen in developing countries. Recent studies of health statistics in Sweden relating to the 4.5 million workers covered by national insurance show that 110 million days per year are lost as sick days. Of these, about a third relate to back disorders, of which 61% are given as pain in the low back area; 75% of these people with low back pain are between 30 and 59 years of age, i.e. during their most productive years.

There is a growing trend for more people to take more time off work because of back problems (Table 6).

During the period 1970-1987, Sweden had a 6000% increase in permanent disability pensions awarded for low back problems. These figures for disability pensions are 5-20 times higher than those of other industrialized nations, but to a certain extent reflect improvements in insurance benefits, which are often accompanied by increased absence from work due to back pain.

Table 6
Work absence from low back pain (Swedish figures)

Year	Percentage of insured	Average days sick
1970	1	20
1975	3	22
1980	4	25
1987	8	34

Etiology

Low back pain is a symptom and not a diagnosis. Only a small proportion of patients suffer from identifiable organic diseases, such as disc herniation, spondylolisthesis, instability defined by flexion-extension X-ray, osteopenia, fracture, tumour, infection, or rheumatic diseases (e.g. ankylosing spondylitis).

In several community-based studies in different countries, of the 50% of patients still unable to work one week after the onset of symptoms, only 2% had such valid organic diagnoses; while after six weeks, when 12% were still unable to work, only 15% had a definite diagnosis. Finally, after three months, when 5% of the patients were still not working, an anatomically definable diagnosis could be found in only 30%.

These findings indicate that the cause of back pain in most patients is unknown. It has been clearly demonstrated in many studies that X-ray examination does not reveal a cause. For example, degeneration of a single disc is found more often in people without pain than in people with pain. There are few radiologically valid signs of back pain. Magnetic resonance imaging (MRI) may delineate disc “degeneration” and other signs of aging better than simple X-ray examination. More importantly, MRI will also demonstrate ruptures and bleeding, either in ligaments, in myotendinous junctions, or in muscle fibres.

In certain patients it is likely that joint instability due to spondylolisthesis or premature disc aging might cause pain. Improved diagnostic techniques with small tantalum balls inserted into the vertebrae, followed by two-dimensional radiography and a computer evaluation (the Selvik photogrammetric method), will help to define the instability problem better.

Our knowledge of pain is improving. At the cortical level, fear, worry, dissatisfaction and tiredness have been found to increase pain, whereas joy, calmness and confidence decrease perception of pain. There are a number of diagnoses, such as facet or sacroiliac syndromes, where the contribution of the patient's psychological state to perceived symptoms is unclear.

12.2 Treatment

The literature on treatment of low back pain was thoroughly studied by the Quebec commission on industrial low back pain in 1984. Most randomized studies failed to confirm the value of treatment methods used all over the world. In summary, bed rest for not more than two days, the provision of information on the avoidance and alleviation of back pain, and mobilization as early as possible should be the main components of an acceptable treatment programme for patients with nonspecific low back pain.

The time-honoured method of immobilizing the patient has been proved wrong from a biological, psychological and healing point of view. Some

studies have demonstrated the ill effects of immobilization, and others have confirmed the beneficial effect of general conditioning exercises. The strengthening of certain muscle groups, especially the back extensors, seems to be of importance for both prevention and treatment. There is no proof, however, that special mobilizing exercises for the back are beneficial. On the contrary, some studies have shown that, in certain groups of patients, the stiffer their backs the better they feel.

Studies in animals and in patients with injuries of connective tissue demonstrate that these lesions may heal better through early controlled movement than through immobilization. Nutrition of the intervertebral disc is improved by motion and deteriorates after immobilization. Although manipulative treatment is widely advocated, there is little proof that such treatment in any way alters the course of the disease.

Waddell's concept of low back pain encompasses the well-known fact that hurt and harm are not the same. An undefined pathological process in the back leads to pain perception and psychological distress; this results in illness behaviour and its social consequences. This illness behaviour rarely signifies a pathological lesion in the anatomical sense, and thus the doctor is deprived of objective information that could be used to reassure and motivate the patient. Consequently, behavioural studies of pain have helped the medical profession to construct treatment programmes that increase patient self-motivation by using positive reinforcement. In randomized controlled studies, these programmes have proved more effective than other commonly used methods for the treatment of patients with acute, subacute and chronic low back pain.

12.3 Prevention

Since the exact cause of low back pain is not known, it is difficult to prevent it. In the Boeing study, 180 variables were studied in three thousand blue-collar workers over four years. The following factors were found to be of no consequence for reported back injury:

- workload
- physical fitness
- muscle strength
- mobility
- age
- sex.

The factors of importance were:

- previously reported back pain
- smoking
- abnormal personality
- job satisfaction
- relationship with fellow workers and superiors.

For the employer, better organization of the working environment seems to be important. Of the clearly demonstrated physical factors at work, forward flexion and rotation with more than 10 kg in the hands, repeatedly performed over the day, should be avoided.

In the treatment programme, the doctor must take care to carry out a thorough examination, and not to “medicalize” the problem by using false diagnostic labels. Rather, the doctor must develop the concept of rapid mobilization in the patient’s mind. Insurance companies should avoid delays in patients’ obtaining treatment, since it has been repeatedly demonstrated that an adversarial system enhances pain behaviour and disability. There is great hope that the current epidemic of low back pain in industrialized societies can be stopped. This will only be achieved through the combined efforts of doctors, employers, patients and politicians.

The present emphasis on physical workload may be of less importance in absenteeism due to low back pain than the general psychosocial work environment and degree of work satisfaction. Healthier living, including stopping smoking and taking more exercise, is more likely to influence back pain. This has been demonstrated with regard, not so much to symptoms, but to shortening the length of recurrences of back pain and diminishing the risk of chronicity.

At present, too many unproven remedies are tried in patients with back pain. These remedies are not only expensive, but may even prolong the illness and disability.

