A synopsis of RHEUMATIC DISEASES

DOUGLAS N. GOLDING

Fourth edition

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Fourth edition

WRIGHT · PSG

BRISTOL LONDON BOSTON
1982

Published by:
John Wright & Sons Ltd, 42–44 Triangle West, Bristol BS8 1EX, England.
John Wright PSG Inc., 545 Great Road, Littleton, Massachusetts 01460, USA.

First edition: 1966
Second edition: 1973
First French edition: 1968
First German edition: 1967
Second German edition: 1971
First Spanish edition: 1974
Third edition: 1978
Second Spanish edition: 1981
Fourth edition: 1982

British Library Cataloguing in Publication Data
Golding, Douglas N.
A synopsis of rheumatic diseases.—4th ed.
1. Rheumatism
I. Title
616.7'23 RC927

IBSN 0 7236 0627 7

Library of Congress Catalog Card Number: 81-71453

Printed in Great Britain by John Wright & Sons (Printing) Ltd, at the Stonebridge Press, Bristol BS4 5NU

PREFACE TO THE FOURTH EDITION

Rheumatology continues to advance rapidly. For example, amongst immunological advances our understanding of the HLA systems and clinical implications perhaps has pride of place. New anti-inflammatory drugs continue to appear with monotonous regularity, some appearing to act at different points of the inflammatory reaction. The concept of seronegative spondarthritis has become established, and the relationship of intestinal and genito-urinary disease to these disorders is becoming more clear. We are learning more about the role of crystals in the pathogenesis of a variety of joint diseases, both acute and chronic.

In this edition the new layout conforms to recent ideas of classification of the principal rheumatic disorders into rheumatoid arthritis, degenerative joint disease (including traumatic and neuropathic arthritis), seronegative spondarthritis, reactive arthritis (including Reiter's disease) and systemic connective-tissue disorders. Some chapters have been virtually rewritten, others extensively revised and there are additional references to articles in the better-known rheumatology journals. At the end of the book, eighteen additional multiple choice questions set in recent MRCP (UK) examinations have been added to the twenty questions set in the third edition. A close interrelationship is maintained with *Concise Management of the Common Rheumatic Disorders,* edited by the same author and published in 1979.

1982 D. N. G.

PREFACE TO THE FIRST EDITION

The study and practice of rheumatology is rapidly assuming great importance. This *Synopsis* is intended to cover the main aspects of the subject briefly and is orientated towards the needs of the general physician and postgraduate student. It is also hoped that general practitioners and undergraduates might find it useful, particularly as standard rheumatology textbooks tend to be lengthy and directed mainly towards specialists in the field.

In writing *A Synopsis of Rheumatic Diseases* an attempt has been made to be dogmatic and thus avoid controversial issues which tend to abound in such a 'young' subject. This will inevitably invite criticism, but it is the price that must be paid for a book which aims to be a short guide to the aetiology, diagnosis and management of the rheumatic disorders.

The style of the book is 'telegraphic', in line with the other synopses in the series which together replace the original *Synopsis of Medicine* by Sir Henry Tidy. Several standard works such as Copeman's *Textbook of Rheumatology* and Hollander's *Arthritis and Allied Conditions*, as well as numerous articles, have been freely consulted.

1966 D. N. G.

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PART I

GENERAL ASPECTS OF RHEUMATOLOGY

Chapter 1

ANATOMY AND PHYSIOLOGY OF SYNOVIAL JOINTS AND CONNECTIVE TISSUE

STRUCTURE OF SYNOVIAL JOINTS

Most varieties of arthritis involve some or all of the structures comprising synovial joints (*Fig.* 1).

1. Joint Cavity (Joint Space). Normally this is a *potential* space, containing only a film of synovial fluid. In arthritis the fluid often accumulates, distending the joint. This is lined by synovial membrane (*see below*).

