Systemic Inflammatory Disease and the Eye

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Dedication to my mother and father

Preface

Several years ago I began a programme of reading with two objectives in mind. The first was to achieve an overview of the many systemic conditions associated with ocular inflammation. The second and more alluring one was to gain substantial insights into the reasons for ocular involvement in some conditions and not in others.

Encouraged by colleagues and convinced that others would find it both helpful and interesting, I have here recorded the outcome of this pursuit. The book is aimed at the middle ground between internists and ophthalmologists. I hope it will provide ophthalmologists with an informed background to ocular inflammation, and also help internists gain a better understanding of the nature of the ocular lesions. The latter may find the introductory chapter on signs of ocular inflammation of particular value.

While the pursuit of my first objective has been personally very rewarding, I find myself frustrated in the second. I firmly believe that the necessary revelations will eventually be found in the study of immunopathology, but the torrent of information which is adding daily to our knowledge of the mechanisms of disease seems to generate scarcely a trickle about the true *cause* of disease. My present feelings are well expressed by Robert Musil:

> In these hundred years we have got to know ourselves and Nature and everything very much better, but the result is, so to speak, that whatever one gains in the way of order in matters of detail one loses again where the totality is concerned, so that what we get is more and more systems of order and less and less of order itself.
>
> *Der Mann ohne Eigenschaften*, 1930

My gratitude is due to the many colleagues who have been so generous with encouragement and constructive criticism, and to the medical librarians who, with their unfailing cheerfulness, patience and understanding always make me feel welcome in their domains.

W. J. D.

Acknowledgements

I am most grateful to the many colleagues who have provided illustrations for this book. Their names have been added to the appropriate captions.

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Foreword

by **G. Richard O'Connor** MD
Professor of Ophthalmology, Emeritus,
University of California, San Francisco

There has long been a need for a clinical text that would aid both internists and ophthalmologists in their struggle to diagnose and treat inflammatory disorders of the eye with efficiency and safety. William Dinning's latest literary effort, *Systemic Inflammatory Disease and the Eye*, provides just such a book.

In the past, ophthalmologists and internists have dealt with the subject patients as if the latter belonged to a discrete domain. For his part, the ophthalmologist has generally regarded the ocular inflammation as an isolated lesion that should be treated with corticosteroids. The possibility of coexistent, related systemic disease is often disregarded, particularly if the patient in question has no systemic complaint, or at best, a few minor aches and pains. It is now known that such patients may well have incipient rheumatoid disease that can be confirmed at an early stage only by laboratory tests or roentgenographic examinations. On the other side of the coin, immunologically compromised hosts, such as patients with early sarcoidosis or 'acquired immune deficiency syndrome' (AIDS), may have no systemic symptoms at all at the beginning of their disease. An ocular lesion may be the only manifestation of a potentially lethal systemic disease. To treat such a patient with orally administered corticosteroids without a thorough investigation might be extremely dangerous, particularly if the ocular lesion were attributable to an opportunistic pathogen such as *Candida albicans* or *Toxoplasma gondii*.

On his part, the internist, upon receiving a referred patient from a concerned ophthalmologist, will often subject the patient to a broad battery of laboratory tests, many of which have no relevance to the case at hand. Such mistakes, though generally harmless, are nevertheless the causes of needless expense and inconvenience. The internist often regards uveitis, for example, as a single disease. For lack of specific orientation from the referring ophthalmologist, he proceeds to order useless laboratory tests such as the ones for 'rheumatoid factor' in cases of focal chorioretinitis. The lesion in such cases is much more likely to be caused by an infectious organism, e.g., *Toxoplasma gondii* or *Treponema pallidum*. The internist may also order multiple tests for diabetes, hepatitis, and chronic renal disease, most of which net no useful information.

The major problem in both situations is a lack of familiarity with the applicable syndromes. Although one generally learns in medical school

the components of the various syndromes that relate eye diseases to systemic disorders, it is easy to forget some of these items. Recently acquired information, such as that dealing with AIDS, was never available to those of us who attended medical school several decades ago. In this book Dinning defines all the important syndromes relating to ocular inflammation. He describes their characteristic presentation, detailing the physical appearance and location of the lesions as well as their usual clinical course. Useful definitions of the terms frequently used by ophthalmologists to describe the lesions are presented in the first chapter. Dinning presents current and appropriate ideas about the common pathogenesis of the ocular and systemic lesions, although much of this material must still be regarded as theoretical. Lastly he provides cogent ideas about the treatment of patients suffering from the specific diseases under discussion.

Readers of this book will find the material accurately portrayed. The references are up-to-date and appropriately placed. The style of writing is that of an experienced medical observer and conscientious scholar.

Chapter one

The Signs of Ocular Inflammation

Physicians reading this book will meet many terms from the jargon of ophthalmology with which they may be unfamiliar. This chapter aims to explain and illustrate many words used to describe inflammatory signs in the eye. In addition, reference is made to pathological findings which may be relevant to the genesis of these lesions and their relationship to associated systemic disease.

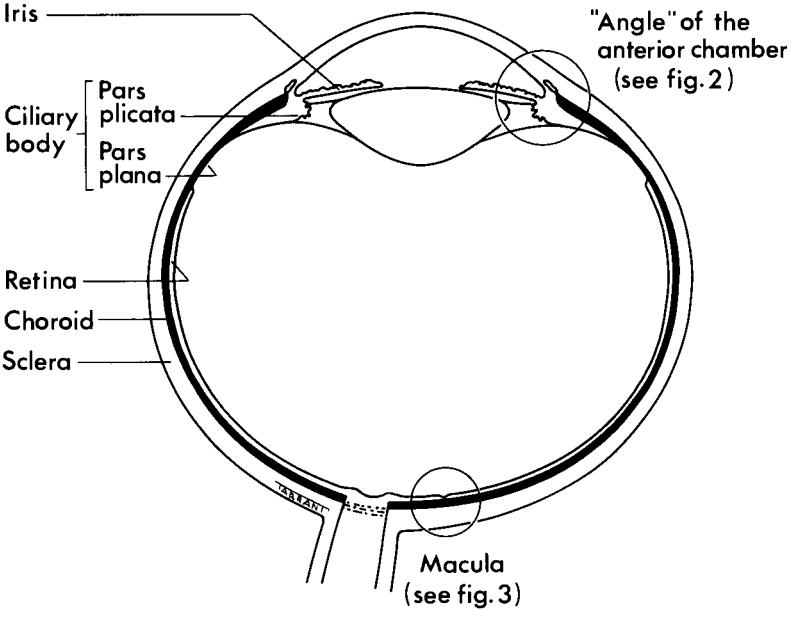


Figure 1 Horizontal section of the eye.

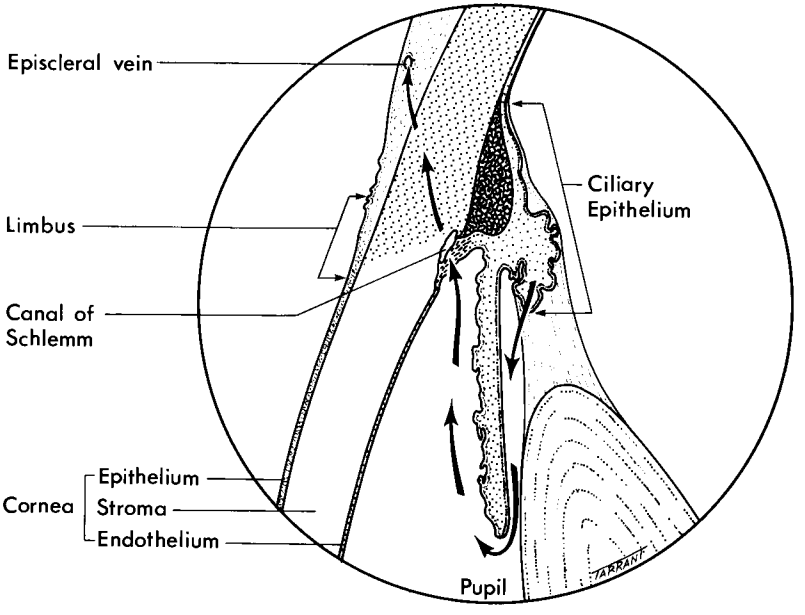


Figure 2 The angle of the anterior chamber showing the route of aqueous flow.

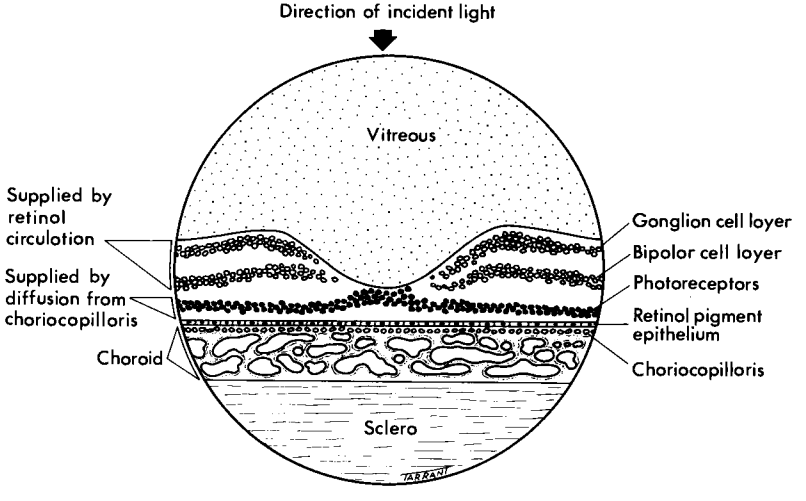


Figure 3 The retina at the macula.

Eyelids

Patients with scleroderma may have cicatricial contraction of the eyelids leading to poor closure and secondary exposure keratitis (q.v.).

Conjunctiva

(1) Conjunctivitis
(2) Nodules

1 Conjunctivitis

In *conjunctivitis* the redness extends uniformly from the edge of the cornea to the periphery of the eye. Only a segment of the eye may be affected. The dilatation of the superficial blood vessels is not normally confined to the conjunctiva of the eyeball but involves that of the lids as well. Unless there is secondary infection, any associated discharge is clear and watery.

2 Nodules

These occur in the conjunctiva in sarcoidosis. They are distinguished from common degenerative and cystic changes by their yellowish, solid, fleshy and somewhat vascular appearance. They occur most commonly in the lower fornix and on the plica semilunaris. They vary from one to several millimetres across, and may be single, multiple or confluent. (*Fig.* 4.)

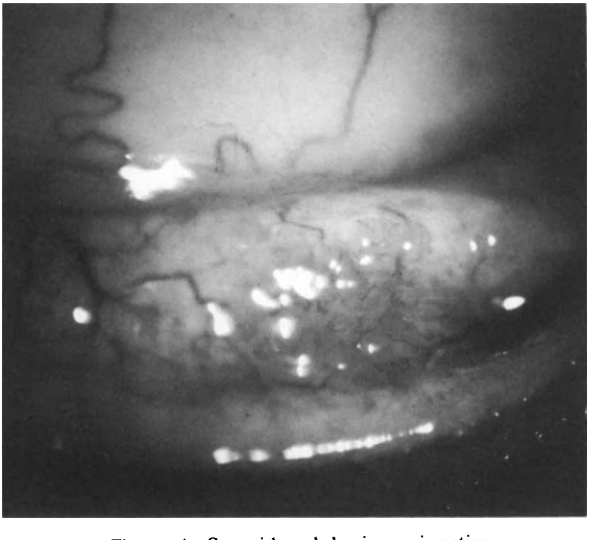


Figure 4 Sarcoid nodules in conjunctiva.
(Dr Robert Nussenblatt.)

Lacrimal Glands

In Sjögren's syndrome the lacrimal glands tend to be enlarged initially, becoming small and firm later in the disease. Enlarged glands may present a visible bulge under the outer part of the upper eyelid. The palpebral lobe of the gland can normally be brought into view by forceful elevation of the outer part of the eyelid while the patient looks down and inwards.

Episclera

Dilated episcleral vessels can be identified because the conjunctiva can be moved over them while they remain relatively fixed. Episcleritis usually involves only a segment of the surface of the eye, the redness contrasting with the adjacent white of the sclera. It is a deeper red than conjunctivitis.

Sclera

Scleritis is discussed fully in the chapter on rheumatoid arthritis. It may be diffuse or nodular. The conjunctiva is elevated over it, and the redness has a bluish tinge. Nodules tend to become yellow after the initial inflammation has begun to settle. (*Fig.* 5.)

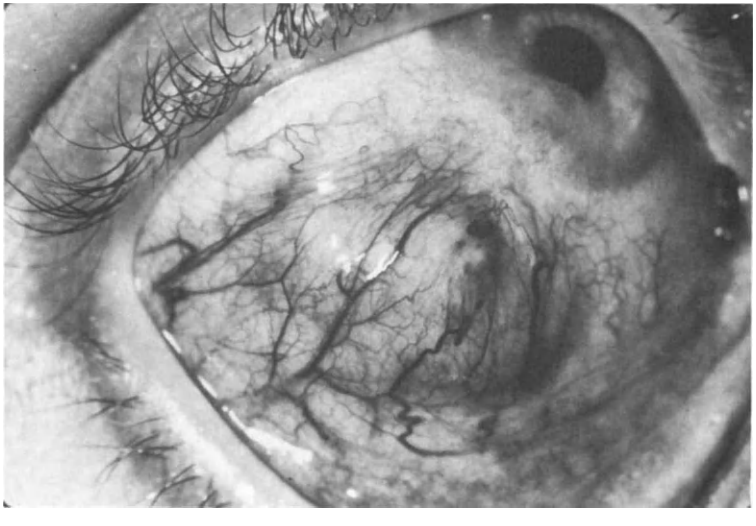


Figure 5 Sclerokeratitis.
(Dr Robert Nussenblatt.)

Ciliary Injection

Ciliary injection derives its name from the fact that the dilated vessels giving the classic circumcorneal blush are twigs from the anterior ciliary arteries, which anastomose within the major arterial circle of the iris, and ciliary efferent veins from the ciliary venous plexus. This circumcorneal redness is the hallmark of inflammation of the iris and ciliary body, but surface redness is confined to this area only in mild cases. It is often much more widespread, involving the episcleral and conjunctival vessels as well. In acute anterior uveitis the whole eye is often red. Sometimes the lids and even the side of the face are swollen and injected. (*Fig.* 6.)

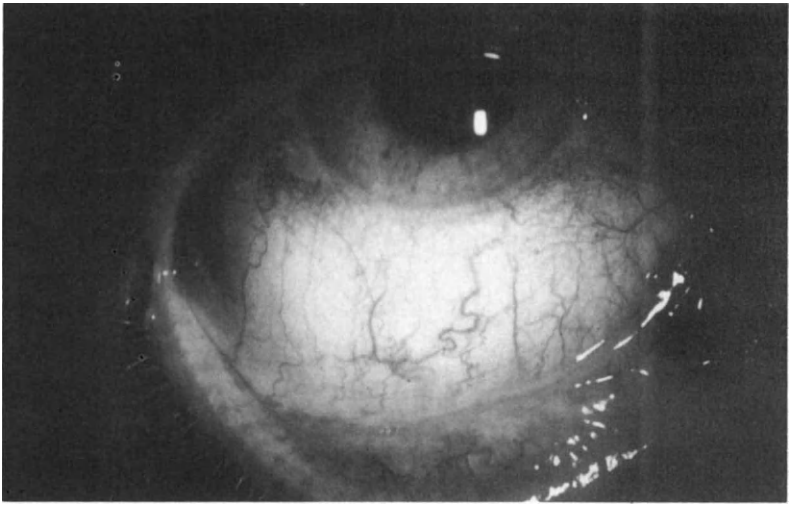


Figure 6 Mild ciliary injection.