12.4 Recommendations for training and research

The medical profession needs to be better educated about back pain so that its members can conduct proper examinations enabling them to identify specific treatable causes of low back pain syndromes. They also need to be educated to avoid unnecessary X-ray examinations and the use of unproven labels for idiopathic back disease, such as “disc degeneration”.

12.4.1 *Etiology*

Very few patients with back pain have a valid, scientifically proven diagnosis. There is an obvious need to discover the cause of back pain in more patients. It is important to distinguish between general low back pain and sciatica, where the pain radiates below the knee. Patients with sciatica, who make up 2-5% of the population with low back pain, usually have a more easily identifiable cause for their pain.

There is a need to establish a causal relationship, if one exists, between different types of back pain and various work factors. More detailed knowledge is needed about the influence of these factors on the movement of the lower spine and its most important mechanical part, the intervertebral disc, and how such movement relates to pain. The intervertebral disc may be involved in the production of pain. Even if it is

not, the mechanical integrity and functioning of the mobile segment of the spine are dependent upon its health. The technique of MRI can help to demonstrate this integrity and should be used whenever available.

12.4.2 ***Treatment***

Studies are needed on the true efficacy of many poorly proven or unproven treatment methods currently in vogue all over the world. Because of very good natural healing, most patients recover from an episode of back pain within a week. Research needs to be directed at prevention of prolongation of symptoms due to the chronic low back pain syndrome. More attention should also be paid to surgical methods of treatment for patients who do not have a demonstrable disc herniation.

12.4.3 ***Long-term disability***

More needs to be known about the relative influence of physical workload, psychosocial factors at work, different treatment methods, and sickness pay on absenteeism and disability due to back pain.

Although it cannot be used widely in epidemiological studies because of financial constraints, MRI should be employed in the study of low back pain, particularly where there are injuries to the musculotendinous structures of the spine; the technique has great potential in both diagnostic and therapeutic assessment.

Spinal instability, a probable cause of back pain, particularly of the recurrent and chronic type, can be investigated by stereophotogrammetry, whereby movement can be studied in different planes. At present, spinal instability is the most commonly used diagnosis and indication for surgery.

Because of the importance of external factors in back disease, international studies, comparing people in similar occupations, could be useful in assessing the importance of variables such as the sickness insurance system or standard of living.

13. **Osteoarthritis**

13.1 **Introduction**

Osteoarthritis (OA) was first categorized towards the end of the nineteenth century when first pathologists and, subsequently, radiologists recognized that joint diseases fell into two main categories. The first, the atrophic group, includes sepsis, gout, rheumatoid arthritis and other erosive, inflammatory disorders. The second, the hypertrophic group, has not been split into as many distinct disorders and it is this group of conditions that has become known as OA.

OA has emerged as the most common and important form of joint disease in almost all populations studied. It includes a heterogeneous spectrum of joint disorders, and can cause pain and disabling destruction of major

synovial joints. The condition is strongly age-related. Severe OA of the hip and knee joints has become an increasingly important burden on the health services of generally healthier societies with a growing elderly population. Little is known about the pathogenesis of OA and no disease-modifying treatments are known. Palliative treatment and restorative operations, such as hip replacement, are therefore of major importance.

In spite of being by far the commonest form of joint disease, OA has attracted less basic research, clinical interest and health resources than many other arthropathies. This situation is now changing, but we still remain relatively ignorant about this disease.

13.1.1 **Definition**

There is no satisfactory definition of OA, and a number of different terms are still used to describe the condition. The disorder affects synovial joints, is generally slow to evolve and is characterized by the development of focal areas of destruction of the articular cartilage, with coexisting hypertrophy and “lipping” of adjacent subchondral bone. There is a variable inflammatory synovitis that is quite different in its nature and severity from that seen in rheumatoid arthritis and related conditions.

Difficulty in defining OA has arisen for a number of reasons:

1. OA is largely the visible reaction pattern of a joint to a variety of forms of damage, disease or abnormal anatomy. It is not a single disease entity.
2. There is poor correlation between the pathology, the radiological changes, which are often synonymous with pathological changes in the minds of epidemiologists and clinicians, and the clinical presentations of OA. Only a minority of joints affected by OA become symptomatic, and the severity of symptoms and disability vary for unknown reasons. As a result, epidemiologists, primary health care workers, rheumatologists and orthopaedic surgeons have quite different perceptions of the condition.
3. OA is heterogeneous. Not only is the severity of an individual joint's reaction to damage variable, but the nature of the response is also quite different depending upon the joint involved.

OA is, therefore, the visible result of the slow but dynamic response of a joint to injury. This response depends upon the specific cause, the age of the patient, the anatomical site of the joint, and the variable nature of the individual's reaction. In some patients the process may stabilize, while in others there is destruction and failure of the joint that require surgical treatment.

13.1.2 **Etiology**

The cause of OA is unknown. It can result from a number of other disorders of joints, and severe joint injury predisposes to the condition. OA that follows trauma or another disease is known as secondary OA. In most cases, however, where there is no apparent cause, the condition is called

primary OA. More than one joint is usually involved, suggesting that simple mechanical theories are probably inadequate to explain the condition.

OA is a multifactorial condition where the aging of specialized connective tissues, abnormal anatomy and biomechanics, and a systemic predisposition all play a part. The different etiological factors vary in importance between individuals and at different joint sites.

13.1.3 **Pathology**

The pathological definition and recognition of OA are relatively straightforward. The main feature is focal areas of damage to cartilage. The cartilage surface becomes disrupted (fibrillation), clefts appear, there is a loss of cartilage volume, and deep ulcers extending to bone can develop. It is common for only one part of a joint to be involved, the cartilage in the remaining areas appearing intact but biochemically abnormal. Areas of fibrocartilaginous repair may develop and can result in apparent healing. The whole synovium is usually metabolically hyperactive, with an increase in cell numbers, often in clusters, and excess matrix synthesis.