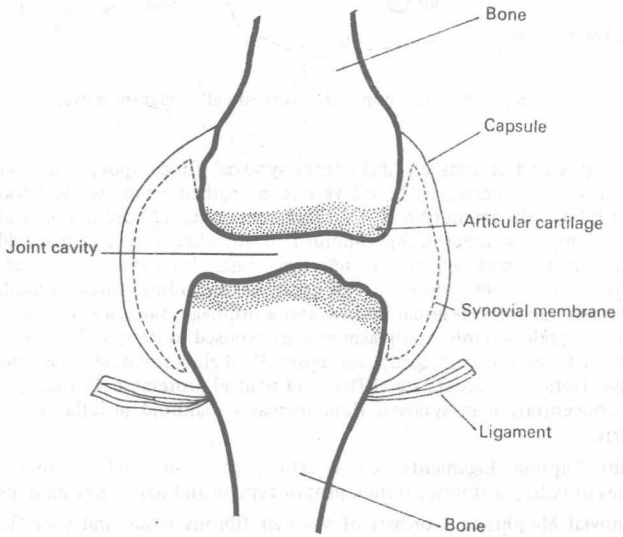


Fig. 1. Diagrammatic representation of a synovial joint.

2. Articular Cartilage. Covers articular surfaces. Cartilage is made up of matrix (collagen fibres and ground substance) and cells. Matrix consists of (*a*) Type II collagen fibres disposed radially in 'arcades', (*b*) ground substance composed of *proteoglycan* which is composed of chondroitin sulphate and keratin sulphate, and responsible for compressive stiffness of cartilage. Cartilage cells lie in spaces (lacunae) and are thought to form collagen and proteoglycan. As seen by the naked eye, the cartilage surface is rough, with

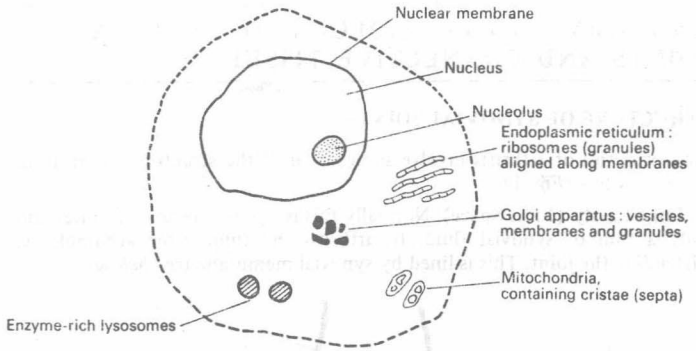


Fig. 2. **Electron microscopy of a normal cell (diagrammatic).**

shallow pits and strands of fibrin from synovial fluid. Sponge-like, with tiny 'pores'. No nerves or blood vessels; nourished from synovial fluid. Repair is by replacement fibrosis. Cartilage cells contain *lysosomes,* granules bounded by a semipermeable lipoprotein membrane containing acidic destructive enzymes which are activated when lysosome membrane is damaged. Lysosomes consist of cell organelles including storage granules, pinocytosis vacuoles, residual bodies, and autophagic vacuoles. Lysosomal enzymes are released into cytoplasm in cells exposed to immune complexes. These enzymes are principally cathepsin D, β-glucuronidase, acid phosphatase, lactic dehydrogenase (LDH) and neutral proteinase. For example, LDH concentration in synovial fluid increases manifold in inflammatory arthritis.

3. Joint Capsule Ligaments. Unite articulating bone ends. Consist of bundles of collagen fibres. Contain proprioceptive and pain nerve endings.