Cornea

(1) Band keratopathy
(2) Keratoconjunctivitis sicca
(3) Keratitis
(4) Corneal endothelium
(5) Keratic precipitates

1 Band Keratopathy

In grossly deranged and shrunken eyes deposition of calcium salts beneath the corneal epithelium is common. It is not often seen in

sarcoidosis, but in the field of ocular inflammatory disease is most commonly met with in the uveitis associated with juvenile chronic polyarthritis.

A frosted glass appearance is first detectable near the limbus of the cornea at 9 and 3 o'clock, but separated from it by a clear zone. These areas become denser and extend horizontally towards each other. There may be circular clear areas within the zones of opacity. They may join across the visual axis and produce visual impairment. Symptoms are usually the result of small ulcers produced when calcareous fragments flake away. These areas become rapidly reepithelialized.

Pathological examination shows granular deposits of calcium along Bowman's membrane and a layer of fibrous tissue between Bowman's membrane and the corneal epithelium.

In cases of chronic uveitis that develop band keratopathy there is presumably a defect of corneal nutrition. The interpalpebral location suggests a role for temperature, hydration and gas exchange. *(Figs.* 7 and 8.)

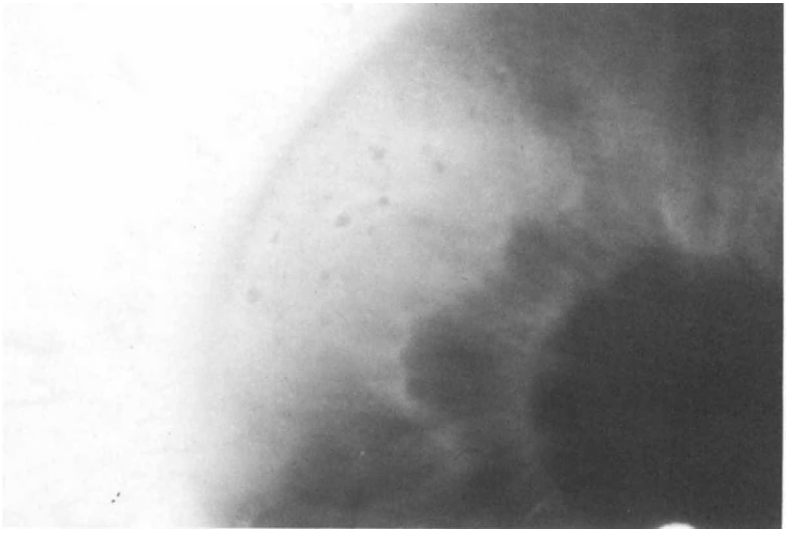


Figure 7 Mild band keratopathy.

2 *Keratoconjunctivitis Sicca*

When the eye is dry the cornea loses its lustre. Mucus tends to precipitate from the tears and forms strands in the lower conjunctival fornix. It may adhere in blobs to the epithelium and form filaments with tags of epithelium.

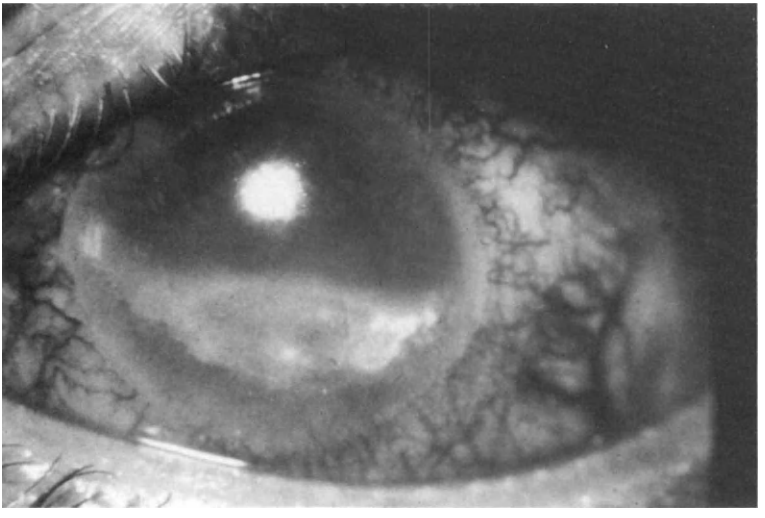


Figure 8 Severe band keratopathy.
(Dr Henry Kaplan.)

Under the slit lamp microscope the cornea has a finely spotted appearance known as punctate epithelial keratopathy. The dull grey spots are tiny patches where the epithelium is devitalized or absent. Dyes such as fluorescein or Rose Bengal adhere to these areas and make them easier to see. Similar spots occur on the conjunctiva but are difficult to detect without the contrast of Rose Bengal staining.

Rose Bengal appears a very dark blue under green light. A small drop is inserted in the lower fornix of the conjunctival sac, for example on the end of a sterile glass rod. It usually stings and provokes watering of the eyes. The epithelium is examined after the patient has blinked once or twice. Patients need to be able to wash the dye from their eyelids before leaving the clinic, and care must be taken not to get it on their clothes. It is a simple test to perform but unfortunately the need for magnification to see the spots in typical cases makes it difficult for the internist to detect all but gross cases with his unaided eye.

3 Keratitis

Various forms of active inflammation of the cornea may accompany systemic diseases. The affected cornea is hazy, and the eye is red. Pain and watering are usually marked. An epithelial keratitis is typical of acute Herpes simplex lesions of the eye (q.v.). However, keratitis associated with systemic disease is more likely to involve the stroma of

the cornea also. Biomicroscopy in the active stage shows oedematous thickening of the stroma. Ingrowth of blood vessels is common. The inflammation in syphilis is classically in the superficial and mid-stroma (*interstitial keratitis*). On resolution this form of keratitis leaves the cornea permanently cloudy, in a pattern resembling a combination of cirrus and nimbus clouds. The vessels remain in ghost form as empty, whitish ramifying tubes.

Signs of secondary uveitis, such as keratic precipitates (q.v.), are also seen in keratitis.

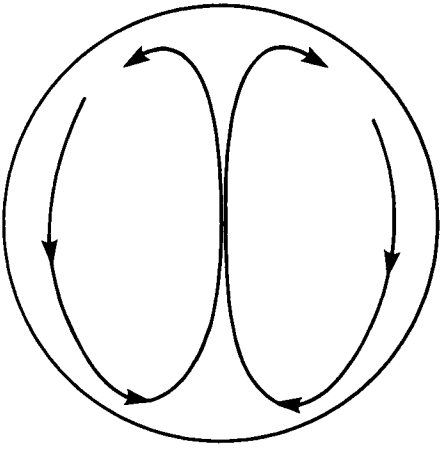


Figure 9 Convection currents in the aqueous.

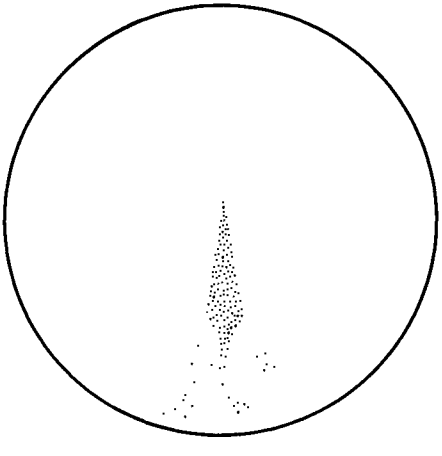


Figure 10 KP: cellular deposits in a spindle-shaped distribution.

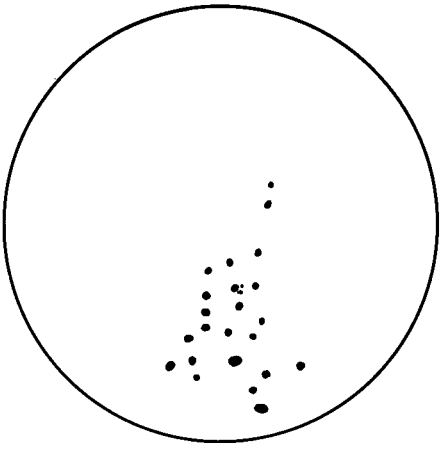


Figure 11 KP: typical appearance.

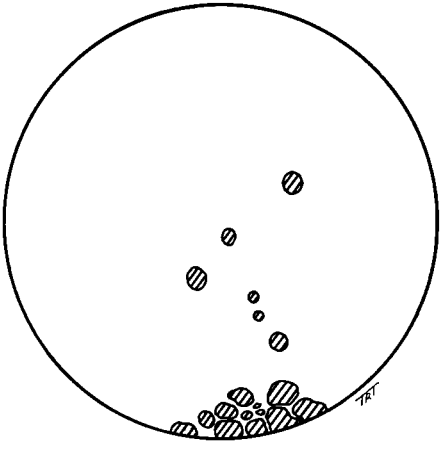


Figure 12 KP: large and becoming confluent.

4 Corneal Endothelium

Disturbance of the corneal endothelium is common in relation to stromal keratitis, but *active* inflammation of the endothelium is probably uncommon in intraocular inflammation. Studies are few, but it is possible to distinguish endotheliitis from the simple deposition of keratic precipitates (Sundmacher, 1984).

5 Keratic Precipitates (KP)

Keratic precipitates are deposits of cells and debris on the corneal endothelium. They occur in keratitis and uveitis, especially when the ciliary body is inflamed. In inflammation localized to the iris aggregation into clumps on the corneal endothelium is uncommon, but single cells deposit in abundance in the same areas in which KP are found.

Deposition occurs in a triangular area of the lower cornea, apex upwards, and is believed to be determined by the currents of aqueous circulation. In the anterior chamber these pass downwards in the periphery and upwards centrally. (*Fig.* 9.)

KP are usually pale, sometimes transparent, but may be lightly pigmented. They also vary in shape, usually being round, but sometimes crenellated. Crenellation is taken to indicate deposits in the process of formation or of absorption.

Sometimes the KP have a waxy or fatty appearance and are described as 'mutton fat' precipitates. These may be several millimetres across. They tend to occur in granulomatous diseases such as sarcoidosis. KP may become confluent (*Figs.* 10–14.)

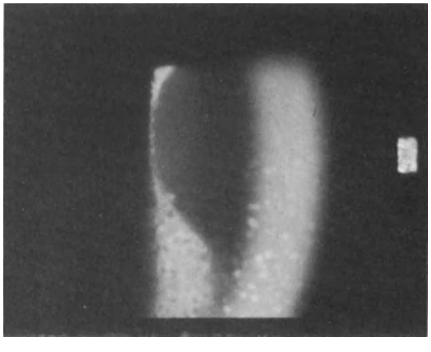


Figure 13 Fine keratic precipitates.

The factors determining the deposition of KP are not understood. They can be present for long periods yet on resolution leave the endothelial cells undamaged. In a study of experimental uveitis in rabbits lymphocytes and plasma cells have been seen to penetrate between the endothelial cells, but not to invade Descemet's membrane (Inomata and Smelser, 1970).

KP are more likely to be found in some diseases, for example sarcoidosis, than in others, like ankylosing spondylitis. The nature of the cells in the KP would appear to be more important in causing adherence than the endothelium itself.

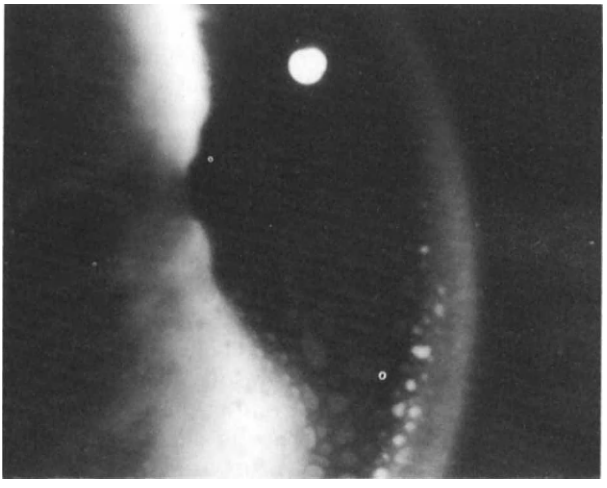


Figure 14 Larger waxy keratic precipitates.

The dynamics of KP formation is entirely unresearched and available pathology is scanty. Different patterns or types of KP have been associated with various conditions but studies have not been done to determine whether there are differences in the components of these types of KP.

In the more acute inflammatory conditions one can imagine from their appearance the progressive accretion of cells into a nodule or plaque. Such KP are pale, slightly opaque and granular.

One study of 'mutton fat' KP showed them to consist of large and small mononuclear cells, but exactly similar changes were found in retinal deposits in this case of toxoplasma retinochoroiditis (Zimmerman, 1961). In another example polymorphs and lymphocytes were shown on the endothelium, with transformation of the underlying endothelial cells into fibroblast-like cells (Polack, 1983)

On resolution it is usually impossible to tell where the KP have been. When they have been present for months they may leave behind a ghost which appears to be a translucent membrane on the endothelium. The pathological changes giving rise to this appearance remain to be elucidated.

Changes in the Aqueous

(1) Flare
(2) Cells
(3) Hypopyon

1 Flare

The earliest change in inflammation is the appearance of slight turbidity in the aqueous. When viewed with the slit lamp microscope this is known as 'flare'. In Europe it is referred to as 'Tyndall', after the English natural philosopher John Tyndall (1820–93), who studied the phenomenon of light-scatter. The turbidity varies from barely detectable in mild cases to a haziness dense enough to obscure the details of the iris in severe cases (*see* Grading of Severity). Normally the aqueous is absolutely clear. Inflammatory alterations in the vessels of the iris and ciliary body permit the leakage of significant amounts of protein, the molecules of which scatter light in proportion to their number and size.

The flare decreases as inflammation resolves. In acute uveitis it clears completely, but some degree of flare often persists in chronic cases. This must be appreciated as a permanent change in vascular permeability. In this situation it does not necessarily denote ongoing active inflammation and is not resolved by persistent steroid treatment. (*Figs.* 15, 16.)

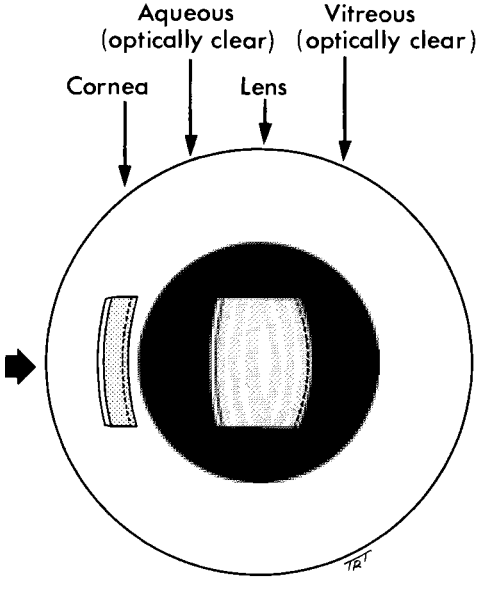


Figure 15 Anterior view illustrating slit lamp beam section of the eye.

2 Cells

Inflammatory cells actively migrate into the aqueous. They are not released simply by a process of barrier breakdown. It is unusual to see red blood cells in the aqueous except in very severe cases or when the uveitis is complicated by neovascularization of the iris.