Hypertrophy of bone is the other major feature of the disorder. Patchy sclerosis accompanies an increase in metabolic activity and vascularity of subchondral bone. In some cases, the abraded bone takes on the appearance of thick ivory (eburnation). Marginal growth of cartilage and bone results in osteophytosis, altering the contour of the joint.

Soft tissue changes include a variable, patchy chronic synovitis and thickening of the joint capsule. The significance of these changes in early disease is unclear, but both are usually extensive in late cases of OA coming to surgery. Muscle wasting and abnormalities in periarticular tissues are also common, both of which are probably secondary features but may nevertheless contribute significantly to symptoms and to disability from the disease.

OA is a disorder of synovial joints. OA of the spine affects the apophyseal joints and should not be confused with age-related changes in the intervertebral discs, although there does appear to be a strong association between the two. The rest of this section is concerned only with OA affecting peripheral (limb) joints.

OA can affect any synovial joint, but has a clear age-related predilection for certain sites. The commonest sites are the knee, the hip and certain joints in the hand (distal interphalangeal joints and the carpometacarpal joint at the base of the thumb) and foot (first metatarsophalangeal joint). A variety of patterns or associations of disease at different sites have been described. A combination of disease of the hand and knee joint is particularly common. Overall, however, OA of the knee and of the hip are the major causes of health care problems.

13.1.4 **Radiology**

The plain radiograph has been the main tool for the diagnosis and assessment of OA for many years. The reasons for this are the following:

- The result reflects, in part, the pathological process.
- The procedure is cheap and simple and the result can be used for epidemiological studies.
- The technique is readily understood by clinicians.
- Apart from crude clinical procedures, no other method for the diagnosis and assessment of OA exists.

OA is characterized radiographically by narrowing of the joint space, the presence of osteophytes, and sclerosis and cysts in subchondral bone. A variety of crude methods exist to grade the severity of these changes. However, there are several problems in the interpretation and grading of X-rays:

1. The inter-bone distance seen on a radiograph (joint space) decreases with the patient's age. In addition, slight changes in joint contour, marginal osteophytosis and chondrocalcinosis are all age-related changes that can confuse the diagnosis of OA.
2. The various grading systems do not account for the heterogeneous expression of OA; for example, some joints may show severe bone changes with little narrowing of the joint space, and vice versa. Furthermore, surprisingly little is known about the validity and reproducibility of radiography in OA.
3. Radiographs are very insensitive to pathological changes and provide no more than a record of changes that have taken place in the past; they give no indication of disease activity or of changes currently taking place in the joint.

For these reasons, several other techniques for the diagnosis, measurement and assessment of OA are being investigated. These include magnetic resonance imaging (MRI) and scintigraphy, and a variety of biochemical and immunological measurements of changes in cartilage and bone.

13.1.5 **Clinical features**

Probably most joints with pathological and radiographic changes indicative of OA never produce symptoms. The worse the apparent joint disease on X-ray, the more likely it is that symptoms will appear; however, the relationship is not invariable and there are differences between joints and between the sexes.

Clinical OA affects women more often than men and is age-related. It rarely starts before the fourth decade of life and thereafter its incidence rises sharply. Patients complain mostly of pain and stiffness.

Pain is the major symptom. It is variable in severity and in character, but occurs principally when the affected joint is used. Its causes are uncertain; raised intraosseous pressure, subchondral microfractures, periarticular lesions, muscle spasm and inflammation can all contribute.

Stiffness is characterized by difficulty in initiating movement after a period of immobility. A reduced range of joint movement and pain on movement may also result in the subjective sensation of stiffness. Disability occurs as a result of pain, weakness, instability of the joint and a reduced range of movement. The main physical signs are bony swelling, crepitus, a reduced range of movement with pain at the limits of movement, articular and periarticular points of tenderness, and minor soft tissue and inflammatory changes.

13.1.6 ***Treatment and outcome***

Little is known about the natural history of OA, and the efficacy of some forms of treatment is uncertain. Medical management aims to reduce pain and maintain optimum function. This is achieved by analgesics, physiotherapy and other approaches to pain relief. It has been shown that the treatment offered by, often expensive, paramedical services improves the quality of life of patients with OA. Nonsteroidal anti-inflammatory drugs and intra-articular steroid injections are widely used, but with little justification. There is concern that, in the long term, some medical treatments may be harmful to joints. In some countries, drugs are in use that are claimed to be “chondroprotective” or helpful in modifying the disease process. At present, there are no data from adequately controlled clinical trials in humans to justify the use of so-called chondroprotective drugs.

Surgery is used to treat joints that are grossly damaged and causing severe pain. Hip replacement is well established as the best treatment for a badly damaged hip joint. Knee surgery includes osteotomy, which can promote healing, as well as joint replacement. Although data on long-term outcome are not available, relatively few joints with OA are treated surgically, even in countries where the service is generally available.

Many joints affected by OA stabilize spontaneously and the disease progresses no further. Symptomatic improvement with time is common and, rarely, spontaneous healing occurs.

13.2 **Epidemiology**

It is appropriate to consider OA from an epidemiological standpoint. The model used assumes that OA can be studied in terms of prevalence, risk-factors, the disease process, and outcome. This approach has been adopted for the two joints most often affected, the hip and the knee, which are considered separately.

13.2.1 ***Prevalence***

Figures for prevalence are often unreliable because of the problems with radiographs noted above and the variety of methods used in different surveys. Moreover, most epidemiological studies do not take symptoms and disability into consideration.

OA of the knee is rare before the age of 35 years, but about 20-40 % of people over the age of 70 have significant radiological changes. However, only about 30% of these will be symptomatic, and an even smaller proportion will be significantly disabled. Women are affected about twice as often as men. Most data are available on white Caucasians, but American blacks have been found to have a particularly high prevalence, as do some African and West Indian populations.