4. Synovial Membrane. Consists of vascular fibrous tissue and superficial branching synovial cells—a thin superficial layer and a thick supporting layer. Lines capsule and covers all intra-articular structures *except articular*

cartilage, which is thus directly in contact with synovial fluid. Internal surface raised in villi. Cytochemistry shows enzymes such as lactic dehydrogenase, acid phosphatase, cathepsins. Electron microscopy shows two types of lining synovial cell: *Type A cells* (phagocytic)—abundant

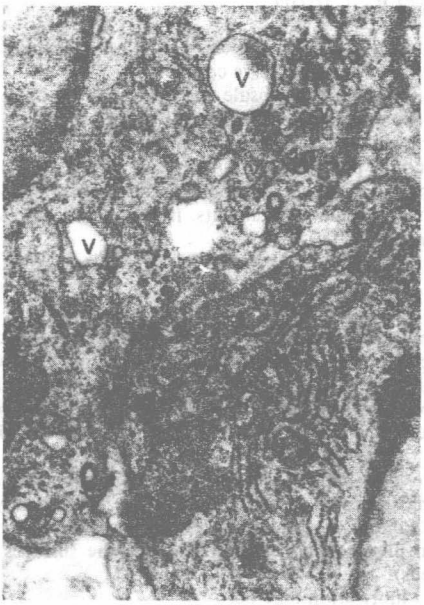


Fig. 3. Electron micrograph of synovial membrane. Type A cells contain numerous vacuoles (V) and vesicles (v). Type B cells contain abundant rough endoplasmic reticulum (R) (X 15 000). (*By courtesy of Dr F. N. Ghadially.*)

Golgi apparatus, large vacuoles, scanty endoplasmic reticulum. *Type B cells* (synthetic)—smaller Golgi apparatus, few small vacuoles, abundant rough endoplasmic reticulum. Type A cells are phagocytic. Type B cells are probably site of synthesis of hyaluronate and protein, which confer viscosity on synovial fluid (*Fig.* 3).

5. Intra-articular Structures. Articular cartilaginous discs and menisci, fat pads.

BLOOD SUPPLY OF JOINTS

Blood vessels from metaphysis and epiphysis enter joint at capsular attachment and form arterial circles around joint. From these arise capillary networks and superficial layers of synovial membrane.

NERVE SUPPLY OF JOINTS

In general, nerves supplying muscles acting on a joint also supply the joint (Hilton's law). An articular nerve contains:

1. Pain afferents from capsule and ligaments.
2. Pain afferents from adventitiae of vessels.
3. Proprioceptive afferents from capsule.
4. Autonomic postganglionics to vessels.

Synovium and cartilage are poorly innervated: joint pain arises mainly from stretched capsule or ligaments. It is poorly localized, often *referred* down the limb.

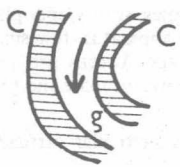
JOINT LUBRICATION

Very efficient (low coefficient of friction). Depends on properties of articular cartilage and synovial fluid (*see below*). Synovial fluid is *non-Newtonian*, i.e. the faster the joint moves the less viscous the fluid becomes (relationship between shear stress and shear rate is non-linear). Fluid becomes Newtonian (like water) when less viscous, in inflammatory conditions.

There are two main types of joint lubrication (*a*) *Fluid film*, joint surfaces being separated by a film of synovial fluid (mainly at high rubbing speeds), (*b*) *Boundary*, joint surfaces being separated by fluid molecules which are in physicochemical contact with the surfaces (mainly at high rubbing speeds).

Fluid film lubrication may be:

1. Hydrodynamic. Thick synovial film separates articular cartilage, surfaces moving at an angle to each other, gap produced (g), fluid drawn into g produces pressure separating surfaces (C). Probably important in stopping and starting movements.



2. Squeeze Film. Fluid squeezed out from porous cartilage to replenish fluid forced away.

3. Boosted Lubrication. Under load, plasma dialysate portion of synovial fluid squeezed out, hyaluronic-acid–protein complexes form 'sticky' skin over rough areas; *trapped pools* formed in undulations in cartilage which act as reservoirs. Fluid film and all methods of boundary lubrication may be involved at different stages of joint movement.

