Lecture Notes on Rheumatology

John Edmonds MB BS FRACP

Graham Hughes MD FRCP

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John Edmonds MB BS FRACP
Staff Physician, St George Hospital, Sydney, Australia

Graham Hughes MD FRCP
Consultant Rheumatologist, St Thomas' Hospital, London SE1

Blackwell Scientific Publications
OXFORD LONDON EDINBURGH
BOSTON PALO ALTO MELBOURNE

Blackwell Scientific Publications
Editorial offices:
Osney Mead, Oxford, OX2 0EL
8 John Street, London, WC1N 2ES
23 Ainsdale Place, Edinburgh, EH3 6AJ
52 Beacon Street, Boston
Massachusetts 02108, USA
667 Lytton Avenue, Palo Alto
California 94301, USA
107 Barry Street, Carlton
Victoria 3053, Australia

First published 1985

Set by Butler & Tanner Ltd
Frome and London

DISTRIBUTORS

USA
Blackwell Mosby Book Distributors
11830 Westline Industrial Drive
St Louis, Missouri 63141

Canada
Blackwell Mosby Book Distributors
120 Melford Drive, Scarborough
Ontario M1B 2X4

Australia
Blackwell Scientific Publications
(Australia) Pty Ltd
107 Barry Street
Carlton, Victoria 3053

British Library
Cataloguing in Publication Data

Edmonds, J.
Lecture notes on rheumatology.
1. Rheumatism
I. Title II. Hughes, G. R. V.
616.7'23 RC927

ISBN 0-632-00368-5

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Preface

It is perhaps surprising that it has taken so long to include a text on rheumatology in the Lecture Notes series. For the enthusiast, rheumatology has the attractions of combining a very 'clinical' subject with a rapidly broadening scientific base.

In this volume we have included new scientific concepts, but have not forgotten that rheumatology is a very practical, clinical and pragmatic subject.

We are grateful to our colleagues who have helped with comments, criticisms and illustrations, to our wives, Sue and Monica, who helped with the proof reading, and to Miss Penny Smart, who helped us through the final preparation of this book.

John Edmonds
Graham Hughes

1 Introduction

SCOPE OF RHEUMATOLOGY

Rheumatology is concerned with diseases of the joints and connective tissues. These structures can be damaged by a variety of pathological processes including infection, inflammation, degeneration, metabolic disturbances and systemic diseases such as leukaemia or haemochromatosis, which have their principal effect on other body systems.

The full list of disorders falling within the province of rheumatology is a long one and includes well over a hundred defined conditions. These notes concentrate on those which are common or are important because they require early recognition for correct management.

Until the aetiology of the various arthropathies is understood, attempts at classification are necessarily unsatisfactory. Table 1.1 is simply a list of the major groups of rheumatic diseases.

Table 1.1 Major groups of the rheumatic diseases

Group	Disease
Inflammatory arthritis of unknown aetiology	Rheumatoid arthritis Seronegative arthropathies: ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, enteropathic arthritis
Connective tissue disease	Systemic lupus erythematosus Scleroderma, progressive systemic sclerosis The arteritides: polyarteritis nodosa, other forms of arteritis Dermatomyositis and polymyositis Sjögren's syndrome
Crystal deposition disease	Gout Pseudogout Others