The hip is a less common site for OA than the knee, but a higher proportion of patients have symptoms and severe disability. There is a significant incidence of cases in relatively young adults, particularly men, and a less striking increase with age than for knee disease. Some 5-10% of older adults have significant radiographic changes. OA of the hip is equally common among older men and women, but unlike OA of the knee, hip disease is much less prevalent among African and some Asian populations than among Caucasians.

Considering these data, OA of the knee will be a formidable health care challenge in the future, as populations worldwide become older and more health-conscious.

13.2.2 **Risk-factors**

Risk-factors for OA can be divided into intrinsic factors, such as age, sex and race, and extrinsic or environmental factors, such as trauma and joint usage. There is some evidence that initiation and progression of OA may be controlled by different factors with different associated risks.

OA of the knee is predominantly a disease of females and is strongly related to age. The other main risk-factor is obesity. The relationship is strong, with a roughly linear increase in risk from below average in the underweight to a sevenfold increase in risk in the very obese. Knee disease is strongly linked to OA in the hand and at other sites, and obesity is also strongly associated with OA of the hand. OA of the knee may therefore reflect an OA diathesis and not just a mechanical problem. This has implications for prevention. In men, OA of the knee is strongly associated with previous trauma.

OA of the hip predominantly affects males and is seen most often in white Caucasians. Age is a risk-factor, but less so than for knee disease. Other risk-factors include developmental disorders causing anatomical abnormalities of the hip joint, for example acetabular dysplasia and slipped femoral capital epiphysis. Hip disease is only weakly associated with OA in other joints and has little or no association with obesity. Osteopenia (osteoporosis) may be a negative risk-factor. OA of the hip may have more to do with anatomical and biomechanical changes, and less with a systemic diathesis, than knee disease. Other possible risk-factors include joint usage, diabetes mellitus and other metabolic disorders, smoking – a possible negative risk-factor – and hysterectomy.

A number of models and theories of etiology have been proposed on the basis of existing data and known risk-factors, but more case-control studies are badly needed.

13.2.3 ***The disease process***

The disease process is largely invisible to clinicians and epidemiologists. Cross-sectional data indicate a tendency towards a slowly progressive anatomical derangement of joints, but the results of some more recent case-studies refute this and demonstrate potential for stabilization and spontaneous healing. These and other studies have also emphasized:

- The complexity of the reactions in target tissues such as cartilage.
- The dynamic nature of the disease process and the potential for tissue healing.
- The complex interactions between biochemical events and the mechanical forces acting upon the joint.

Basic research should be carried out to improve our understanding of cartilage as a tissue, and the factors that normally control its integrity. Methods for monitoring the disease process at a biochemical level are also needed.

13.2.4 ***Impact and outcome***

In some developed countries, the impact of OA has been calculated in terms of numbers of physically disabled people, the use of hospital and primary care medical resources, its effect on work, and the use of surgical procedures. All of these indicate that OA is perhaps the most important cause of physical disability in people over the age of 65 years. It is a far more important cause of lost working days than rheumatoid arthritis; for example, in the USA it has been estimated that OA results in about 50 times as much medical expenditure as rheumatoid arthritis. In many parts of the world there are very few data on the impact of OA.

There is a need for a changed perception of OA by both the general public and the medical profession. OA is a dynamic biological process, capable of stabilization and repair, and a more optimistic outlook is now justified, emphasizing the potential for future understanding and therapeutic control of the disorder at the cellular level.

13.3 **Education**

There is a great need for up-to-date information on OA to be disseminated through public and professional education channels. In particular, it is urgent to dispel the myth that OA is caused by aging and “wear and tear” on joints, and that it is a “degenerative” progressive disorder.

Public education about OA should emphasize the following:

- The term OA covers a heterogeneous group of disorders that all lead

ultimately to joint failure. This is analogous to kidney or heart failure, and describes an abnormal state of joint structure and function, and not a specific disease.

- OA is age-related, but not caused by aging alone. As a result of people living longer and being generally fitter, OA is becoming an increasingly important problem.
- Mechanical factors influence OA, but it is not merely a “wear and tear” disease. Activity and occupation probably play little part in causing most cases of OA. Genetic factors and conditions such as obesity influence overall predisposition to the disorder.
- An osteoarthritic joint is characterized by areas of damaged cartilage on weight-bearing surfaces. The underlying bone and surrounding soft tissues are also affected to variable degrees. Both degradative and reparative processes are going on in the joint simultaneously.
- The principal joints affected are those of the spine, the knee and the hip, and certain joints in the hand. The disorder behaves differently according to which site is involved.
- Progressive joint damage resulting in severe pain and disability occurs in some patients with OA. However, in many people the condition stabilizes, and pain and the degree of handicap wax and wane. In a minority, spontaneous joint healing and improvement occur.
- Patients with OA are recommended to maintain a full range of joint movement and strong muscles by means of regular exercises. The maintenance of regular normal function is also important. Prolonged rest and joint immobility are contraindicated.
- There is no cure for OA. Medication may help to reduce symptoms, but should be used cautiously. Physiotherapy is beneficial and surgery is reserved for patients with progressive joint damage and intolerable symptoms. Current research suggests that medical treatment is a realistic long-term goal.

Professional education about OA should emphasize the following:

- OA is not a degenerative disorder and the term “degenerative joint disease” should no longer be used. In OA, cell-driven degradation and repair are occurring simultaneously.
- OA is not a single disease entity and has many different predisposing factors. It is therefore inappropriate to study the disease as a whole without stratifying patients by age, sex, predisposing factors, and principal joints involved.
- Aging, degeneration of articular cartilage, and OA are three separate conditions with quite different biochemical and morphological characteristics. Remodelling and repair are major features of OA.
- The discrepancies between radiographs, symptoms, and handicap indicate that the causes of pain and disability need separate consideration. Pain can result from synovitis, bone and periarticular changes, and muscular strain and spasm. Each cause requires a different approach to treatment.