SYNOVIAL FLUID

Derived from plasma, to which is added mucopolysaccharides (polymers of long-chain hyaluronic-acid–protein molecules), and cells from synovial membrane.

Table 1. Characteristics of Normal Synovial Fluid

Appearance	Clear, pale yellow
Relative density	1·010
pH	7·4–7·8
Viscosity	Variable from joint to joint (average relative viscosity 230)
Cell-count	10–200 per mm^3
Polymorphs	Average 6 per mm^3
Mononuclears	Average 70 per mm^3
Synovial cells	Average 5 per mm^3
Total protein	10–20 g per l
Albumin	Less than 1·0 g per dl
Globulin	Less than 0·5 g per dl
Urea, Uric acid	Slightly less than serum
Glucose	Average 3 mmol per l (50 g per dl, about half the blood glucose)

Glucose and ionic concentration in synovial fluid roughly equals plasma, proteins are immunologically the same as plasma but reduced (under 2 g per cent) and in different proportions of immuno-electrophoresis; high molecular weight and asymmetrical proteins, e.g. fibrinogen, are absent. Synovial cells produce hyaluronate which is firmly bound to synovial fluid proteins.

Synovial fluid nourishes articular structures and provides joint lubrication. Synovial fluid changes in various joint disorders are described in Chapter 4.

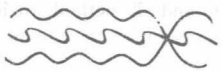
STRUCTURE OF CONNECTIVE TISSUE

Connective tissue is formed of:

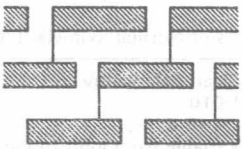
1. Cellular Components—fibroblasts, macrophages and tissue mast cells.

2. Fibrillar Components

a. COLLAGEN. Collagen element is tropocollagen, rods composed of three polypeptide strands, each consisting of amino acids, arranged in *triple helix:*



These are joined by cross-links to form *collagen fibrils* which have characteristic axial periodicity.



In young (newly-formed) collagen, cross-links are soluble and more easily disrupted (labile aldinine cross-links). In older lesions stable keto cross-links occur. Rationale of D-penicillamine in early systemic sclerosis is that this inhibits soluble cross-link formation.

b. RETICULIN. Fine branching filaments, in loose connective tissue.

c. ELASTIN. In ligaments.

3. Ground Substance. Gelatinous, composed of proteins and acid mucopolysaccharides.

Two types of collagen: Type I Collagen (in skin), Type II collagen (in cartilage). Collagen is broken down by enzyme *collagenase.*

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IMMUNOLOGY OF RHEUMATIC DISORDERS

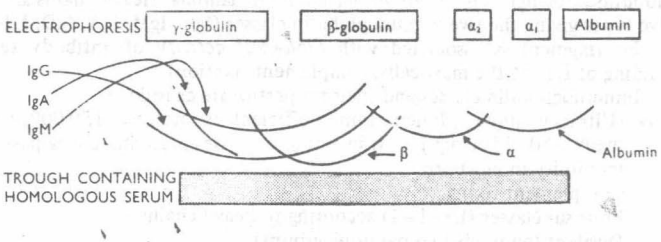
Immunology has assumed great importance in the rheumatic diseases, both regarding pathogenesis and treatment. Therefore, a relatively full account of the principles and applications of the subject is given in this chapter.

REVIEW OF IMMUNOLOGICAL PRINCIPLES

Antigens are substances which stimulate an immune response.

Antibodies are substances, usually large molecular-weight protein, synthesized by cells derived usually from plasma cells in response to antigenic stimulation. Resulting antigen–antibody combination either may provide defence to infection or may be harmful (e.g. in causing tissue damage). *Epitope* is combining site of antigen, *paratope* is combining site of antibody. Antibodies may be free (i.e. extracellular) or bound to cell surfaces.