Table 1.1 *continued*

Group	Disease
Degenerative joint disease	Primary Secondary
Arthritis associated with infection	Septic arthritis Non-septic arthritis occurring in association with recognised infections: *bacterial*, e.g., gonococcus, meningococcus, salmonella, shigella; *viral*, e.g., rubella, hepatitis, mumps; *other*, e.g., fungal, protozoal etc. Post-infective arthritis: rheumatic fever, post-salmonella and shigella
Arthritis associated with systemic disease	Cardiovascular: bacterial endocarditis Endocrine: acromegaly, thyroid and parathyroid disease, diabetes Gastroenterological: inflammatory bowel disease, Whipple's disease Haemopoietic: haemophilia, haemoglobinopathies, leukaemia, myeloma Heritable developmental and storage diseases: Marfan syndrome, hypermobility syndrome Immunological: hypogammaglobulinaemia, serum sickness Metabolic: haemochromatosis, hyperlipoproteinaemia Metabolic bone diseases: osteoporosis, osteomalacia Neurological: neuropathic arthropathy Renal: chronic renal failure, chronic dialysis Respiratory: hypertrophic pulmonary osteoarthropathy Miscellaneous: sarcoidosis, amyloidosis
Non-articular rheumatism and localised pain	Tenosynovitis, bursitis, fibrositis Enthesopathies: tennis elbow Entrapment neuropathies: carpal tunnel syndrome Postural and post-traumatic syndromes Localised pain syndrome: shoulder pain, foot pain

It is included here to provide a brief summary of the main areas this book will cover and to draw attention to the range of disorders which cause arthritis. It is also useful to have a check list of disease subgroups such as this, particularly when confronted with the patient whose disease is atypical and does not fall clearly within one of the common diagnostic categories.

RHEUMATIC DISEASES IN PERSPECTIVE

It is obvious that, within the long list of rheumatic diseases, some are very common and others exceedingly rare. Some are uncommon but of importance because failure to recognise them early and treat them correctly may result in long-term deformity.

Commonest rheumatic diseases

Non-articular rheumatic syndromes—soft tissue rheumatism
Degenerative joint disease including spondylosis and disc disease
Rheumatoid arthritis
Gout
Systemic lupus erythematosus

Rheumatic diseases requiring early recognition and treatment

Septic arthritis
Juvenile chronic polyarthritis
Polymyalgia rheumatica with giant cell arteritis
Rheumatoid arthritis

2 Normal Joint Structure and Synovial Fluid

Joints are divided into three types:

1 Fibrous joints which allow almost no movement, e.g. cranial bone sutures.

2 Cartilaginous joints which allow limited movement, e.g. articulations between vertebral bodies, pubic symphysis.

3 Synovial joints which allow a wide range of free movement, e.g. all the joints of the limbs.

Only the synovial joint will be considered in more detail as it is this type which is usually involved in rheumatic disease. The intervertebral disc will be discussed in the section on degenerative disease.

SYNOVIAL JOINTS

Synovial joints (Fig. 2.1) have several characteristic features:
Opposing bony surfaces, covered with articular cartilage.

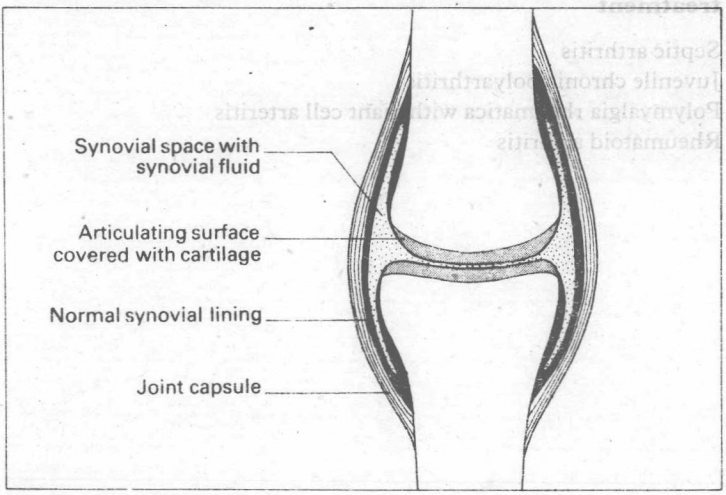

Fig. 2.1 The synovial joint.

A joint cavity which is only a potential space in life.
A surrounding fibrous capsule.
A synovial membrane which lines the whole interior of the joint space with the exception of the articular cartilage.
Lubrication with synovial fluid.