- It is important to maintain joint mobility, muscle strength, and normal loading of joints in order to preserve joint integrity and to promote healing. Physical activity should be encouraged.
- Progression is not inevitable in OA. Stabilization often occurs and sometimes spontaneous repair.

13.4 **Principal areas for research**

13.4.1 ***Epidemiology***

Although OA has been associated with a variety of host and environmental factors such as race, heredity, obesity, bone density, trauma, and geography, these associations have been identified largely in cross-sectional studies so that their etiological importance is unclear.

Risk-factors for the initiation, progression and disability of OA may not be the same, and require clarification. Host, genetic, environmental and other factors that may be protective or ameliorative also require definition. The effects of treatment with analgesics, nonsteroidal anti-inflammatory drugs, and “chondroprotective” agents on the natural history of OA in humans need to be determined.

There is a particular need for a reliable and validated method for establishing a preclinical or subclinical diagnosis. This method should be noninvasive, readily available and relatively inexpensive, for example a serological marker or imaging procedure.

13.4.2 ***Clinical subsets***

Since there are so many different clinical classification schemes for OA, it is unclear whether the various types (subsets) of OA are fundamentally different diseases or whether OA results from the reaction of the diarthrodial joint to damage. In the latter case, differences between disease subsets, such as cartilage calcification, hypertrophic change, and atrophic change, may simply reflect biological differences in the response to damage (repair) or in the damage itself. In addition, the influence of genetic and other factors on the clinical picture is unknown.

13.4.3 ***The role of trauma***

More research is needed to elucidate the different types of trauma that lead to OA; for example, the effects of acute severe trauma compared with low-grade repetitive trauma. We need a better understanding of how trauma causes joint damage, i.e. its effect on articular cartilage (calcified and uncalcified), subchondral bone, synovium, and supporting structures such as ligaments. Research is needed to determine the stress thresholds required to induce pathological change. A better understanding is required of how the chondrocyte transforms a mechanical stimulus into a metabolic response, and improved experimental systems are needed to study this. More needs to be known about the capacity of specialized connective

tissue, such as cartilage, to repair after trauma and about the factors that interfere with repair and modify the response to trauma, for example aging, drugs, and physical activity.

13.4.4 ***The role of aging***

Although age is the strongest risk-factor for OA, its relationship to OA is unclear. The biochemical changes that occur in articular cartilage with age are different from those of cartilage in OA. There remain many unanswered questions about the basis for age-related changes and their mechanisms; about the mechanisms that lead to alteration in the biomechanical properties of cartilage and render it more susceptible to wear and therefore to the development of OA; about the influence of genetic factors on the capacity of cartilage for repair; and about the effect of age on the ability of the chondrocyte in normal articular cartilage to synthesize matrix constituents. Another important area of research concerns the biological role of changes in growth factors during aging and their effects on articular cartilage.

13.4.5 ***The role of inflammation***

Although synovial inflammation is present in patients with advanced OA, the extent to which it is present at earlier stages (e.g. when radiographs are still relatively normal) is unclear. The temporal relationship between inflammation and cartilage damage remains unclear, especially in certain disease subsets such as erosive OA. Whether or not inflammation brings about cartilage damage in OA is uncertain, despite evidence that cytokines synthesized during an inflammatory response may initiate catabolic responses and inhibit the anabolic activity of the chondrocyte.

Pain in OA may originate in different articular and periarticular structures such as subchondral bone, synovium, osteophytes, and muscle. Careful clinical studies are needed to help to clarify pain patterns and to correlate these with response to treatment.

Experimental data suggest that some nonsteroidal anti-inflammatory drugs may accelerate existing cartilage damage. To what extent this is true in patients requires clarification. It is not known whether these drugs accelerate cartilage damage by a direct effect on the chondrocyte or by virtue of pain relief, permitting use of and therefore further injury to already damaged tissues. Indeed, it is not even clear whether nonsteroidal anti-inflammatory drugs are more effective than compounds providing a comparable degree of analgesia but no anti-inflammatory action.

13.4.6 ***The role of extracartilaginous structures***

More research is needed on the role of hardened subchondral bone in the initiation and progression of cartilaginous changes in OA. The contribution of hydraulic changes within the joint to the development of subchondral bone stiffness is also unclear.

We know little about the importance of the effects of mediators derived from the synovium, such as interleukin-1 and tumour necrosis factor, on chondrocytes and the extracellular matrix, and about the natural history of OA after periarticular connective tissue injury.

13.4.7 *The role of the neuromuscular system*

More needs to be known about the relationship of the neuromuscular system to joint integrity; for example, the extent to which muscle weakness contributes to the progression of OA or to disability. The mechanism by which an intact nervous system protects the joint should be elucidated, since it is known that, after transection of a cruciate ligament, the absence of afferent neuronal input from the joint may accelerate degenerative changes.

13.5 **Recommendations for research**

- Since OA is not a single disease entity, clues to its etiology should be sought among other groups of diseases, for example infections, and among conditions such as diabetes mellitus when occurring in a patient who also has OA.
- A serological marker or simple imaging procedure should be developed in order to detect subclinical OA and to monitor disease progression.
- A uniform database should be developed to facilitate longitudinal observation, the documentation of disease features, and comparison among populations of patients with OA. The database should include standardized radiographic, pathological, and clinical information. By using an international coding system such as ICD-10 for standardization, these data could serve as criteria for the reliability and validity of research and information.
- A classification of OA suitable for national and international epidemiological studies should be developed.
- Existing data should be carefully analysed; both cross-sectional and epidemiological data may be available. Environmental factors could be identified by studying the appearance of OA in populations migrating from developing to more developed countries.
- Longitudinal case-control studies are needed, following people at risk for OA or with early OA, in order to discover factors associated with progression or amelioration of clinical features such as pain, structural changes, and disability.
- In populations where OA is rare, existing data should be analysed for the relationship of trauma to joint symptoms, physical findings, and radiographic change. Elderly people without OA should be studied in order to identify possible protective factors for the disease.
- Epidemiological studies should focus on people engaged in high-risk activities for joint injury (e.g. football players at risk of meniscus tears) matched to similar groups who are not at risk. Long-term follow-up will be necessary.