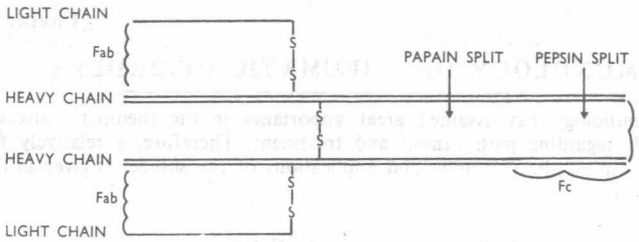
The Immunoglobins. Humoral antibodies are in gammaglobulin fraction of serum. When serum is subjected to immuno-electrophoresis, immunoglobulins of different classes and specificities migrate varying distances according to their charge, molecular weight, etc. If allowed to react with antisera to immunoglobulins in agar, precipitation lines are formed. A resulting pattern is as follows:

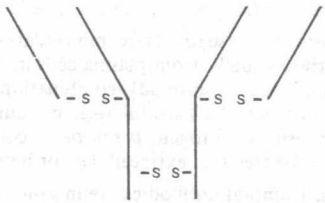


Five classes of immunoglobulins: IgG, IgM, IgA, IgD, IgE (IgD and IgE normally do not show on immuno-electrophoresis).

Immunoglobulins composed of two *light chains* and two *heavy chains*, joined by disulphide bonds (*see* p. 8).

Papain splits IgG molecule into three fragments: two called Fab (fragments binding to antigen), one called Fc (crystallizable fragment). Pepsin splits IgG to destroy Fc, leaving $F(ab)_2$ (divalent). Electron microscopy shows IgG actually to be Y-shaped molecule whose arms open on combination with antigen, S-S bonds joining heavy chains acting as 'hinge':





Fab fragment is associated with *antibody specificity*. Immunoglobulins made up of amino-acids which can be studied in myeloma paraprotein (*see* Chapter 21). Bence Jones protein excreted in urine in myeloma is composed of principally light chains, either kappa or lambda, and in any immunoglobulin both light chains are either kappa or lambda. Heavy chains are of five types giving the five immunoglobulin classes (IgG, IgM, IgA, IgD, IgE).

Fc fragment is associated with *biological activity* of antibody (e.g. binding of IgE on the mast cells, complement fixation).

Immunoglobulin classes and their properties are as follows:

IgG (Ultracentrifuge sedimentation coefficient 7s; mol. wt. 150 000; normally 880–1500 mg per dl in serum.) Crosses placenta, giving passive immunity in newborn.
Complement fixing.
Four subclasses (IgG 1–4) according to heavy chains.
Divalent (contains two paratope groups).

IgM (Sedimentation coefficient 19s; mol. wt. 1 000 000; normally 50–100 mg per dl in serum.)
Cannot cross placenta (large molecules—macroglobulins).
Complement fixing and agglutinating.
Two subclasses (IgM 1–2).
Polyvalent.
Examples: Antibacterial antibodies, rheumatoid factor.

IgA (Sedimentation coefficient 7s; mol. wt. 160 000, normally 200–400 mg per dl in serum).

Synthesized in mucus membranes, occurring in secretions (saliva, tears, etc.)—first defence of epithelial surfaces against infection—combined with 'secretory piece' synthesized by epithelial cells. Usually not complement-fixing. May be raised in Sjögren's syndrome (*see* Chapter 12).

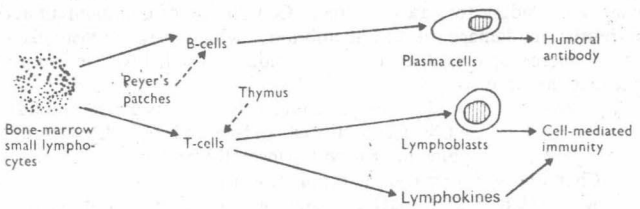
IgD (Sedimentation coefficient 7s; mol. wt. 185 000; normally 0–400 mg per dl in serum). Function unknown (occasionally occurs in myeloma).