Articular cartilage

Usually hyaline.
Firmly attached to underlying bone by its deep calcified layer.
Smooth surface without covering perichondrium.
Contains neither nerves nor blood vessels.
Derives nourishment from the vascular network of adjacent synovium, synovial fluid, blood vessels in the underlying bone.

Fibrous capsule

Consists of white fibrous tissue thickened in some areas to form named ligaments.
Usually attached to bone close to the edge of the articular surface.
Has little elasticity and causes pain if subjected to sustained tension.

Synovial membrane

Forms a relatively smooth lining surface covering all of the interior of the joint with the exception of articular cartilage and articular discs, or menisci. In some joints fringe-like processes (synovial villi) project into the joint cavity.
Consists of a layer of surface cells (synoviocytes) 1–3 cells deep overlying fibrous, fatty, or areolar connective tissue which contains the synovial blood vessels, capillary loops and lymphatics.
The membrane is capable of both phagocytic and synthetic activity and this correlates with the function of the two different types of synoviocytes recognised on electron microscopy:

- cell type A: appears to be responsible for removing particulate matter from the joint cavity and transferring it to cells in the deeper part of the membrane
- cell type B: synthesise and secrete the hyaluronate-protein complex of synovial fluid.

Is poorly supplied with nerve fibres and is relatively insensitive to pain.

SYNOVIAL FLUID

Viscous, pale yellow and clear. Present in small amounts (e.g. 0.1–4.0 ml in knee joint).
Consists of a dialysate of plasma and hyaluronate-protein complex.

Constituents (Table 2.1)

1 Hyaluronate-protein complex.
— secreted by type B synoviocytes
— responsible for the fluid's high viscosity
— concentration is decreased in presence of inflammation.
Mucin clot test. Addition of acetic acid to synovial fluid precipitates the hyaluronate-protein complex as mucin. In normal fluid with high concentration of hyaluronate, the clot is tight, white and ropy; in inflammatory fluid, with a low concentration of hyaluronate, the clot is poor, fragmented or friable.
2 Proteins.
— normal concentration is about one-third of that in plasma (transudate) and is mainly albumin; there is no fibrinogen and the fluid does not clot
— in inflammatory fluid the protein concentration rises to approach that of plasma (exudate); fibrinogen enters the fluid which can then clot.
3 Other.
— electrolytes, uric acid, glucose, etc. present in approximately the same concentration as plasma

Table 2.1 Normal synovial fluid

Synovial fluid	Average value	Range
Volume (in knee) (ml)	2	0.1–4.0
Total protein (g/l)	20	10–30
Leucocytes/mm³	<200	30–200
Lymphocytes (%)	50	20–80
Mononuclear (%)	15	2–40
Polymorphs (%)	<25	10–60
Glucose	Approximately the same as plasma	
Uric acid		
Electrolytes		

— lysosomal enzymes present in very low concentration and correlate roughly with the cell count
— cells: total leucocyte count usually less than 150/mm^3, predominantly lymphocytes with some monocytes and polymorphonuclear cells, also occasional synovial lining cells.

Functions

Lubricates the joint and supplies nutriment to avascular articular cartilage.

3 HLA Antigens and Rheumatic Diseases

The association between certain diseases and specific HLA antigens has been a major biological discovery because it provides an insight into the complex contribution of genetics and immunology to the pathogenesis of these diseases.

One of the earliest reported associations, and still the most striking, is that between ankylosing spondylitis and HLA-B27. The antigen B27 occurs in 6–10% of Caucasians but is present in more than 90% of patients with ankylosing spondylitis. Some of the other seronegative arthropathies also show increased frequency of B27 and, more recently, associations have been reported between other rheumatic diseases and antigens determined by other genes of the major histocompatibility complex. This chapter outlines the nature of the HLA system, the rheumatic disease associations with HLA antigens, and the pathogenic and clinical significance of these associations.

THE HLA SYSTEM

HLA Antigens

These are cell surface glycoproteins which are present on nucleated cells. Their function is not fully understood but they are the cellular markers of individuality and they have an important role in immunological reactivity at the level of cellular communication.