- International studies of OA in well-defined animal models and occurring spontaneously in animals in various parts of the world should be conducted. Particular emphasis should be given to analyses of the differences between models with respect to the clinical, biochemical, metabolic, and biomechanical features of the disease.
- Unique forms of OA, such as Kashin-Beck and Meleni disease, should be further studied since they represent unique experiments of nature.
- Further studies are needed of the response of cartilage and bone to injury. Such studies should examine changes in individual macromolecular components, such as collagen and proteoglycans, and the interactions between these components, the effects of trauma on the mechanical properties of joint cartilage and subchondral bone, and the significance of such alterations in the pathogenesis of OA.
- For the soft tissues of the joint, the threshold limits for joint instability above which OA develops should be elucidated. The reversibility or amelioration of OA resulting from the repair of soft-tissue lesions should be examined.
- Data suggesting that normal articular cartilage undergoes mechanical failure with age, perhaps related to changes in proteoglycans and collagen, should be verified.
- The relationship of joint mechanics to inflammation should be investigated. Studies should also be conducted on the effects of movement and loading on an existing inflammatory reaction within a joint and on the importance of inflammation in promoting or retarding repair.
- Studies are needed of the significance of inflammation in the early stages of OA, in relation both to symptoms and to the progression of joint damage.
- Research should be conducted to improve the management of chronic musculoskeletal pain.
- Studies are needed to identify the sources of joint pain in OA and to relate its management to those sources, for example whether it is due to inflammation, a microfracture, or instability.
- Controlled studies should be conducted to demonstrate the efficacy of joint lavage and abrasion arthroplasty.
- Studies are needed to compare the effectiveness of nonsteroidal anti-inflammatory drugs with simple analgesics in OA and, above all, to determine whether the presence of synovial inflammation indicates the need to use a particular nonsteroidal anti-inflammatory analgesic.
- Research should seek to clarify the relationships between synovitis, pain, cartilage damage, and disability.
- The extent to which idiopathic OA in humans may be related to a subtle neurological deficit should be examined.

14. **Soft-tissue rheumatism**

14.1 **Introduction**

The symptoms of rheumatic disease are extremely common, yet more than half of all patients with such symptoms do not have arthritis or a known connective tissue disease. The most common symptom that brings the patient into contact with the health-care system is pain. It is important, therefore, to categorize these non-arthritic rheumatic complaints, broadly known as soft-tissue rheumatism, and to determine their causes, assess their severity and, if possible, plan their management.

The commonest conditions in the category of soft-tissue rheumatism are fibromyalgia; tendinitis, tenosynovitis and bursitis; polymyalgia rheumatica; and shoulder-hand syndrome. Soft-tissue rheumatism is also a common cause of low back pain (see p.36).

14.1.1 ***Fibromyalgia***

Fibromyalgia, often called fibrositis, is said to be a common rheumatic complaint in developed countries. It is, however, an ill-defined entity, and reports of its prevalence vary among different physicians and types of practice. In developing countries its frequency is not known. Women account for 80% of all patients with fibromyalgia. However, this figure has not been adjusted for such variables as willingness and ability to visit health-care facilities for minor complaints. This type of complaint is seen more frequently and is more severe in anxious patients and during periods of damp or wet weather.

A characteristic clinical feature is the presence of tender “trigger” points in periarticular muscles, sometimes associated with palpable nodules. In most studies, these trigger points have not proved to be reproducible with different examiners. The nodules, however, can usually be detected by the different examiners.

The pain of fibromyalgia usually responds poorly to analgesic and anti-inflammatory drugs. In some patients it may respond better to antidepressant drugs.

There is probably a large psychosomatic component to the disorder, and some preliminary studies have shown that many patients with fibromyalgia have abnormal electroencephalograms (EEGs).

14.1.2 ***Tendinitis, tenosynovitis, and bursitis***

Pain and limitation of movement are the main features of tendinitis, tenosynovitis, and bursitis. These conditions can be caused by infection or may be associated with systemic inflammatory disorders of connective tissue such as SLE or systemic sclerosis. For the most part, however, they occur as isolated events, sometimes related to specific trauma or to occupational hazards involving repetitive movement. The most common

sites are the shoulder (bicipital tendon, rotator cuff, and joint capsule); the elbow (lateral and medial epicondyles); the wrist and hand (De Quervain syndrome and other forms of flexor and extensor tenosynovitis); the hip (trochanteric and iliopsoas bursae); the knee (Baker cyst and anserine bursa); and the foot (Achilles tendon). Traditional forms of such occupational disorders, for example weaver's bottom, policeman's heel, and housemaid's knee, have to some extent been replaced by modern-day equivalents, such as those related to the use of computer keyboards. Treatment by immobilization, local steroid injection or, in rare cases, surgery, is usually effective, together with avoidance of the activity responsible. Physiotherapy may also be helpful for rehabilitation.

14.1.3 ***Polymyalgia rheumatica***

Polymyalgia rheumatica causes muscular pain, usually severe, around the shoulder and pelvic girdle. It is age-related, occurring almost exclusively in people aged 55 years or more, affects both sexes equally, and is seen mostly in temperate climates. It is often abrupt in onset and there is a tendency for cases to cluster. Morning stiffness is a prominent symptom. The erythrocyte sedimentation rate is usually very high and the disorder responds dramatically to relatively small doses of a corticosteroid (10 mg/day of prednisone or less).