IgE (Sedimentation coefficient 8s; mol. wt. 200 000; normally only minimal amounts in serum.)
Found in atopic states (reagin antibodies); fix firmly to skin mast cells and circulatory basophils, causing degranulation and release of vaso-active amines.
Cannot cross placenta; no baby is born with allergy.
Not complement fixing.

Biological Mechanism of Antibody Production. Following antigen challenge in the body, two types of immune response may occur:

A. HUMORAL RESPONSE. Mediated by antibody released into circulation and body fluids. Antibody is made by plasma cells derived from *B-cells* (bone marrow-derived cells). B-lymphocytes probably originate in bone marrow and are possibly processed by Peyer's patches of gut. In blood, 10 per cent lymphocytes are IgG-carrying, 6 per cent are IgM-carrying. B-cells are demonstrated by fluorescence of adsorbed antihuman immunoglobulin.

B. CELLULAR RESPONSE. Mediated by small lymphocytes from bone marrow processed by thymus to become *T-cells* (thymus-derived cells), which are responsible for cell-mediated immunity. On meeting antigen these cells turn into lymphoblasts and function by direct cell contact or by release of lymphokines.



(*Note:* T-cells also help—'cooperate' to present antigen to B-cells, giving better antibody response.)

T-cells can be demonstrated by *rosette-formation* of sheep red cells: they cluster round red cells forming 'rosette'.

Antibodies are synthesized from basic amino-acids. Sequence of amino-acids in immunoglobulin molecules thought to be genetically controlled—

i.e. DNA (in nucleus) controls synthetic function in cytoplasm via messenger RNA. Antibody specificity possibly instructional, following antigen acting as 'template'. Alternatively, clones of cells able to produce infinite number of antibody specificity exist as 'memory' cells, and are stimulated by antigen to divide and synthesize antibody (clonal selection theory).

Properties of Antigens. Antigens must be small molecules, probably processed by macrophages before becoming reactive. They are foreign to the organism, being either *heterologous,* from animal of different species; *homologous,* from another animal of same species (e.g. iso-antibodies to ABO cells); or *autologous* if directed against individual's own antigenic determinants. They are usually proteins (highly antigenic), rarely lipids (poorly antigenic) or simple chemicals (which act as haptens).

Antigen–antibody Reactions. Occur in two stages: (*a*) The combination of epitope with paratope—a physical (not chemical) binding due to coulombic forces (between negative acidic and positive basic radicals of amino-acid), van der Waal's forces (between 'electron clouds' around molecules—electrons in one molecule form dipoles which induce dipoles in the next), hydrogen bonding between hydrophilic groups, and hydrophobic bonding. (*b*) The formation of detectable antigen–antibody reactions, which are: *precipitation* (soluble antigen and soluble antibody); *agglutination* (particulate antigen and antibody); *complement fixation* (leading to cell lysis); and *neutralization* (antibody neutralizes activities of antigen).

Complement. This is a complex group of proteins (C1, C2, C3 etc.) (mainly beta-globulins) acting in sequence. C1 is subdivided into C1q, C1r and C1s. Complement is activated by immune complex following binding of C1q to Fc part of immunoglobulin. Activated C1 then itself activates next component, etc. leading to 'cascade effect'. Completion of complement activation results in damage to cell membranes, which may be visualized by electron microscopy as discrete holes, leading to cell lysis. In simplified form, sequence is as follows:

C1q binds to Fc: → C1s releasing esterase, which acts on C4 and C2
→ C4, C2 activated and bound to cell, acts on C3 which has the following activities:

1. Chemotaxin I formation (for polymorphs);
2. Anaphylatoxin I formation (histamine release from mast cells);
3. Immune adherence to cells (for phagocytosis);
4. Immunoconglutinin formation (antibody to C3)
   → C5–7 complex formed and bound,
   → C8–9 complex formed and bound, causing:
5. Anaphylatoxin II formation;
6. Chemotaxin II and III formation;

finally