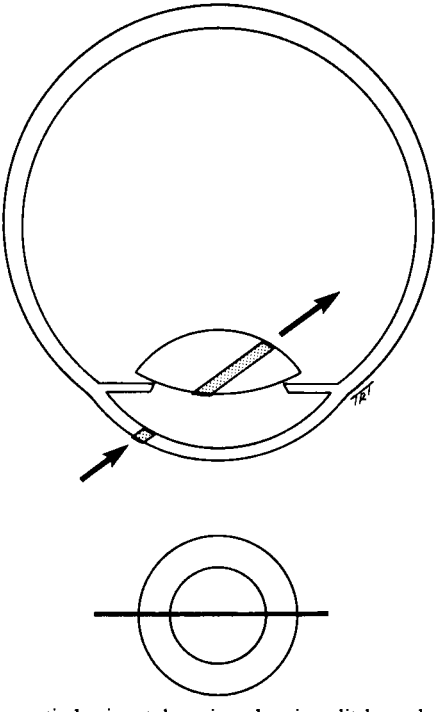


Figure 16 Schematic horizontal section showing slit lamp beam section of the eye.

These particles are seen as glistening points of light moving in the slit lamp beam. When only a few are present it takes patience to detect them. One needs to look steadily at a 1 mm-deep beam directed obliquely towards the pupil, observing that part of the beam in front of the lens.

Cells may aggregate into clumps. Sometimes irregular aggregates are seen which presumably contain cells and inflammatory debris.

Examination of the size and colour of these cellular particles permits some estimate of their nature. Lymphocytes are colourless and small. Larger pale cells are likely to be macrophages or polymorphs. Large pigmented cells are macrophages which have engulfed pigment. Red cells are small pigmented cells, like particles of brown dust.

Cells and protein may form aggregates on the corneal endothelium (*see* KP), on the lens, on the iris, and also on the structures of the drainage angle of the anterior chamber.

A dense proteinaceous exudate may clot in the anterior chamber, giving rise to clumps or strands, especially in relation to the iris or lens surface. Such a coagulum in the pupil may form a framework for the development of permanent adhesions. (*Fig.* 17.)

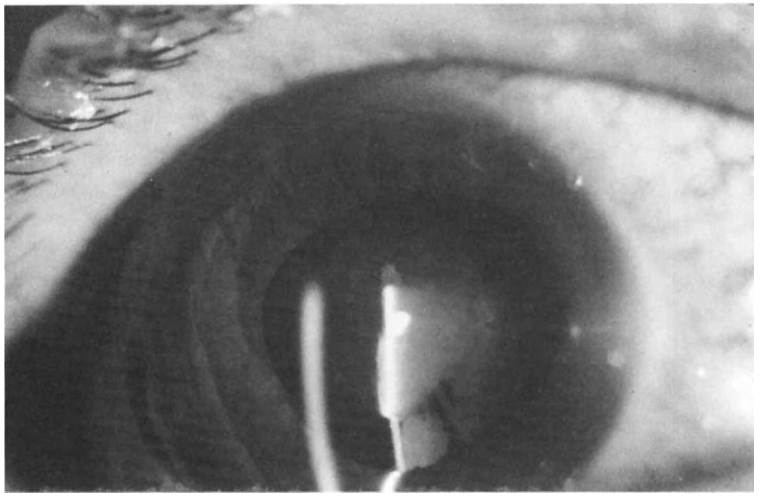


Figure 17 Coagulum on surface of lens.

3 Hypopyon

Sometimes in very severe acute inflammatory episodes cellular and inflammatory debris settle under gravity to form an hypopyon. This may contain an admixture of blood.

It must be appreciated that although these changes in the anterior chamber have been described in some sort of order of increasing severity they are only approximately interdependent and not sequential.

Hypopyon appears to represent the consequences of a sudden and severe exudation of cells from the uveal vessels. It may come and go quickly. Hypopyon tends to remain fluid, does not clot, and moves slowly with changes in posture. The factors governing the speed of resolution of hypopyon are not understood. The very rapid disappearance often seen in Behçet's syndrome suggests the presence of some peculiar lytic mechanism in the aqueous of these patients. (*Fig.* 18.)

Clinical Assessment of Changes in the Ocular Media

Grading of Severity

In order to follow the progress of inflammation in the eye it is essential to be able to record the severity of changes in the ocular media. A scheme suggested by Hogan and coworkers (Hogan et al., 1959) has been modified by the author and has proved useful in practice. It is presented in *Table* 1.

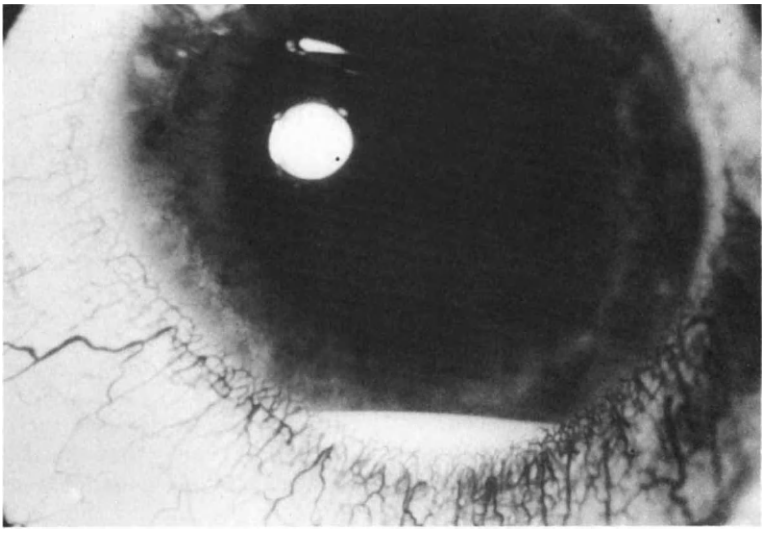


Figure 18 Hypopyon.

Table 1 Severity of changes in the ocular media

Grade	*A/C flare*	*A/C cells*	*Lens op.*	*Vitreous op.*
0	nil	nil	nil	nil
+1	slight (just detectable)	5–10/s.l. field	slight	slight (fundus clear)
+2	moderate (iris and lens details clear)	10–20/s.l. field	moderate (retinal details clear)	moderate (fundus slightly blurred)
+3	marked (iris and lens details blurred)	20–50/s.l. field	marked (retinal details blurred)	marked (fundus very blurred)
+4	dense (aqueous clotted)	>50/s.l. field	dense (vitreous & retinal details completely obscured)	dense (fundus not visible)

(s.l. field = 1 mm-deep slit lamp beam)

For the purpose of grading, the anterior segment of the eye is observed with the slit lamp (s.l.) microscope, the beam being set to a height of 1 mm. Unfortunately many slit lamps do not have a 1 mm beam setting and the ophthalmologist will have to estimate. The posterior segment is observed with the powerful indirect ophthalmoscope.

Grading of vitreous opacification can be further standardized by comparison of the indirect ophthalmoscopic view of the retina with a series of standard photographs (Nussenblatt et al., 1985).

Changes in the iris

(1) Nodules
(2) Atrophy
(3) Vascular changes
(4) Synechiae

1 Nodules

(a) SPECIFIC Nodules occur in the iris stroma in diseases such as sarcoidosis, tuberculosis, syphilis and leprosy and they have the histological structure of the granulomatous lesions associated with these conditions. Nowadays sarcoidosis is the most likely cause, tuberculomas and gummas being rarely seen. Granulomatous nodules tend to be yellowish, fleshy and solid-looking, often with visible blood vessels in them. They occur singly or in multiples in all parts of the iris. In the peripheral iris they may fill the drainage angle of the anterior chamber and come into contact with the cornea. They resolve slowly under treatment and may leave areas of iris atrophy.

In the above conditions the non-specific nodular changes described next are also commonly seen. (*Fig.* 19.)

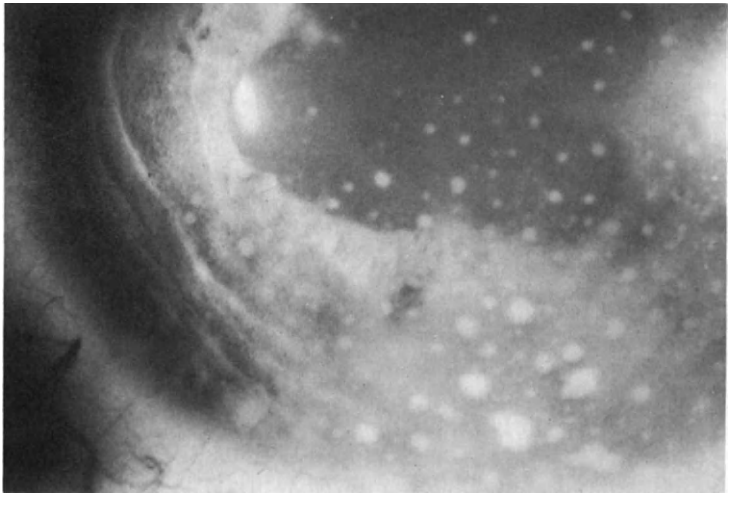


Figure 19 Large nodules in iris, keratic precipitates, and posterior synechiae.

(*b*) NON-SPECIFIC A thorough pathological redefinition of these alterations is long overdue. The traditional division into two eponymous types is an oversimplification of what can be seen in inflammatory conditions. In many cases it is impossible to make. It would be more helpful if observers described their findings in detail instead of using the eponyms.

Non-specific nodular changes occur in all parts of the iris and also on the ciliary body, lens capsule and anterior chamber drainage angle.

Small nodules related to the neuroectodermally derived posterior iris pigment epithelium occur at the pupil margin, and are known as *Koeppe* nodules (Koeppe, 1917). Pupil movements may either hide or reveal their presence. They are usually only 1–2 mm in diameter, whitish, grey or lightly pigmented, and sometimes look cystic. Histologically they consist of lymphocytes and epithelioid cells, the latter possibly originating from the iris itself. Mononuclear plasma cells and epithelioid cells are also found in the neighbouring iris.

In practice, nodules which are clinically identical with these may occur in other parts of the iris (Derby, 1927). These nodules tend to persist for weeks. (*Fig.* 20.)

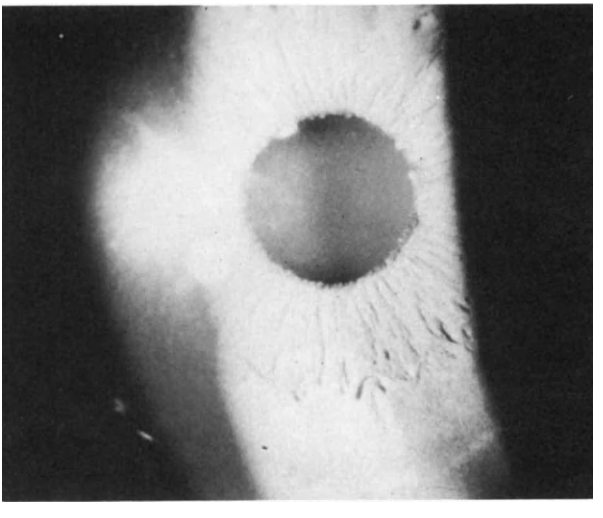


Figure 20 Nodules on pupil margin.

Another type of nodule consists of accumulations of pigmented cells, small and large round cells and degenerating cells (Busacca, 1932) and is found on the anterior surface of the iris. Busacca postulated that these were deposited from the aqueous and were akin to KP. This seems likely to be true. They are small, grey nodules which may appear

and disappear very rapidly, and often occur in large numbers. They have come to be known as 'mesodermal floccules of *Busacca*', despite the fact that Busacca avoided the term 'floccule' and chose 'flake' instead. The word 'mesodermal' is also misleading as it suggests an origin from within the mesodermal layers of the iris. (*Fig.* 21.)

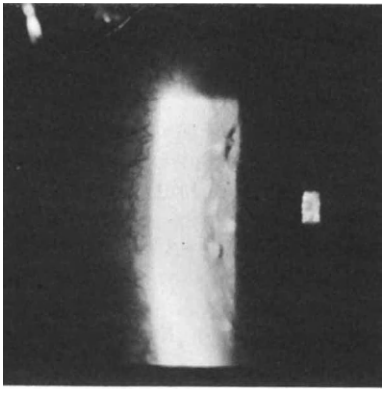


Figure 21 Fine nodules in the iris.

Insufficient study has been made to permit firm statements to be made about the genesis and histopathology of these various clinical appearances. Modern immunopathological techniques may resolve these matters.

Figure 22 Iris sphincter atrophy (retroillumination).

2 Atrophy

Atrophy of the iris is best appreciated by retroillumination. With the slit lamp beam set so that it makes an angle of only a few degrees with the microscope, a narrow beam of light is projected through the pupil. Thinned areas of the iris diaphragm permit the passage of some light reflected from the ocular fundus. (*Figs.* 22–24.)

Figure 23 Iris sector atrophy (retroillumination).

Figure 24 Massive iris atrophy (retroillumination). (*See Fig.* 27.)

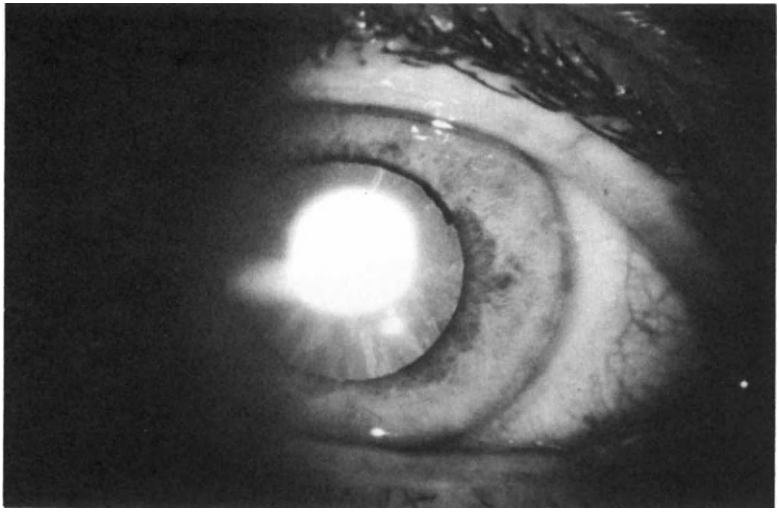


Figure 25 Sphincter atrophy.

The commonest finding is patchy atrophy of the sphincter area. When viewed directly the pigment frill may be seen to be defective. (*Fig.* 25.) Atrophy may occur at the site of previous nodule formation.

Another type of atrophy occasionally seen following acute anterior uveitis is massive atrophy of much of the iris. A fixed, dilated pupil is the result. (*Figs.* 26, 27.)

Segmental atrophy, based upon disturbance of a sector of the iris vasculature, is a typical finding in Herpes zoster ophthalmicus.

3 Vascular Change

(*a*) generalized dilatation of vessels in response to inflammation;
(*b*) abnormal vessels.

The vascular architecture of the iris is arranged in a radial fashion. When vessels are seen running circumferentially or obliquely, or apparently on the very surface of the iris, they should be suspected as being abnormal. However, the vessels of the peripheral iris circle are commonly visible on gonioscopy of the drainage angle of the anterior chamber and should not be mistakenly interpreted as pathological.

Granulomatous nodules may have visible vessels in and around them.

Neovascularization of the iris is believed to be a response to tissue hypoxia rather than to inflammation itself, and this remains a reasonable hypothesis. In inflammatory conditions the new vessels certainly appear no different from those seen in diabetes mellitus and central retinal vein occlusion.