On temporal artery biopsy, about 30% of patients with polymyalgia rheumatica show evidence of giant-cell arteritis. This latter condition can lead to sudden and irreversible blindness as well as cerebral symptoms. Overall, however, only 5-10% of these patients develop clinical symptoms as a result of arteritis.

With the worldwide aging of populations, polymyalgia rheumatica is becoming commoner and is an important cause of disability. The disease tends to be underdiagnosed and is often mistaken for other causes of pain in the elderly, such as cervical spondylosis. Patients with polymyalgia rheumatica should be warned about the risk of blindness from giant-cell arteritis and advised to consult an ophthalmologist at the first warning sign.

On muscle biopsy, inconsistent changes are sometimes seen in the myofibrils. Careful studies using joint scintigraphy and needle exploration may indicate mild to moderate shoulder synovitis. These findings do not explain the severe muscular pain and marked rise in the erythrocyte sedimentation rate that characterize polymyalgia rheumatica.

14.1.4 ***Shoulder-hand syndrome***

In the shoulder-hand syndrome, diffuse and usually painful swelling of the hand is often followed by muscular atrophy, poor circulation and contractures (reflex sympathetic dystrophy). In most cases there is no apparent cause. Some cases, however, are associated with preceding myocardial infarction, external trauma, cervical spondylosis or bronchial carcinoma, and patients presenting with the syndrome should be

investigated for these other conditions. The condition appears to be a neurovascular disorder that may resolve as the underlying medical problem improves. Its etiology is poorly understood, involving abnormalities in neurotransmission (sensory, motor, autonomic, and internuncial spinal pathways, and cortical influences) and in the activity of chemical mediators such as the neuropeptides and substance P and somatostatin.

14.2 **Education**

There is great need for more professional and public education in the area of soft-tissue rheumatism. Since people with painful soft-tissue rheumatic disease represent over half of all patients entering the health-care system because of rheumatic complaints, these conditions must be identified and distinguished from the other rheumatic diseases. Although nonspecific, this group of disorders can cause considerable pain and discomfort and affect the patient's quality of life. They merit much greater study.

Health education should familiarize people with the occupational and recreational causes of conditions such as tendinitis, tenosynovitis and bursitis, and how best to avoid them.

14.3 **Recommendations for research**

14.3.1 ***General recommendations***

International diagnostic criteria need to be established for these common conditions. It is also necessary to study further the genetic patterns of inheritance and predisposition to these diseases, as well as the value of psychometric testing and noninvasive investigation of cerebral functioning in their assessment.

Present studies into the role of neurotransmission and chemical mediation in the soft-tissue rheumatic disorders need to continue and to be expanded. It is also important to assess the impact of these disorders in certain occupations and industries.

14.3.2 ***Fibromyalgia***

Our knowledge of the incidence, sex distribution and genetic patterns of this condition in both developing and developed countries is poor, and epidemiological studies are needed. They could be a component of other population health studies, so that in the course of epidemiological studies in developing countries, for example, inquiry could be made about the typical pain patterns of fibromyalgia. HLA typing could be performed on random groups. Standardized diagnostic and classification criteria are also needed.

Nodules associated with trigger points should be biopsied and studied to determine their pathological nature.

Patients with fibromyalgia should undergo psychiatric and psychometric

testing as well as studies of the brain, using position emission tomography, magnetic resonance imaging, and EEG, which may elucidate the nature of associated sleep abnormalities and help to reveal organic disease if it exists.

14.3.3 ***Tendinitis, tenosynovitis, and bursitis***

Cultural differences in patterns of activity, for example squatting versus sitting, need to be evaluated as possible causes of these disorders and steps taken to avoid harmful activities.

Further knowledge of the incidence of these conditions in relation to changing patterns of occupation is needed, and the benefits of treatment by local injections and surgery should be evaluated by controlled clinical trials.

14.3.4 ***Polymyalgia rheumatica***

The role of climate in this condition needs to be clarified by comparing population groups in temperate climates with genetically similar groups in subtropical regions.

By comparing monozygotic twins and patients living in temperate and subtropical climates, it may be possible to identify an infectious cause and assess the importance of heredity and environment.

Investigation of synovial membrane, muscle, and fascia using modern techniques may reveal as yet unrecognized tissue abnormalities.

14.3.5 ***Shoulder-hand syndrome***

Neurovascular studies may elucidate the pathogenesis of this condition. In the course of studies of myocardial infarction, the occurrence of shoulder-hand syndrome should be evaluated and comparison made between those who develop the syndrome and those who do not.

15. **Gout**

15.1 **Introduction**

During the past 50 years advances in our knowledge of gout and how to treat it have been greater than those made for almost all other rheumatic diseases.

15.1.1 ***Hyperuricaemia***

The original idea of a single gene being responsible for hyperuricaemia has, with a few striking exceptions, been superseded by knowledge of the many factors, inborn, environmental and metabolic, that can influence the uric acid concentration in the body. The most significant of these was the discovery of hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency in 1967, and the subsequent demonstration of the many

different mutations of the enzyme and identification of specific amino acid substitutions in the deficient enzymes. However, such abnormalities, important as they are, appear to be very rare. Considerable progress has been made in understanding other aspects of purine metabolism and the mechanism of action of common environmental influences such as diet, alcohol, or drugs. Less common factors leading to hyperuricaemia include lead poisoning and the haemoglobinopathies.

15.1.2 ***Crystal-induced inflammation***

Although Garrod in the nineteenth century incriminated sodium urate as the cause and not the effect of gouty inflammation, it was only thirty years ago that urate crystals became accepted as the cause of gouty arthritis. This important observation led to the development of a common diagnostic test and heralded the study of other arthropathies caused by complex crystal deposition.