There are two main groups of antigens; the class I antigens (HLA-A, B and C) are found on most nucleated cells, the class II antigens (HLA-D DR) are restricted to certain cells within the immune system.

The class I antigens have two components: a small fragment identified as $\beta 2$ microglobulin, and a larger component which carries the antigenic specificity. The class II antigens also have two chains. The DRβ chain plays an important role in the functional expression of these antigens recognised as the HLA-D

specificity. The base of the antigen is anchored in the cell membrane and the remainder projects above the cell surface with the antigenic portion exposed at the distal end.

Genetics of the HLA system

Although any one individual has a limited number of antigens on the cell surface—his or her pattern of biological individuality—the HLA system is strikingly polymorphic and a large number of different antigens have been identified. The HLA antigens are genetically determined and it is possible to divide the antigens into groups on the basis of the gene locus which codes for them.

These loci, on chromosome 6, have been designated A, B, C and D/DR (Fig. 3.1). At each locus, a number of different alleles (alternatives) may occur and these code for the antigens of the A, B, C, D/DR series. International studies have identified about 20 different antigens of the A locus, 30 antigens of the B locus, 8 of the C locus, about 10 of the D locus, and a similar number of the DR specificity.

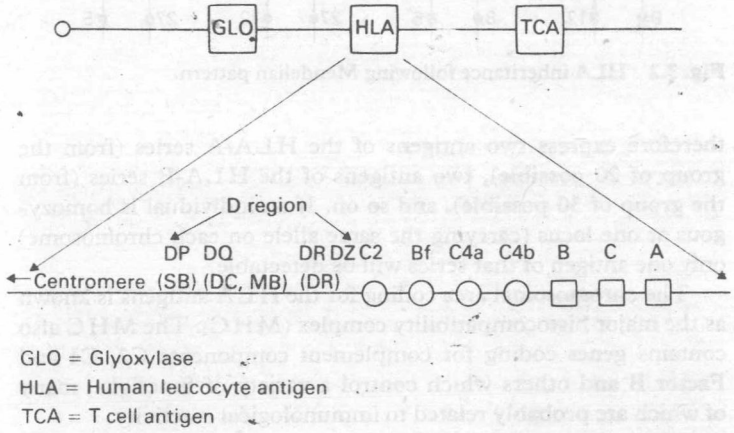

Fig. 3.1 Diagrammatic representation of the short arm of chromosome 6.
Class I loci are located away from the centromere and code for HLA-A, B and C antigens.
Class II region is complex; it is located on the centromeric side of the MHC and codes for α and β chains of the HLA-D and DR antigens.
Class III loci lie between these regions and code for the complement components C2, Bf and C4.

Since the genes for HLA antigens are co-dominant and one allele occurs at each locus of the paired homologous chromosome, an individual will express two antigens determined at each locus. One chromosomal set, known as the haplotype, is inherited in a Mendelian manner from each parent (Fig. 3.2). An individual will

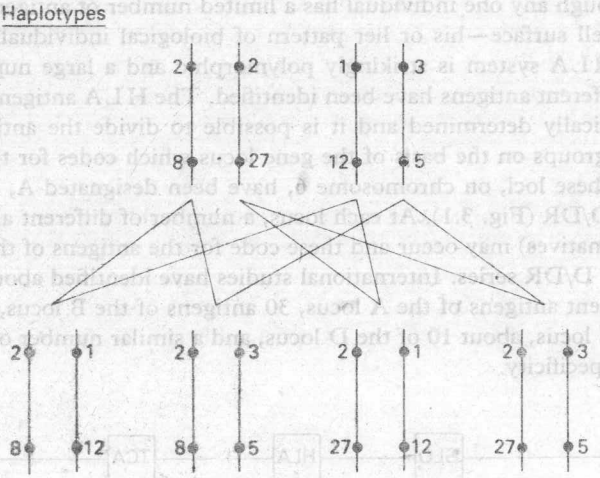

Fig. 3.2 HLA inheritance following Mendelian pattern.

therefore express two antigens of the HLA-A series (from the group of 20 possible), two antigens of the HLA-B series (from the group of 30 possible), and so on. If an individual is homozygous at one locus (carrying the same allele on each chromosome) only one antigen of that series will be detectable.