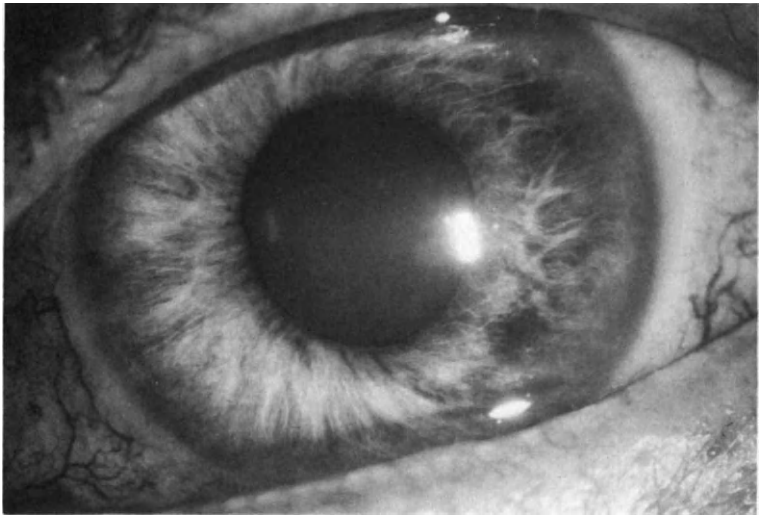


Figure 26 Massive atrophy: external view. The right side is atrophic.

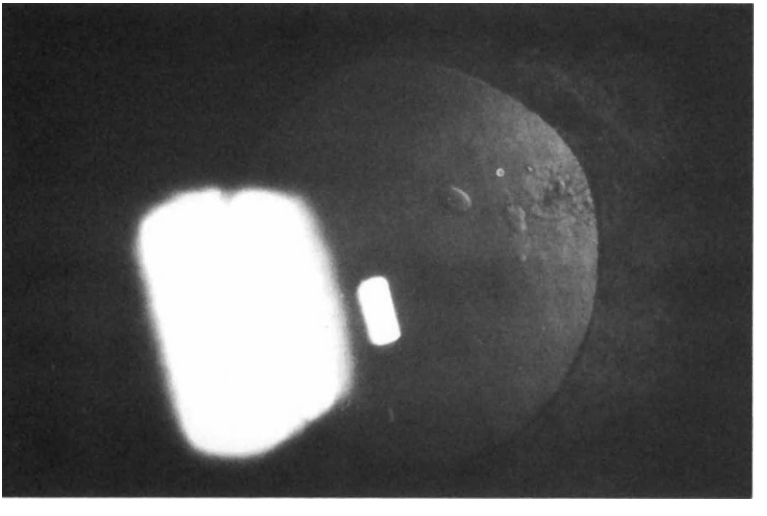


Figure 27 Massive atrophy: retro illuminated view. Same eye as *Fig.* 26.

Fine skeins of new vessels are often detected first around the pupil margin, but thorough examination may reveal extensive involvement. In the iris root the vessels involve the drainage angle. Secondary glaucoma is the serious consequence. (*Fig.* 28.)

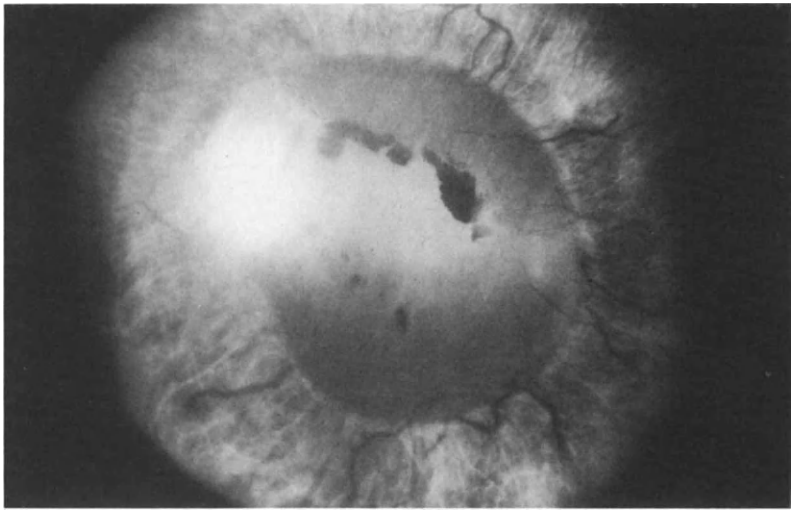


Figure 28 Iris neovascularization.
(Dr Robert Nussenblatt.)

Failure of aqueous production and terminal softening of the eye sometimes occurs after severe chronic uveitis. At this stage the eye is usually functionless. New vessels commonly appear in the iris and also in the cornea.

4 Synechiae

(*a*) anterior; (*b*) posterior.

In both acute and chronic uveitis fibrinous adhesions are common between the iris and the adjacent lens. These are known as 'posterior synechiae' (*see Fig.* 19). If they are not broken by therapeutic pharmacological dilatation of the pupil they become organized into fibrous adhesions. Synechiae may still form from a dilated pupil but when mydriatic drugs are withdrawn they rarely give rise to distortion of the pupil, presumably because they break when the pupil returns to its constricted configuration. More central synechiae commonly result in irregularity of the pupil shape.

Synechiae may be single or multiple. They may occupy more and more of the pupil circumference by a process of local extension until the whole of the pupil is bound firmly to the lens. This may be associated with a membrane, at first fibrinous, then fibrous and finally even vascularized, across the lens surface. Such occlusion of the pupil interrupts the flow of aqueous from the posterior chamber into the anterior chamber. Raised pressure in the posterior chamber bows the iris forward and produces the appearance of a balloon tyre. This is known as 'iris bombé' (*see Figs.* 29–31). Peripherally the iris may come

into contact with the cornea and the structures in the drainage angle and lead to a precipitous rise in intraocular pressure. Prolonged contact of this nature gives rise eventually to synechia formation from the anterior surface of the iris periphery. These are known as 'peripheral anterior synechiae'. They may also form from organization of inflammatory debris in the anterior chamber angle and cause progressive impairment of the aqueous outflow from the eye, leading to chronic glaucoma.

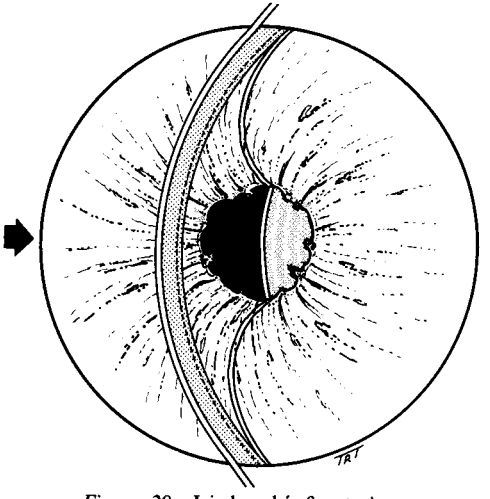


Figure 29 Iris bombé: front view.

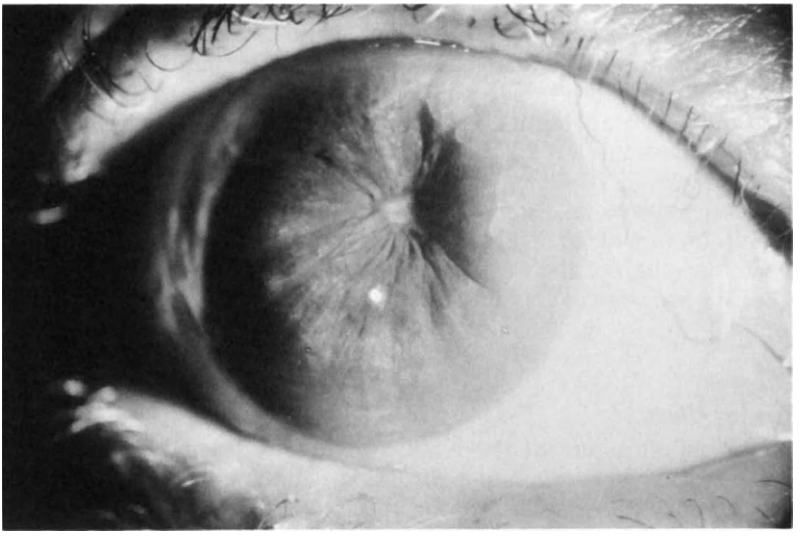


Figure 30 Iris bombé: front view.

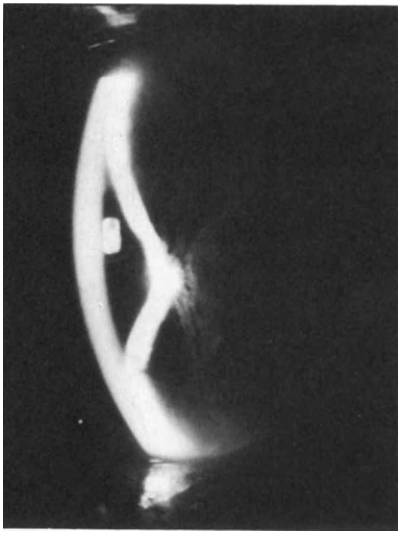


Figure 31 Iris bombé: slit lamp view.

The Lens

Opacification of the posterior subcapsular zone of the lens is the type of cataract usually found with ocular inflammatory disease but in prolonged cases the whole lens may become opaque. Initially the posterior lens capsule loses its clarity and acquires a polychromatic sheen when viewed with the slit lamp microscope. The underlying lens cortex develops a greyish-yellow opacity which gradually extends peripherally and into the deeper cortex.

A similar cataract occurs with prolonged corticosteroid therapy. It is unusual before therapy has been continuous for more than a year and at daily doses of 10–20 mg of prednisolone or equivalent.

In patients who take steroids and suffer from intraocular inflammation it is impossible to determine to what extent each factor contributes to the formation of their cataracts.

Local opacities are common in and beneath the lens capsule at sites of synechiae.

Vitreous Changes

The normal structure of the vitreous is barely detectable in healthy young eyes. An impression of a fibrillar structure may be obtained, and a few hyalocytes seen. The vitreous becomes more fluid with age and the fibrils tend to aggregate together. Lacunae of clear vitreous

irregularly bounded by membranous condensations appear, and partial or complete detachment of the posterior hyaloid membrane from the surface of the retina may occur. These degenerative processes are accelerated in the presence of intraocular inflammation. In addition inflammatory cells appear and the vitreous becomes hazy. Cells are seen, singly and in clumps, together with other inflammatory debris. If inflammation is mainly of the anterior part of the uveal tract the cellular infiltrate tends to be confined to the anterior vitreous. Deposits akin to KP (q.v.) are sometimes seen on the vitreous membranes and detached posterior hyaloid face.

Inflammatory exudates may form masses like snowballs in the peripheral vitreous. These tend to be associated with underlying retinal oedema, peripheral retinal vasculitis, and sometimes oedema, exudate and membrane formation on the pars plana ciliaris. The lower part of the eye is mainly affected. (*Fig.* 32.)

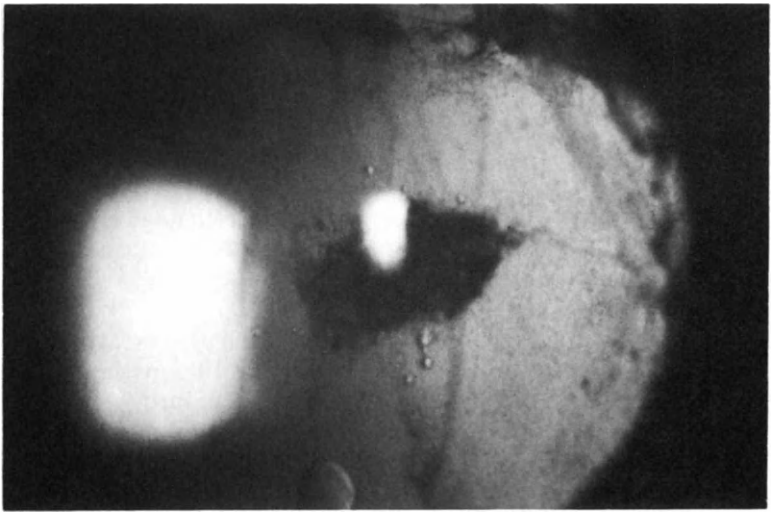


Figure 32 Vitreous opacity.

In cases of severe and prolonged vitreous inflammation retrolental membranes may develop. They are known as 'cyclitic membranes' (Kimura and Hogan, 1963). It has been suggested that macrophages, arising from the inner surface of the ciliary body as part of a fibrinous exudate, changed into a connective tissue cell type and produced the fibrous element of the membrane (Lamb, 1938). A case was recently described in which the membrane contained mainly glial elements and no lymphocytes or macrophages, and it was suggested that basement membrane components were deposited by glial cells derived from the retina (Chan et al., 1986).

The cyclitic membrane is not readily visible on clinical examination because many of the eyes so affected have cataract as well. However, it is well recognized by surgeons who are now frequently able to salvage severely damaged eyes by removing the cataracts and vitreous opacities with sophisticated instrumental techniques.

Sometimes a membrane resembling a snowbank is seen on the peripheral retina and pars plana ciliaris. Pederson and coworkers (1978) have examined several cases. They described this as a fibrovascular membrane over the pars plana ciliaris which in places is continuous with a similar preretinal fibroglial membrane. Microscopically it consists of a loose fibrovascular layer containing occasional cells resembling fibrocytes, and scattered mononuclear cells, adjacent to hyperplastic non-pigmented epithelium of the pars plana ciliaris. Electron microscopic studies of this fibroglial tissue showed condensed vitreous collagen and cells that are probably fibrous astrocytes. Little evidence of choroiditis or cyclitis was found in these cases, but peripheral retinal veins often showed lymphocytic cuffing. This suggests that retinal rather than uveal inflammation is more important in producing this clinical picture (Pederson et al., 1978). However, others have reported more signs of uveal inflammation (Brockhurst et al., 1961; Kimura and Hogan, 1963). Such studies are from advanced cases and must be interpreted accordingly.

Cyclitic membranes appear to be of more than obstructive importance. They seem to impair the function of the ciliary body. Division of even very fine membranes has resulted in an improvement of intraocular pressure, presumably by an increase in the formation of aqueous in previously very soft eyes.

The presence of haze and inflammatory cells in the vitreous is sometimes referred to as 'hyalitis'. Whether the vitreous can itself be the primary site of sterile inflammation is undetermined.

Retinal Changes

(1) Retinal vasculitis
(2) Retinal exudates
(3) Pigmentation
(4) Retinitis
(5) Atrophy
(6) Neovascularization
(7) Macular oedema
(8) 'Cherry red spot'
(9) Optic neuritis

Descriptions of the ophthalmological appearances of changes directly or indirectly due to inflammation tend to be greatly influenced by an

all too limited understanding of the pathology. Few of the appearances are known to be specific to a single pathological process. A diagnosis can rarely be made on the ocular fundus findings alone without the interpretative biases imposed by other findings within the eye and systemically. Fundus fluorescent angiography has greatly improved the clinician's ability to determine the position of lesions in relation to the choroidal and retinal layers. Leakage of fluorescein bound to albumin often indicates degrees of impaired vascular integrity which are impossible to appreciate clinically.

Many of the conditions discussed in this book have inflammatory signs in systemic arteries, veins or both. Vasculitis of retinal vessels is also found in some of these.