15.1.3 ***Population studies***

Since the plasma urate concentration is strongly influenced by environmental factors, significant differences are found between various populations and even within the same population at different times. The high incidence of gout in Maori and Polynesian people rises still further following emigration to Western society. Average plasma levels of urate have risen in the inhabitants of countries as far apart as Japan and Finland, where the ingestion of diuretics has been partly incriminated. Data have also emerged from South Africa, where the incidence of gout, previously very much higher among whites, is increasing among urban blacks. South African blacks in urban communities have higher concentrations of plasma urate than those who have remained in rural communities.

Diuretic-induced gout has become common in many countries. It is seen characteristically in elderly women, who sometimes develop tophi in the absence of a typical history of gout. However, usually some other factor, often renal functional impairment, is contributing to the hyperuricaemia.

15.1.4 ***Sustained hyperuricaemia***

It is difficult to define hyperuricaemia in either statistical or physicochemical terms. For practical purposes, the upper limit of normal may be taken as 420 $\mu\text{mol/l}$ (7.0 mg/100 ml) in men and 360 $\mu\text{mol/l}$ (6.0 mg/100 ml) in women. Higher levels are sometimes found on routine screening in people who have never had gout, and therefore the extent to which hyperuricaemia is a risk-factor for gout, renal disease, and ischaemic heart disease must be determined.

Prolonged hyperuricaemia certainly carries a risk for gouty arthritis proportional to its severity and duration. However, the particularly high degree of risk found in the Framingham study, with small numbers of people who had marked hyperuricaemia, has not been confirmed. For

example, recent data show that healthy men from Boston (USA) have an annual incidence of gouty arthritis of 0.1% for urate concentrations below 420 $\mu\text{mol/l}$, 0.5% for those of 420-534 $\mu\text{mol/l}$, and 4.9% for those of 540 $\mu\text{mol/l}$ or above. The risk of gout developing thus appears to be low.

Of the renal complications of hyperuricaemia, acute uric acid nephropathy, which occurs most commonly after chemotherapy for malignant disease, is easily prevented by giving allopurinol. Estimations of the frequency of stone formation among patients with gout range from 4 to 73%. Moreover, stones may be associated with hyperuricaemia in the absence of gout.

Interstitial deposition of urate can impair renal function. However, abnormalities of tubular or glomerular function may themselves lead to hyperuricaemia. Working out the sequence of events in an individual patient is often difficult. Recent studies, while not providing a definitive answer, indicate that hyperuricaemia itself does not cause significant renal insufficiency.

15.1.5 *Juvenile familial gout*

Several studies have highlighted families with a high incidence of gout, clearly genetic in origin, but without an identified biochemical basis (such as HGPRT deficiency). Two very rare disorders are seen. One is characterized by a vast increase in uric acid excretion and reduced renal function, and the other by hyperuricaemia associated with a chronic compensated haemolytic syndrome of unknown etiology.

An increasing number of families have been described where gout is distinguished by a low age of onset, equal involvement of both sexes, and associated renal disease, usually with hypertension, in the absence of overt uric acid overproduction. The condition has a dominant pattern of inheritance. The original concept of urate deposition in the kidney as the underlying cause is no longer thought to be likely. The basic defect may be a form of renal disease, as yet uncharacterized. Some members of these families pass into renal failure with no history of gout or other symptoms. It has been suggested that allopurinol can halt the rapid decline in renal function.

15.2 Treatment

It is possible both to treat the acute inflammation of gout with anti-inflammatory drugs and to control hyperuricaemia with uricosuric agents and allopurinol. Thus, gout has become a straightforward disease to treat. Gouty arthritis and attendant tophaceous disease now respond so well to treatment that it is difficult for the young doctor to appreciate the dread once inspired by this disorder.

Apart from drug treatment, doctors should be aware of the environmental factors that have been shown to influence urate levels, such as overeating, excessive consumption of alcohol, and prolonged use of diuretics.

There is evidence that hyperuricaemia is a graded risk-factor for gouty arthritis, but not, on its own, for renal disease or coronary heart disease. Hyperuricaemia, in the absence of any complicating feature, does not in itself require treatment. Hyperuricaemia may, however, accompany obesity, alcoholism, hypertension, hyperlipidaemia, renal disorders, or haematological disease, which may themselves require attention. Therefore patients with hyperuricaemia, like those with gout, should be assessed from a cardiovascular, renal, and haematological viewpoint.

It is now generally accepted that, in order to avoid diagnostic error, the demonstration of urate crystals in joint fluid or tophi is highly desirable before a diagnosis of gout is regarded as established.

15.3 Recommendations for research

Urate levels in populations may fall as well as rise. Serial urate measurements repeated in a large population in the USA showed a steady rise between 1961 and 1978, and then an apparent halting of the trend – a phenomenon that compares with rates of heart disease, which followed a similar pattern during the same period.

There are conflicting results on the relation between asymptomatic hyperuricaemia and cardiovascular disease. It appears that hyperuricaemia may be related to heart disease if the patient is obese or hypertensive, requiring medication, but that it is not itself an independent risk-factor.

It is possible that juvenile familial gout, which can only be identified by full investigation and family studies of young patients with gout, is considerably more common than is realized, and may be an important form of kidney disease in young people.

Urate crystals can be found in the joints of people without gout. Alterations in the properties of these crystals, such as changes in surface charge or protein coating, have been proposed as precipitating events for gout to occur. Knowledge about crystal deposition in joints has implications outside gout, extending to other and less well-defined forms of crystal-associated arthropathy.

The changing patterns of plasma urate levels in relation to gout in both individuals and populations should continue to be monitored.

The outcome and significance of asymptomatic hyperuricaemia are incompletely documented and should be further investigated in a prospective controlled study.

The disorders currently classified as juvenile familial gout need to be studied in greater depth.

Further research is needed into the pathological effects of crystals, the factors that govern crystal deposition, and the mechanism of the inflammatory response.

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