The chromosomal area coding for the HLA antigens is known as the major histocompatibility complex (MHC). The MHC also contains genes coding for complement components C2, C4 and Factor B and others which control a variety of functions, many of which are probably related to immunological reactivity.

Detection of HLA antigens

Antigens of the A, B, C and DR series are detected serologically using specific antisera and complement in a microlymphocytotoxicity test. Full tissue typing requires a large panel of specific antisera and is a complex and lengthy laboratory procedure.

Antigens of the D locus series were originally identified by the proliferative response of lymphocytes of non-compatible subjects when mixed together in tissue culture in a system known as mixed lymphocyte reaction. It was later found that specificities detectable serologically on B lymphocytes are similar to those expressed by the MLR and these have been termed the D-related (DR) antigens.

HLA nomenclature

This has been internationally standardised. Antigens are identified by the locus which codes for them: HLA-A1, HLA-A2, HLA-B5, HLA-B27, etc. Antigens which, on further international workshop testing, may be shown to contain more than one specificity are identified by the prefix 'w', e.g. HLA-Cw1, HLA-Dw5, etc.

Distribution within populations

The frequency of occurrence of HLA antigens varies between population groups. In some Caucasian populations frequencies are:

HLA-A1	16%	HLA-B5	6%
HLA-A2	28%	HLA-B7	10%
HLA-A3	14%	HLA-B8	10%
HLA-A29	4%	HLA-B12	14% etc.

In different racial groups, e.g., Japanese, American Indians, the frequencies of certain antigens may differ considerably.

When HLA antigens and disease associations are considered, the significance is determined by the frequency of the antigen in patients with the disease compared with the frequency of the antigen in the general population of the same racial origin.

ASSOCIATIONS BETWEEN HLA ANTIGENS AND RHEUMATIC DISEASE

The seronegative arthropathies show a strong association with HLA-B27. It has also become clear that rheumatoid arthritis shows a significant association with HLA-Dw4 and DR4. Some of the recognised associations are shown in Table 3.1.

HLA associations have been reported in a number of other

Table 3.1 HLA antigens and arthritis

Disease	HLA antigens	% Patients	% Controls
Ankylosing spondylitis	B27	90–95	6–10
Reiter's syndrome	B27	75–90	6–10
Psoriatic arthritis			
with peripheral arthritis	B27	10–20	6–10
with spondylitis	B27	50–60	6–10
Inflammatory bowel disease			
peripheral arthritis	B27	6–8	6–10
spondylitis	B27	50–60	6–10
Reactive arthritis			
Salmonella, Yersinia	B27	70–90	6–10
Rheumatoid arthritis	Dw4	35–55	10–20
	DR4	50–80	20–40

rheumatic diseases but in many the picture is confusing, either because of heterogeneity within the disease entity or as the result of changes which accompany the rapid and continuing developments in the HLA area particularly associated with the definition of HLA-D and DR specificities.

Juvenile chronic arthritis and systemic lupus erythematosus are examples of heterogeneous rheumatic diseases in which the true association of HLA antigens with certain subgroups is yet to be finally determined.

Significance of associations

PATHOGENETIC SIGNIFICANCE

The very strong association of HLA-B27 with ankylosing spondylitis and Reiter's syndrome must be relevant to the development of these disorders. Two main theories have been put forward to explain the association:

1 The antigen, because of its structure, acts as a receptor for or cross-reacts with an infectious agent and thus disturbs normal immunological and other functions.

2 The B locus allele HLA-B27 is strongly linked to another gene which permits the development of disease.

Which theory is correct has not yet been resolved and the mech-