1 Retinal Vasculitis

Active inflammation in and around the retinal vessels results firstly in a loss of the sharply defined appearance of the vessels. The walls become visible and the blood column apparently narrowed. In contrast to the sharp changes found in atherosclerosis, the vessel walls are thickened in a vague, soft, fluffy way. The whitish or yellowish opacification extends laterally into the adjacent retina. Pathologically it is due to collections of inflammatory cells, protein and fluid. Vessels may be involved along their whole length, or in segments. The former is known as 'sheathing' and the latter as 'cuffing' (*Fig.* 33). Cuffing is commonly seen at bifurcations. These findings are much more prominent around veins in most conditions, but it is probably incorrect to assume that disease does *not* involve arteries simply because of this. The adjacent superficial retina may become sufficiently swollen to lose its normal bright sheen.

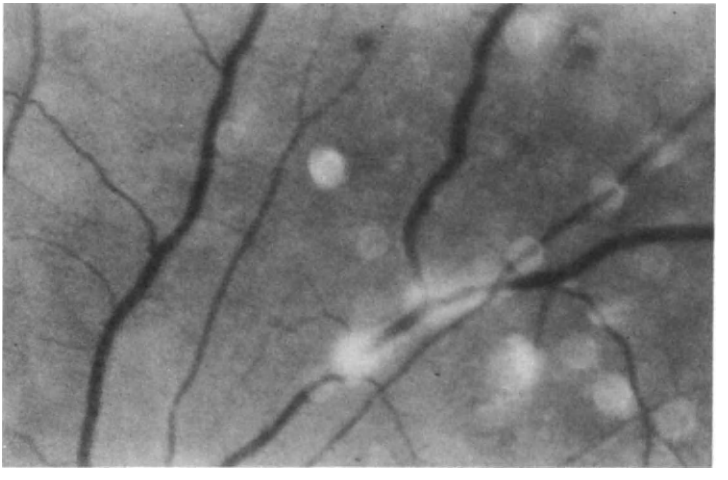


Figure 33 Vessel sheathing and cuffing in retinal vasculitis.

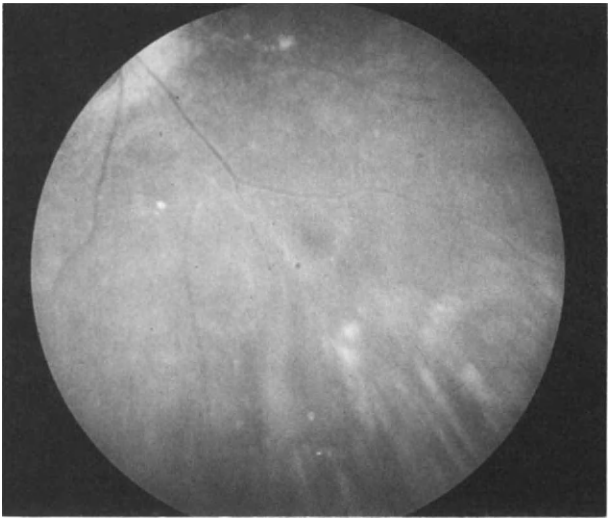


Figure 34 Narrowed retinal vessels.

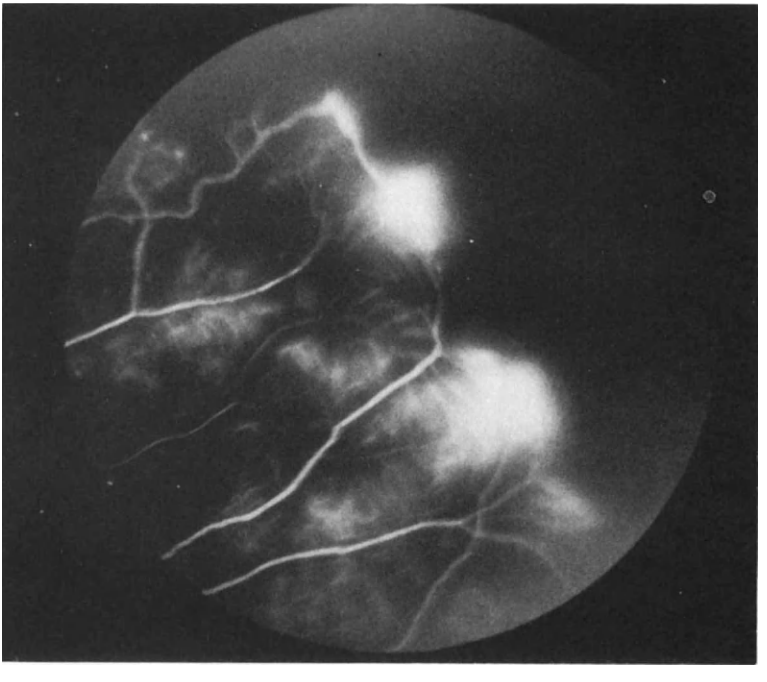


Figure 35 Occluded peripheral vessels with fluorescein leakage.

The finer terminal vessels may appear to be completely occluded (*Fig.* 34). Areas of peripheral retina may appear to have lost their capillary beds (*Fig.* 35), and abnormal blood vessels are sometimes seen. In such cases major haemorrhage into the vitreous may occur.

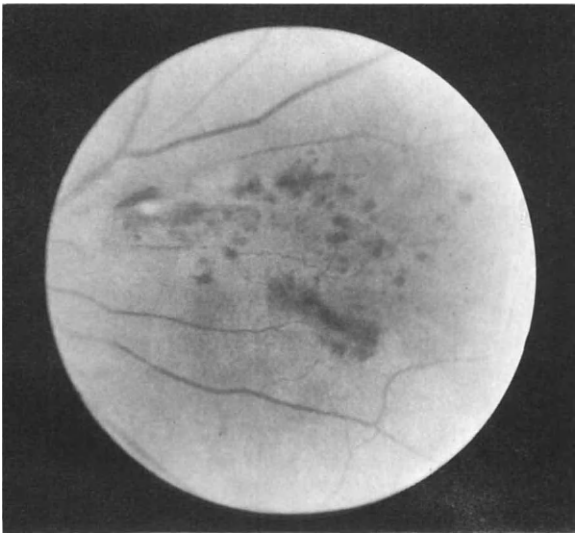


Figure 36 Retinal haemorrhage.
(Dr Robert Nussenblatt.)

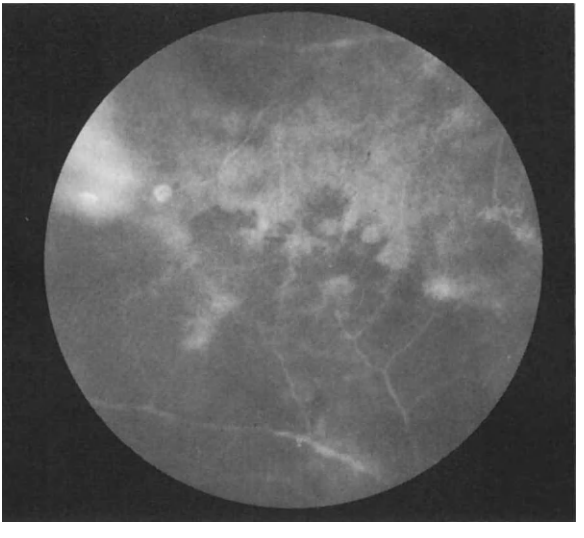


Figure 37 Narrowed retinal vessels and haemorrhage.

Small intraretinal haemorrhages (*Fig.* 36) are common, especially around ischaemic zones, where they are associated with cottonwool spots (q.v.). They may produce microscopic vitreous haemorrhage, adopt a flame-shaped appearance when in the nerve fibre layer, or be more irregular and diffuse when in the deeper retina (*Fig.* 37).

Vessels do truly become narrowed by persistent disease. In remissions all the signs may clear away, but permanent vessel changes often remain. They may finally look like silver wires (*see Fig.* 56).

Arterial occlusion leads to retinal infarction. The oedematous retina has a grey and featureless appearance. Later, thinning of the atrophic retina can be appreciated. Venous occlusion leads usually to less ischaemia, but the retina still becomes oedematous in the acute phase.

2 Retinal Exudates

The most important type of exudate found in inflammation of the retinal vasculature is the 'cottonwool spot' or soft exudate. Cottonwool spots are due to accumulation of axoplasmic organelles in the nerve fibre layer of the retina at sites where axonal ischaemia interrupts axoplasmic flow (McLeod, 1975). In vasculitis they occur at sites of ischaemia and are the same as those seen in diabetic and hypertensive retinal disease. (*Fig.* 38.)

In sarcoidosis a particular type of exudate has been described on the surface of the retina. Because of its greasy appearance and tendency to run down over the retina it has been called 'candle-wax drippings'.

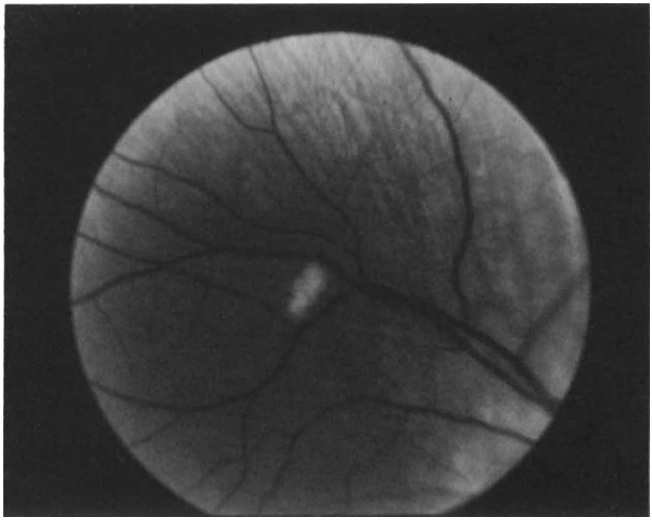


Figure 38 Cottonwool spot.
(Dr Alan Palestine.)

Sometimes these exudates appear to be connected with the retinal vessels, as though leaking from them. Such an appearance is in fact very rare.

It has to be admitted that none of these appearances is unique to vasculitis. They may, for example, be seen in retinal vein occlusion and even in diabetes mellitus. These conditions may coexist, and it is important to be able to recognize major venous occlusion when it occurs as a complication of vasculitis.

At present the author prefers to use the word 'vasculitis' and to specify which vessels are involved. Terms such as 'phlebitis' and 'arteritis' are difficult to employ meaningfully because it is difficult to be certain that disease is in fact confined to veins or arteries, respectively. Even more treacherous is the term 'perivasculitis' which is often applied to retinal appearances but can only have meaning as a pathological description. Indeed, the differences between vasculitis and perivasculitis in pathological terms are by no means clear.

3 Pigmentation

The retinal pigment epithelium may be disturbed by inflammation, and its response gives rise to alterations in the otherwise fairly uniform pattern of pigmentation of the ocular fundus. Release of pigment, with migration and possibly also proliferation of the retinal pigment epithelial cells, produces varying degrees of mottling. Sometimes very dense patches of pigmentation appear. Pigment clumping occasionally follows the linear course of the inflamed vessels. (*Fig.* 39.)

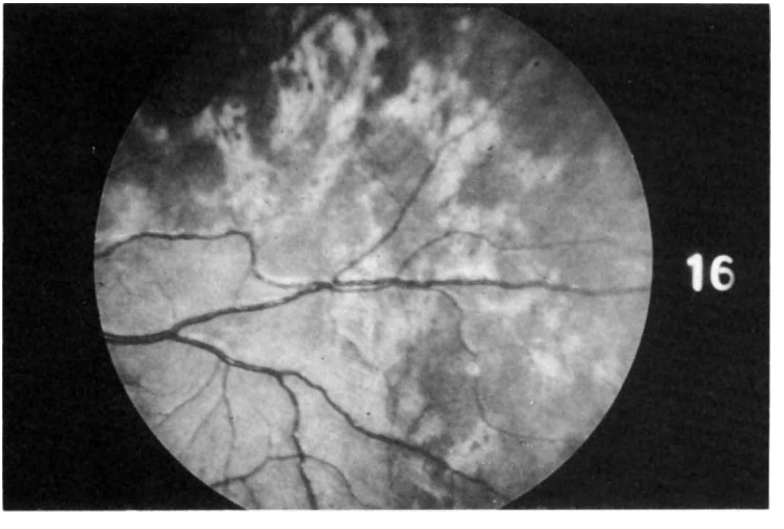


Figure 39 Mottling of fundus from retinal pigment epithelial disturbance.

Inflamed retinal vessels permit marked leakage of protein from the blood. Sodium fluorescein is bound to albumin. Thus in fluorescent angiography the areas around the affected vessels fluoresce, and in addition the vessel walls themselves are also 'stained' with fluorescein. Areas of altered circulation, such as occlusions of large vessels, obliteration of capillary beds, and new vessel formations are also revealed, which may be very difficult to detect otherwise.

Arriving at a diagnosis of vasculitis depends upon interpreting the fundus findings in the light of other ocular and systemic signs, especially the presence of inflammatory cells in the vitreous, and the angiographic findings.

4 Retinitis

A degree of retinal inflammation accompanies retinal vasculitis and choroiditis, but there are conditions in which the retina is the primary site of inflammation. In syphilis the whole of the retina may appear dull and greyish in the acute stage. Retinitis is more focal in toxoplasmosis (*see Fig.* 78), but this condition rapidly leads to an underlying choroiditis and an overlying opacification of the vitreous. The latter may locally obscure the view of the retina. When inflammation settles the final pattern depends upon the degree to which the retinal pigment epithelium is disturbed and how much choroidal damage has occurred. Inflammation involving the retinal pigment epithelium frequently disturbs the choriocapillaris as well.

All the signs described above in vasculitis are found in primary retinitis, for example in the retinitis of cytomegalovirus infection, but they are often obscured at the time of diagnosis by vitreous opacities.

5 Atrophy

Atrophy of the retina is difficult to appreciate except by inference from the narrowed or occluded vessels, pigmentary disturbance or fluorescent angiographic evidence of capillary bed occlusion. The nerve fibre layer running to the disc from areas of focal atrophy is thinned and can sometimes be appreciated as a depressed path running across the retinal surface.

6 Neovascularization

New vessels in the retina are uncommon in ocular inflammation except in conditions associated with occlusion of retinal capillary beds. They form at the edges of ischaemic areas, which tend to be in the retinal periphery. Their presence may only be revealed by angiography. Vessels occasionally form on the optic disc and grow forwards into the

vitreous. It is important not to confuse these with dilated and therefore more obvious normal disc vessels in papilloedema and optic papillitis.

7 *Macular Oedema*

Macular oedema occurs transiently in many cases of severe uveitis. In chronic cases it may persist and become the most important cause of visual loss. The mechanism of this reaction to inflammation remains a mystery.

Thickening of the retina can be detected by examination of the macula with the slit lamp microscope and a contact lens or high-power planoconcave lens in front of the eye. This overcomes the refraction at the air/corneal interface and permits the focus of the slit lamp microscope to be carried to the back of the eye.

The normal macula has a bright reflection of light from the foveal pit. This is lost as soon as oedema begins to collect. Macular oedema may settle completely without trace even after many months. A cystic distribution of the oedema is a serious development. Although it can resolve with restoration of good vision it tends to result in permanent impairment of central vision. Microscopical cysts can be appreciated in the retina around the fovea. The picture is clarified by fluorescent angiography which shows leakage of fluorescein from perifoveal retinal capillaries into the cysts. This produces a characteristic picture like petals of a flower around the fovea. In contrast, the leakage of fluorescein is more diffuse when the oedema is not cystic. The cystic pattern is imposed by the anatomical distribution of fluid in the outer plexiform and inner nuclear layers of the retina. (*Fig.* 40.)

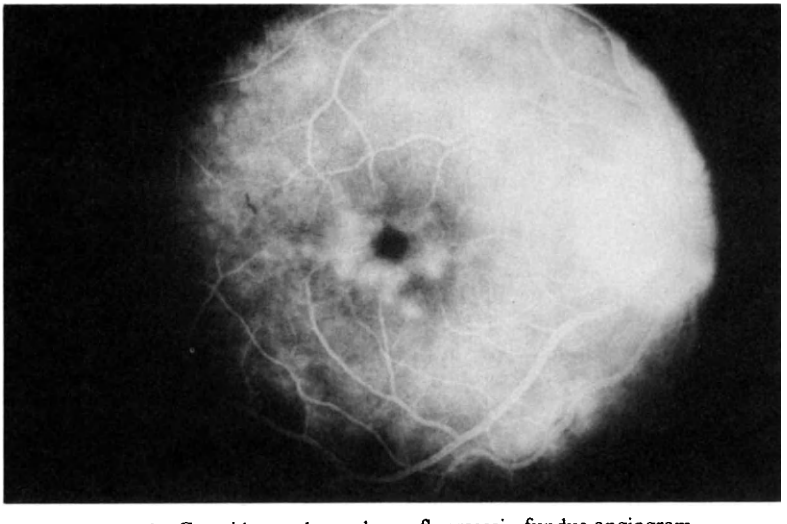


Figure 40 Cystoid macular oedema: fluorescein fundus angiogram. (Dr Henry Kaplan.)

If the macular disturbance persists, structural alterations occur in the retina around the pockets of fluid. The cystic spaces and visual impairment then become permanent. The inner limiting membrane of the retina may also become thickened. This can be appreciated as an alteration in the surface reflex of the retina, like wrinkled silk, or cellophane. Such a membrane is one of the reasons for vision to fail to improve when all the oedema settles.

8 Cherry Red Spot

In central retinal artery occlusion, for example in giant cell arteritis, the retina becomes oedematous in the acute phase and loses its transparency. However, at the fovea it consists only of the photoreceptor cell layer and is very thin. There the normal redness of the blood in the choroid can still be seen, now thrown into contrast with the grey-white pallor of the surrounding retina. This appearance is known as a 'cherry red spot'. It is also seen in other conditions in which the retina becomes opaque, such as Tay Sachs disease, in which the retinal ganglion cells become laden with a ganglioside.

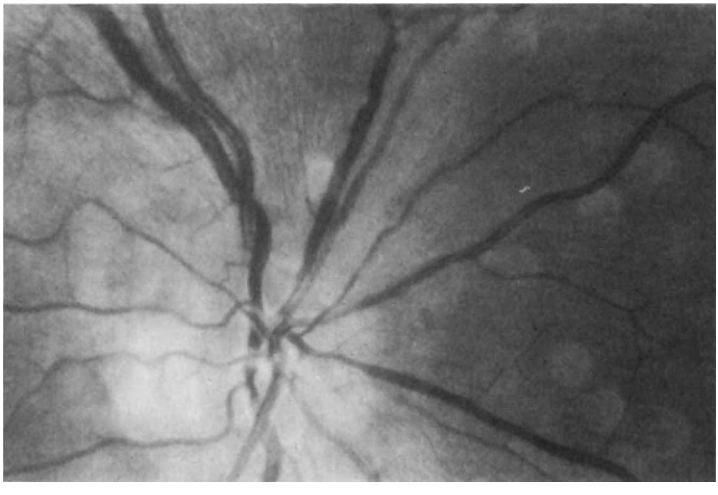


Figure 41 Disc swelling and vasculitis in a patient with sarcoidosis.

9 Optic Neuritis

Inflammation of the optic nerve is revealed by swelling of the optic disc and blurring of its margins. The nerve head looks unusually pink because of dilatation of its blood vessels. There may also be signs of

retinal venous congestion, such as dilated retinal veins and small haemorrhages in the peripapillary retina. Some degree of atrophy is common after primary inflammation of the nerve, as in syphilis. The pink, swollen nerve head gradually becomes pale.

A mild degree of disc swelling is common in chronic uveitis and may persist for years without the appearance of gross atrophy. (*Fig.* 41.)

Changes in the Choroid

(1) Choroiditis
(2) Choroidal detachment

1 Choroiditis

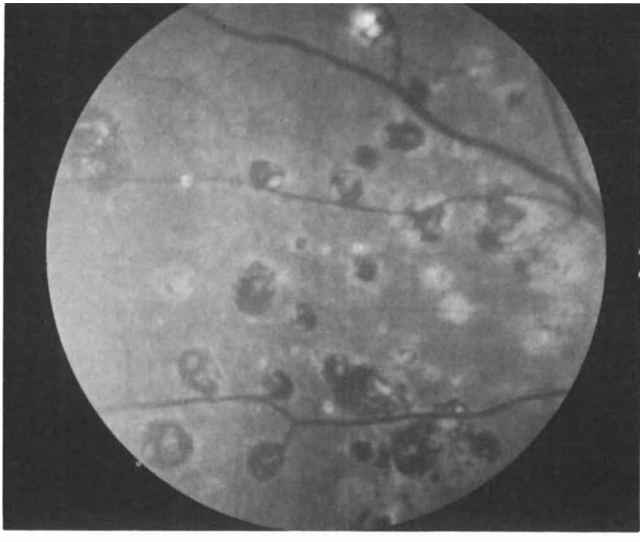
Choroiditis may be focal, multifocal, or diffuse. Fluorescent angiography helps to distinguish choroiditis from retinitis as the primary site of inflammation. The salient feature of choroiditis is that the retinal vessels can be seen to run uninterruptedly over the areas of the disturbance. This is difficult to appreciate when there is secondary retinitis and oedema. However, residual scars are clearly deep to the retina. One of the best conditions in which to appreciate this is tuberculous choroiditis. The retina is elevated over the tubercles. When the tubercles resolve they leave patches in which the normal pink colour of the fundus oculi is lost because the choroidal circulation has been destroyed at these sites, and the transparent retina is lying on 'bare' sclera. Around the edges of these pale areas there may be an increase in pigmentation. Inflammation often also damages the deeper layers of the retina, such as the pigment epithelium. The retina may be lifted forwards by an accumulation of fluid deep to the pigment epithelium. These so-called 'serous' detachments of the retina settle as the inflammation comes under control. (*Figs.* 42–44; *see also Fig. 76.*)

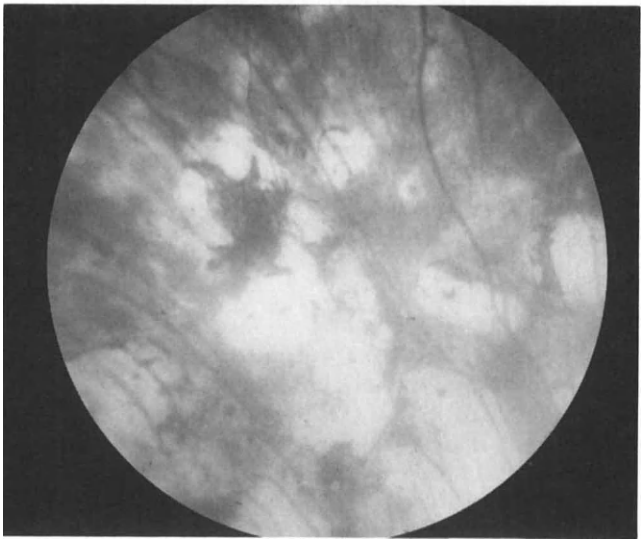
2 Choroidal Detachment

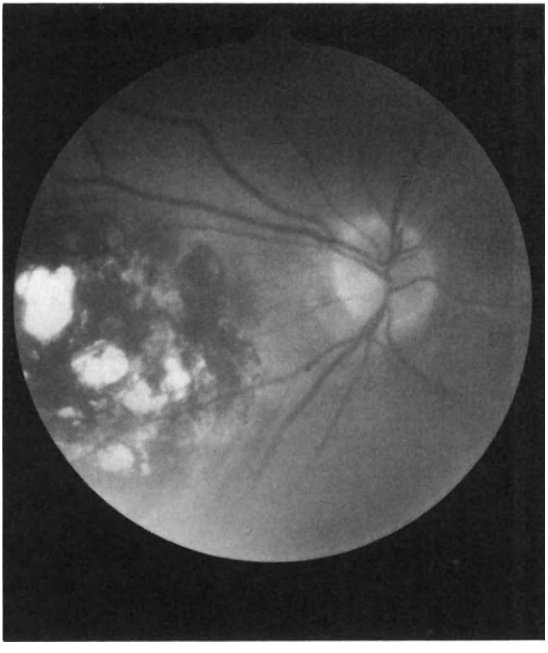
Sometimes fluid accumulates between the sclera and the choroid, producing a focal or widespread choroidal detachment. This may be seen in posterior scleritis. The affected part of the fundus appears much darker than normal, and the choroid and retina are bulged forwards together. The detached choroid may be thrown into shallow folds.

General Conditions

(1) Glaucoma
(2) Phthisis bulbi







Figures 42–44 Different appearances of choroidal scarring.

1 Glaucoma

Occlusion of the pupil by inflammatory synechiae may cause an acute obstruction of the drainage angle structures and a severe rise in intraocular pressure. The eye is red, painful and watering and the patient has a severe headache and sometimes also nausea and vomiting.

An insidious rise in intraocular pressure occurs when the drainage angle becomes scarred from the organization of inflammatory debris. A slow rise in pressure does not cause obvious symptoms, but is detected by regular measurement of intraocular pressure.

2 Phthisis Bulbi

Phthisis, or collapse of the globe, is heralded by a gradual fall of intraocular pressure. This is interpreted as a failure of ciliary body function in producing aqueous. The eye will show other signs of chronic uveitis, including calcific degeneration and vascularization of the cornea. The diameter of the globe diminishes and folds appear in the cornea. The eye is usually blind by this stage, and painless.

Chapter 1 References

Brockhurst R. J., Schepens C. L. and Okamura I. D. (1961) Uveitis. 3. Peripheral uveitis. Pathogenesis, etiology and treatment. *Am. J. Ophthalmol.* **51**, 19–26.

Busacca A. (1932) Anatomische und klinische Beobachtungen der Pupillarsaumknötchen (Koeppeschen Knötchen) bei Iridozyklitis. *Klin. Monatsbl. Augenheilkd.* **88**, 14–40.

Chan C-C., Fujikawa L. S., Rodrigues M. M., Stevens G. and Nussenblatt R. B. (1986) Immunohistochemistry and electron microscopy of cyclitic membrane. *Arch. Ophthalmol.* **104**, 1040–1045.

Derby G. S. (1927) The nature of so-called Koeppe nodules. *Arch. Ophthalmol.* **57**, 561–563.

Hogan M. J., Kimura S. J. and Thygeson P. (1959) Signs and symptoms of uveitis. *Am. J. Ophthalmol.* **47**, 155–176.

Inomata H. and Smelser G. (1970) Fine structural alterations of corneal endothelium during experimental uveitis. *Invest. Ophthalmol.* **9**, 272–285.

Kimura S. J. and Hogan M. J. (1963) Chronic cyclitis. *Trans. Am. Ophthalmol. Soc.* **61**, 397–417.

Koeppe L. (1917) Klinische Beobachtungen mit der Nernstspaltlampe und dem Hornhautmikroskop. 2. Mitteilung. *Graefes Arch. Ophthalmol.* **92**, 117–144, and preceding drawings.

Lamb H. D. (1938) The genesis of the cyclitic membrane. *Am. J. Ophthalmol.* **21**, 503–509.

McLeod D. (1975) Clinical sign of obstructed axoplasmic transport. *Lancet* **2**, 954–956.

Nussenblatt R. B., Palestine A. G., Chan C-C. and Roberge F. (1985) Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology* **92**, 467–471.

Pederson J. E., Kenyon K. R., Green W. R. and Maumenee E. A. (1978) Pathology of pars planitis. *Am. J. Ophthalmol.* **86**, 762–774.

Polack F. M., (1983) *Atlas of Corneal Pathology*. New York, Masson, pp. 99–192.

Sundmacher R. (1984) Endotheliitis corneae. Begriffsbestimmung und klinische Abgrenzung. *Klin. Monatsbl. Augenheilkd.* **184**, 163–167.

Zimmerman L. E. (1961) Ocular pathology of toxoplasmosis. *Surv. Ophthalmol.* **6**, 832–856.

Chapter two

Sarcoidosis

Sarcoidosis is a granulomatous disease with widespread systemic manifestations.

Aetiology

Despite the explosion in knowledge concerning the inflammatory process in sarcoidosis there has been little progress towards determining the cause. The resemblance of the histopathological picture to that of tuberculosis suggests that it might be a modified form of this disease, but tubercle bacilli have not been reliably isolated from sarcoid lesions. It has been possible to produce granulomas in mice on first or second passage of granuloma tissue from human sarcoid (Mitchell et al., 1976) but this does not prove that the lesions were due to a microbial or viral agent.

Epidemiology

Most available figures for prevalence are unreliable but estimates vary from as low as 2 per 100 000 in parts of Poland and Hungary to as high as 60 per 100 000 in Sweden. In Great Britain the prevalence is probably 20 per 100 000 (James and Brett, 1964). Estimates are not available for most non-European countries. It is thought that the disease is commoner in Negroes and less common in Asians, and that women are more commonly affected than men, but one world-wide survey found no sex predominance (James et al., 1976a). Patients may be 10 to 60 years of age at presentation, but most are in the third or fourth decade.

No specific connections have been established between HLA type and disease occurrence or behaviour. In Great Britain patients possessing the B8 phenotype tend to develop arthritis and erythema nodosum as part of their disease picture (Neville et al., 1980). In Washington the disease was found to occur 5·5 times more commonly in Negroes with HLA Bw15 than in those without (Al-Arif et al., 1980).

Clinical Features

In broad terms the disease tends to follow one of three patterns:

1 Asymptomatic Disease

Forty per cent of all cases are discovered when for some routine reason the patient has a chest X-ray. Disease of this sort tends to follow the same course as acute symptomatic disease.

2 Acute Disease

This may present with erythema nodosum and X-ray signs of hilar lymphadenopathy, but no constitutional symptoms. There may be transient malaise, fever, arthralgia and other symptoms of generalized disease. This form of disease is usually benign and apart from the erythema nodosum there are no overt signs of extrapulmonary disease. It resolves completely and spontaneously within two years. Sometimes patients in this benign group present with acute anterior uveitis which may prove to be the most significant aspect of their disease.

3 Chronic Severe Disease

This is less common than benign disease. There is progressive pulmonary parenchymal damage and extrapulmonary manifestations are common. Because of widespread visceral involvement the patient at presentation is more likely to be suffering from weight loss, fever and malaise. In this group treatment may be helpful.

Systemic Involvement

A Pulmonary Disease

Between 30% and 50% of patients have respiratory symptoms. Pulmonary involvement is the lesion most likely to be permanently disabling. On chest X-ray mediastinal or lung hilar lymphadenopathy is found in 90% of patients. The severity of the pulmonary involvement is reflected in the accepted radiological staging as follows:

Radiological Staging

STAGE I At presentation 40–60% of patients belong to this group. There is bilateral hilar lymphadenopathy, with or without paratracheal

lymphadenopathy. Despite the fact that these patients commonly have no symptoms and no radiological signs of pulmonary parenchymal disease, half of them have parenchymal involvement on biopsy, and disordered lung function tests. In 75% of this group liver or scalene lymph node biopsy shows granulomas.

STAGE II At presentation 25–35% of patients have radiographic changes of pulmonary infiltration, as well as hilar or mediastinal lymphadenopathy. The infiltration is symmetrical and may form one or a combination of three patterns. Most common are fine *reticular opacities* radiating out from the hilar nodes. These opacities may be accompanied by fine scattered nodules in a distribution known as an *acinar* pattern. Occasionally the parenchymal pattern is one of a few scattered *larger nodules* (Kirks et al., 1973). These disseminated parenchymal lesions correlate with active disease and are found with elevated levels of lysozyme and angiotensin converting enzyme in the blood. The small acinar lesions may be a non-specific pulmonary response to a primary parenchymal injury.

These patients may have mild symptoms including some breathlessness. Two-thirds resolve but about 20% go on to irreversible pulmonary fibrosis.

STAGE III At presentation 5–15% of patients belong to this stage. The lymphadenopathy clears on X-ray but the pulmonary infiltration persists or progresses to frank fibrosis. There may be distortion of the hilum, honeycombing of the lung or bulla formation. These changes may be accompanied by pulmonary hypertension and right ventricular failure. Some writers describe frank fibrotic changes as Stage IV. With the exception of erythema nodosum, extrapulmonary disease is more likely to be seen with Stage III disease than with Stage I or II. (*Figs.* 45–47.)

Pulmonary Alveolitis

Although radiological staging reflects the degree to which the disease has progressed in the form of fibrosis and other stromal changes it does not reflect the activity of the disease, that is the severity of active inflammation. This can be assessed by bronchial lavage studies and gallium-67 scans (*see below*). These reflect the severity of the alveolitis which is the earliest lesion.

Hunninghake and coworkers regard the alveolitis as *high intensity* when 28% or more of the large cells in lavage fluid are T-lymphocytes, and a gallium-67 scan is positive, and as *low intensity* when fewer than 28% of cells are T-lymphocytes and/or a gallium-67 scan is negative (Hunninghake et al., 1980). They also report that if patients were

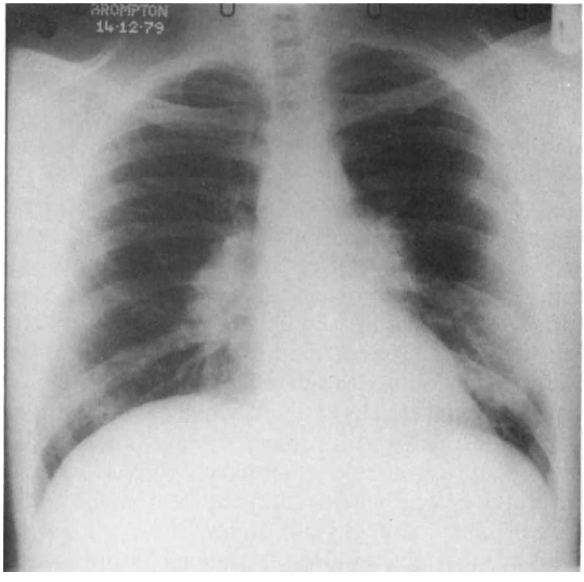


Figure 45 Sarcoidosis: bilateral hilar lymphadenopathy. (Dr Donald Mitchell.)

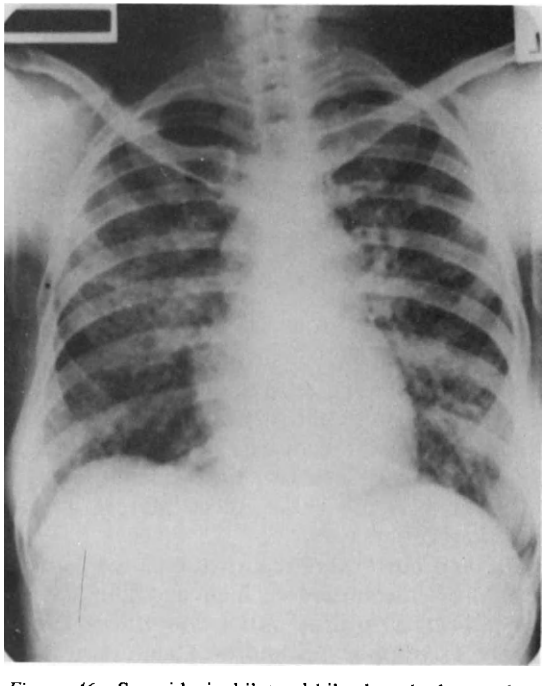


Figure 46 Sarcoidosis: bilateral hilar lymphadenopathy with pulmonary mottling. (Dr Donald Mitchell.)

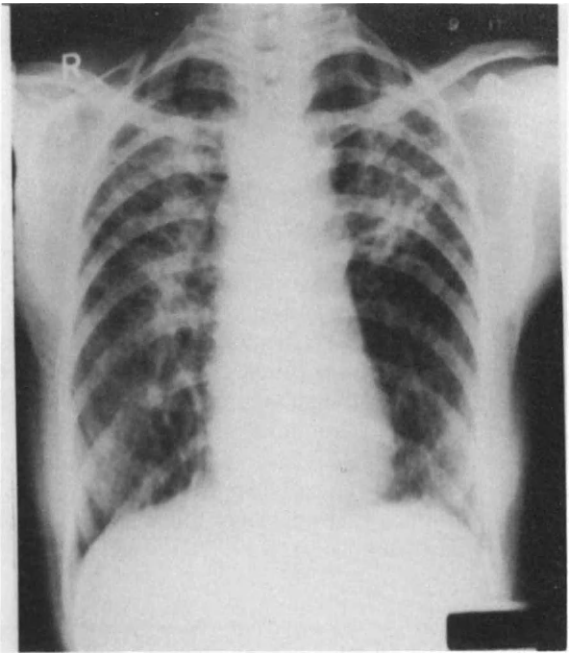


Figure 47 Sarcoidosis: pulmonary mottling alone. (Dr Donald Mitchell.)

divided in this way into high and low intensity alveolitis groups, all the high intensity patients deteriorated if untreated, but most improved or stabilized if treated. Of the low intensity group, 25% deteriorated if not treated but all improved or stabilized on treatment.

Pulmonary Function Tests

Changes in lung function tend to occur early in the disease and almost never return to normal once they are established. Decrease in diffusion capacity, lung compliance and lung volume are the hallmarks of functional impairment and are seen in disease at radiological Stage II. Steroid treatment does improve patients with severe abnormalities, but not those with mild ones. Vital capacity measurement is a popular way of regulating the dose of steroids. These lung function studies correlate more with structural lung changes, such as granulomas and fibrosis, than with alveolitis. The pulmonary diffusing capacity has been found to correlate best with lung pathology and radiological staging, but biopsies commonly show granulomas and interstitial pneumonitis in patients with normal lung function tests (Huang et al., 1979).

Upper Respiratory Tract and Bronchi

Granulomas are sometimes found in the nasal mucosa and are often associated with lupus pernio in the overlying skin (q.v.). Bronchial mucosal lesions are very common (Mitchell et al., 1980).

B Skin Disease

Erythema nodosum is by far the commonest skin lesion. The incidence varies in different parts of the world and appears to be highest in Europe, where it is reported to occur in one to two-thirds of female patients. Most patients with erythema nodosum have radiological stage I disease. In contrast to other cutaneous and extrathoracic manifestations it is found in the subacute type of disease which has a good prognosis. The patient frequently presents with transient joint pains, malaise and fever as well. These and the skin symptoms subside in a few weeks. The lesions typically appear on the front of the legs. They are 1–2 cm in diameter, moderately red and raised and vary in number from one to a dozen or so.

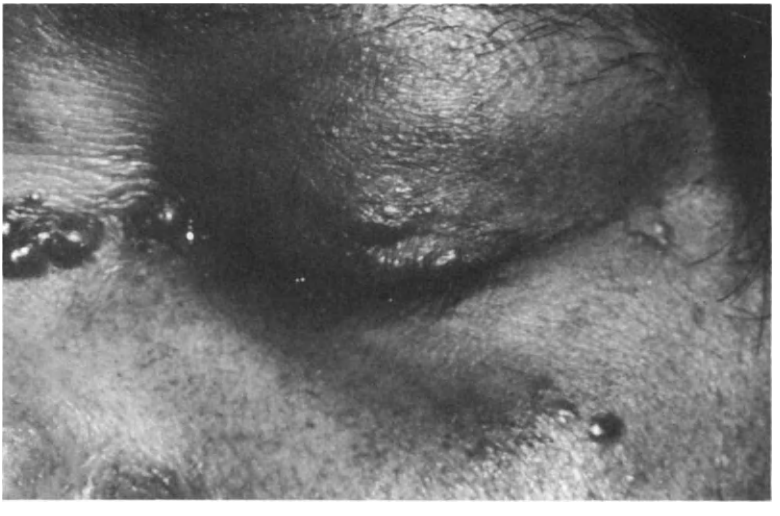


Figure 48 Sarcoidosis: granulomatous skin lesions and lacrimal gland enlargement. (Dr Donald Mitchell.)

The other skin lesions are mostly seen in Negro patients and are morphologically varied. Lupus pernio consists of thickened, bluish maculopapules on the face and limbs. On the fingers they may be

associated with underlying bone changes, and on the nose with nasal mucosal lesions. Plaques are also sometimes seen in the skin, and occasionally lesions resembling psoriasis. Granulomatous infiltration may cause old scars to enlarge. Unlike erythema nodosum, these lesions are chronic and associated with other chronic manifestations such as progressive pulmonary fibrosis and uveitis. (*Fig.* 48.)

C Bone, Joint and Muscle Disease

Bone lesions occur in about 5% of cases, particularly in Negroes with chronic disease, especially skin disease. The phalanges, metacarpals and metatarsals show areas of osteoporosis and cystic rarefaction, and cortical thinning. This is the result of circulatory impairment of the bone from sarcoid infiltration. Affected digits may be swollen but there is no pain, and joints are rarely involved. It has been reported that only 20% of patients with bone lesions eventually show resolution of chest X-ray abnormalities (Neville et al., 1977).

The prevalence of joint disease is variously estimated from 15·6% (Spilberg et al., 1969) to 38% (Gumpel et al., 1967). The commonest pattern is an acute, brief but symptomatically severe polyarthritis at the onset of disease. Less frequent is less widespread disease appearing later and running a more chronic course. In general, radiological changes are uncommon, although in one series they were found in 20% (Kaplan, 1963).

Symptomatic muscle disease is even less common than joint disease, but granulomas are not infrequently found on muscle biopsy. Occasionally, acute myositis is seen, mainly in women.

D Ocular Disease

When cases of keratoconjunctivitis sicca are included, ocular involvement occurs in up to 50% of cases (Crick et al., 1961). Other series give lower frequencies (James et al., 1976b, 27%; Obenauf et al., 1978, 38%). In the series reported by Obenauf and coworkers 19% presented with ocular symptoms. This is an American series, and Blacks outnumbered Whites 3 : 1. No sex bias has become apparent.

Conjunctival Disease

It is difficult to put keratoconjunctivitis sicca into perspective in this disease but it is rarely of practical importance. Obenauf and coworkers report lacrimal gland enlargement in 15·8% of patients, but conjunctival granulomas in only 6·9%. James and coworkers report conjunctival disease in 19%, usually in the form of a non-specific conjunctivitis, overt granulomatous disease being uncommon. Conjunctival biopsy of tissue not clinically involved was unhelpful in establishing the diagnosis.

The lacrimal gland enlargement may be obvious, but the gland may simply feel firmer than normal. Conjunctival nodules are found particularly in the lower fornix and on the plica. They are yellowish-pink and fleshy, and sometimes obviously vascular (*see Fig.* 4). They are usually no more than a few millimetres in size, but may become quite large. Biopsy of suspect lesions is a simple procedure and should be done in cases lacking a positive diagnosis from other tissue. Biopsy of the lacrimal gland presents a more serious problem because there is a risk of producing a dry eye if the excretory ducts are severed, but safe and simple techniques are described (Weinreb, 1981). However, gallium citrate (^{67}Ga) uptake would appear to be more sensitive and safe, although false positive results occur in Sjögren's syndrome, orbital pseudotumour and collagen vascular disease (Weinreb et al., 1981).

Uveitis

In the various series of case reports already referred to, uveitis is by far the commonest form of ophthalmic involvement, accounting for 60–80% of eye cases. Most series have reported panuveitis as the commonest clinical picture but in others the emphasis has been put on anterior uveitis (James et al., 1976b). Between 2% and 4% of all cases of uveitis are due to sarcoidosis (Perkins, 1958).

Uveitis in sarcoidosis is usually a chronic problem, with all the complications of chronic uveitis such as cataract, synechia formation and secondary glaucoma. It is a serious sight-threatening problem, especially as it is usually a panuveitis and posterior changes such as cystoid macular oedema may finally occur.

Granulomatous Uveitis

The term granulomatous uveitis is that given to the chronic uveitis classically associated with sarcoidosis, because granulomatous infiltration of the iris produces nodules. However, nodules may not be seen, and occur also in uveitis associated with other conditions. They may be of two types, both arising from the iris stroma. The first type are large, yellow and even vascular in appearance, but sometimes they produce only elevations of the iris surface. Nodules of this type tend to be persistent, and when they involve the root of the iris they may result in peripheral iris scarring and the formation of peripheral anterior synechiae. Changes in the anterior chamber angle may result in secondary glaucoma (Iwata et al., 1976). The formation of nodules in and on the trabecular meshwork may be unique to sarcoidosis (Henkind, 1982). The second type of nodule is only 1–2 mm across, grey and translucent and occurring sometimes in large numbers. They come and go over a few days, and with treatment disappear within 48 hours (*see Fig.* 20).

Large waxy or 'mutton fat' precipitates on the corneal endothelium are another feature of the uveitis. Why they have this appearance is unknown. Regrettably they are often referred to as granulomatous keratic precipitates, suggesting that they are granulomas.

Posterior synechiae form with chronic disease and eventually may occlude the pupil (*see Fig.* 21). The posterior segment of the eye also shows signs of inflammation (*see below*). Many patients develop some degree of glaucoma (Iwata et al., 1976).

Acute Anterior Uveitis

Isolated acute anterior uveitis may be seen in the clinical group with disease of acute onset and a good prognosis. It has no special features.

Posterior Segment Inflammation

Attention was drawn many years ago to snowball vitreous opacities and retinal and choroidal scarring in sarcoid uveitis (Crick et al., 1961). There is no doubt that changes in the posterior segment of the eye are detected more frequently the more assiduously they are sought (*see Fig.* 33). For example, fundus involvement was found in every one of 36 patients with Kveim or tissue biopsy positive sarcoidosis, most of whom presented with signs of anterior uveitis (Spalton and Sanders, 1981). Papilloedema and periphlebitis particularly of equatorial veins were common. Eight patients had evidence of retinal neovascularization, usually of the optic disc, but in 2 patients at areas of peripheral retinal branch vein occlusion. Thirteen patients had retinal pigment epithelial disturbance in the form of focal mottling. Peripheral sea-fan neovascularization has been described (Asdourian et al., 1975). There have also been occasional descriptions of subretinal neovascular nets at the posterior pole.

Periphlebitis gives rise to exudative lesions which are creamy in colour and when large are said to resemble candle-wax drippings. This appearance is rarely seen. When the exudative lesions resolve, traces of retinal pigment epithelial atrophy remain. Obenauf and coworkers report that choroidal nodules were found in 5·5% of patients with eye disease, and optic nerve disease in 7·4% (Obenauf et al., 1978). Choroidal granuloma has been described as the sole ocular manifestation (Campo and Aaberg, 1984). This produces a swelling beneath the retina which may be impossible to differentiate from secondary tumour if there are no other signs of sarcoidosis.

Severe chronic uveitis is likely to be associated with chronic disease in other systems.

Although a combination of ocular findings as described will suggest a diagnosis of sarcoidosis, it is certainly not specific. Indeed, many

patients present with precisely this ocular picture (minus the conjunctival changes) but no other findings whatever to suggest sarcoidosis. The course of their disease and response to steroids is also the same as in patients with sarcoidosis.

Heerfordt's Syndrome

Subacute uveitis may be one manifestation of Heerfordt's syndrome, or uveoparotid fever. It consists of uveitis, parotid gland enlargement, cranial nerve palsies, fever, drowsiness, arthralgia, night sweats, anorexia and gastrointestinal symptoms, combined with pleocytosis in the cerebrospinal fluid. Symptoms disappear spontaneously in six to twelve months.

E Neurologic Disease

About 5% of patients experience neurologic involvement (Delaney, 1977). Central nervous system disease is usually an early occurrence. It is mainly the result of basal granulomatous meningitis. Diabetes insipidus has occurred from pituitary and hypothalamic involvement, and signs of an intracranial space-occupying lesion are sometimes seen. The most commonly affected cranial nerve is the facial, followed by the optic nerve. Peripheral nervous system and musculoskeletal disease tends to occur later, in the chronic stages of the disease, but it has a better prognosis than central nervous system disease. Response to steroid treatment may be incomplete.

F Lymphadenopathy

Transient extrathoracic lymphadenopathy occurs in 75% of patients, particularly in the cervical nodes. Splenomegaly occurs in 50% but is rarely symptomatic.

G Heart Disease

Granulomas may occur in the pericardium, and in the ventricular walls, where they may cause arrhythmias and heart block. Symptoms of cardiac disease are in fact rare but lung disease may cause cor pulmonale.

H Liver Disease

Overt hepatic disease is rare but liver biopsy in the acute or subacute type of disease is positive in up to 90% of cases. The figure is less for chronic disease. Liver function tests are usually undisturbed.

I Kidney Disease

Granulomas seldom develop in the kidneys, but patients with prolonged hypercalcaemia and hypercalciuria may develop nephrocalcinosis.

Pathology

Irrespective of the tissue involved, the pathology is that of miliary non-caseating granulomas composed of epithelioid histiocytes which are derived from macrophages. Some giant cell formation is seen. The granuloma has a peripheral ring of lymphocytes. Central necrosis is common. As the granuloma matures fibroblasts accumulate around the periphery and lay down collagen. The lesions may resolve completely, spontaneously or with treatment, leaving behind no trace, or else some fibrous scarring. In progressive disease there is extensive scarring. Five per cent of patients eventually develop calcification of the intrathoracic lymph nodes, but not of the lungs themselves.

Having discussed the *granuloma* of sarcoidosis it is important to point out that *the initial lesion in the lung is an alveolitis* from which the formation of lung granulomas may proceed (*see below*). Thus in the lung the pathology may simply consist of lesions which are reversible, that is alveolitis or granulomas, or of additional irreversible features such as pulmonary parenchymal cell destruction and interstitial fibrosis. In inactive advanced disease only irreversible changes will be found.

Immunopathology

Although the cause of the disease remains as much a mystery as ever, recent advances in investigative techniques have led to a much greater understanding of the mechanisms producing tissue damage. They have also provided means of monitoring inflammatory activity, and guiding therapy. From these points of view the traditional staging by X-rays has been of limited usefulness.

Two-thirds of sarcoid patients have negative skin tests to tuberculin and a half have raised plasma globulin levels (James et al., 1976a). The apparent 'anergy' is reflected in peripheral blood T-lymphopenia, and an increase in the proportion of T-suppressor to T-helper cells (Katz et al., 1978).

However, at sites of disease activity there is an absolute increase in the number of T-lymphocytes, with an increase in the proportion of T-helper cells and of spontaneously activated cells (Hunninghake and Crystal, 1981a). These activated cells produce interleukins (IL-1, etc.)

which attract monocytes, which form the granulomas. Fibrosis is induced by the deposition of collagen from fibroblasts which also migrate into the area.

There is polyclonal activation of B-lymphocytes to differentiate into immunoglobulin-secreting cells. The mechanism of this activation is controversial, but the activated T-lymphocytes may be responsible. T-lymphocytes from the blood of patients with active disease, or from the lungs of patients with low intensity disease do not exhibit these capabilities. There is thus a sequestration of activated T-lymphocytes, especially T-helper cells, in granulomas, which may account for the lymphopenia. It may be mediated by spontaneous release from granuloma cells of migration inhibition factor (Yoshida et al., 1979). Yoshida and coworkers found that 60% of their patients had circulating serum migration inhibition factor. There was no correlation with disease activity or steroid therapy, but there was a positive correlation with cutaneous anergy.

It has not been established that sarcoid lymphocytes have any intrinsic functional defect. Recent studies suggest that they are responding to external cellular and humoral influences. Sarcoid patients do not behave like individuals who have immunodeficiency diseases, and in remission their cutaneous anergy and blood changes return to normal. The study of peripheral phenomena has tended to cloud issues which are now being resolved by studies of events at the sites of active disease.

As in the case of T-lymphocytes, there is no general agreement about whether B-cells are qualitatively or quantitatively normal. There is a polyclonal increase in immunoglobulin production, especially IgG. Exogenous antigens appear to provoke a heightened response. Autoantibodies to host antigens are sometimes produced. In the blood the number of IgG and IgM secreting cells is normal, but is markedly raised in bronchial lavage fluid. In patients with pulmonary sarcoid there is a direct correlation between the percentage of bronchoalveolar cells that are T-lymphocytes and the percentage of bronchoalveolar cells that secrete IgG. The lung thus appears to be an important site of immunoglobulin production which is modulated by local, activated T-lymphocytes (Hunninghake and Crystal, 1981b).

Antinuclear antibodies and rheumatoid factor may be found, but their presence in serum has no correlation with the occurrence of joint disease in sarcoidosis. Autoantibodies to B-lymphocytes (Lobo and Suratt, 1979) and to T-lymphocytes (Daniele and Rowlands, 1976) have been described. Those to B-lymphocytes were found to correlate positively with disease activity, but not those to T-lymphocytes.

Circulating immune complexes are found in patients with active disease irrespective of X-ray staging (Daniele et al., 1978). They were found more commonly in patients with extrapulmonary disease (Daniele et al., 1978; Gupta et al., 1977).

Diagnosis and Investigation

Many of the diagnostic features have already been described in the clinical section. No further reference will be made to clinical and X-ray findings. Other causes of granulomatous disease, particularly typical or atypical tuberculosis, should be taken into consideration when making the diagnosis.

Biopsy

It is important to emphasize that most cases of sarcoidosis are benign and self-limiting, and invasive biopsies are commonly unwarranted.

1 Kveim Antigen Testing

In 1941 Kveim described a specific skin reaction to the injection of an antigen produced from sarcoid tissue (Kveim, 1941) and subsequently the importance of biopsy of the injection site was stressed (Siltzbach and Ehrlich, 1954). Biopsy is performed 4–6 weeks after injection in the forearm skin. It is positive in only 80% of cases of disease confirmed by biopsy elsewhere. A positive reaction is the presence of typical sarcoid granuloma tissue at the injection site. The antigen is not available worldwide, and the 4–6 week delay before the test can be read is unacceptable if treatment cannot be delayed. Newer, quicker and more reliable methods are replacing it even in countries such as Great Britain, where it has formed a cornerstone of diagnosis for many years. The test often becomes negative in long-standing cases.

2 Lung

Transbronchial biopsy via fibreoptic bronchoscope is a reliable diagnostic tool (Mitchell et al., 1980). However, material adequate for diagnosis may not be obtained by this technique. Where there is real diagnostic doubt *open lung biopsy* is often performed. *Biopsy of the bronchial mucosa* also gives a high positive yield (Friedman et al., 1963; Mitchell et al., 1980) even when the mucosa appears normal and in cases in which the disease has lasted more than two years and Kveim tests and tissue biopsies may have become negative. There is a 2% risk of pneumothorax or a small pulmonary haemorrhage.

Bronchoalveolar lavage has more recently provided a sensitive diagnostic tool and opened a new dimension in evaluating the activity of the inflammatory disease. Many references have already been made to this in the immunopathology section, but the reader may usefully consult the review by Hunninghake and coworkers (Hunninghake et al., 1979). There is a small risk of hypoxaemia and mucosal damage with the technique.

3 Skin and Other Tissues

Characteristic pathology is found on biopsy of affected areas of skin, conjunctiva or mucous membrane, or enlarged lymph or lacrimal glands. Despite the enthusiasm of some workers for blind conjunctival biopsy, most have found this to be a profitless exercise.

Biochemical Investigations

1 Serum Calcium

Probably fewer than 10% of patients have hypercalcaemia and hypercalciuria. Serum calcium and 24-hour urinary calcium levels may be assessed.

2 Angiotensin-converting Enzyme (ACE)

This enzyme is produced by the epithelioid cells of sarcoid granulomas. Serum ACE correlates with the number of T-lymphocytes recovered from bronchoalveolar lavage fluid, but not with blood lymphocyte levels. It is not as sensitive a marker of disease activity as bronchoalveolar lavage study (Rossman et al., 1982). Elevated serum levels are not specific for sarcoidosis but may also be found in Gaucher's disease, primary biliary cirrhosis, leprosy, idiopathic respiratory distress syndrome of the newborn, and miliary tuberculosis. Normal children up to 17 years of age also have higher levels than normal adults. Serum levels of more than 50 units/ml are considered significant, and are found in about 75% of patients with active untreated disease (Lieberman, 1975; Lieberman et al., 1979). It may not be elevated at the onset of disease and has only occasionally been found elevated in patients with erythema nodosum, an early transient finding in the acute or subacute type of disease (Romer, 1980). Raised levels return to normal after a few weeks of steroid treatment (Allen et al., 1980) or on spontaneous resolution, and levels may change before the clinical features, chest X-ray or lung function alterations begin to improve (DeRemee and Rohrbach, 1980). Elevated levels have been found in the tears of patients with active sarcoid, and these fell to normal after steroid treatment (Sharma and Vita, 1983). It may also be elevated in patients with active uveitis (Weinberg and Tessler, 1976; Romer et al., 1980). ACE activity in the aqueous has also been found to be raised, even when serum levels are normal (Weinreb et al., 1985).

Unfortunately the levels can vary widely in normal people, and overlap with those found in disease.

3 Serum Lysozyme

This enzyme is also probably produced by granuloma cells. Serum

levels tend to parallel ACE levels (Silverstein et al., 1977). Sarcoid lymph nodes have a high lysozyme content.

4 Immunological Tests

Changes in immunological parameters such as plasma globulins, autoantibodies and serum and lung lymphocyte populations have already been discussed in the section on Immunopathology.

Gallium-67 Scanning

Gallium-67 is taken up by abnormal alveolar macrophages and not by normal ones. There is a positive correlation between gallium-67 uptake and the activity of the alveolitis. Positive gallium-67 scan is often obtained in patients with hilar lymphadenopathy only, indicating that they have active alveolitis. It is not specific for sarcoid and may be positive in other pulmonary interstitial disorders, infections and malignancy (Crystal et al., 1981). By combining gallium-67 scanning with ACE assay the diagnostic specificity of non-invasive evaluation can be increased to over 90% (Nosal et al., 1979).

Involved lacrimal glands also take up gallium-67, and local scanning of the glands may be performed. (*Fig.* 49.)

Assessment of Disease Activity, Need for Treatment and Response to Treatment

From the foregoing discussion the reader will have concluded that assessment from X-ray grading, and to a less extent from physiological tests of lung function, is inadequate to monitor the activity of inflammatory disease because these tests essentially reflect *structural* changes. The first event is alveolitis which precedes granuloma formation and alterations in the normal parenchymal cells.

Most patients with acute onset disease need none but symptomatic treatment. Acute uveitis usually responds to local treatment, but patients with chronic uveitis, signs of progressive pulmonary impairment (as assessed by lung function and X-ray studies), or evidence of disease elsewhere (such as cardiac or central nervous system disease) should have systemic therapy. Minor degrees of impaired pulmonary function are less likely to be influenced by steroid therapy than more major ones. In assessing the response to treatment the internist will be guided by the investigations already described, but there is no standard method. The newly expanded capacity to assess the degree to which changes might be reversible (i.e., alveolitis or granulomas) or irreversible (i.e., fibrosis and alveolar structural changes) and therefore likely

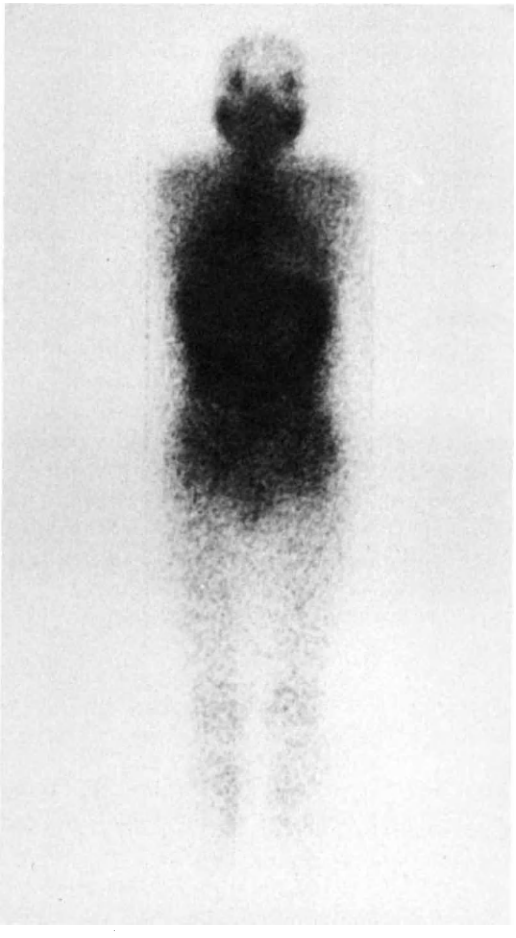


Figure 49 Sarcoidosis: Gallium scan. Active sarcoidosis in a 35-year-old West Indian woman. Increased uptake in hilar and mediastinal glands, parotid and lacrimal glands, and spleen.
(Professor J P Lavender and the Department of Diagnostic Radiology, Hammersmith Hospital.)

or not to respond to anti-inflammatory treatment has helped to make management more rational.

Treatment

Systemic Disease

With significant systemic disease oral prednisolone is begun at 30–40 mg/day, or double this dose on alternate days. Chronic manifes-

tations may require treatment for ten years or more, and so an alternate day regime should be aimed at from the start. Such a regime has been found as effective as daily dosage in pulmonary disease (Selroos and Sellergren, 1979). Depending upon the patient's response this can be reduced over 3–4 weeks to the equivalent of 20 mg/day, and then a more gradual reduction made until a minimum maintenance dose is found. This may be as low as 10 mg on alternate days. If no response is seen within a few weeks it is unlikely to occur later, and treatment should be withdrawn if it has clearly failed. Higher doses are needed in the acute phase of cardiac and central nervous system disease. Clinical response is often incomplete and poorly sustained, and relapse on withdrawal of treatment is common. (Johns et al., 1974).

Hydroxychloroquine may be found more effective than steroids in the management of severe chronic skin lesions, but ocular complications must be anticipated if this drug is used.

Indomethacin has been found very effective in relief of joint pain (Neville et al., 1977).

Intralesional injections of steroids may be helpful in patients with a small number of troublesome skin lesions (Bersani and Nichols, 1985).

Ocular Disease

Steroid drop therapy combined with mydriatics may be effective for acute uveitis but most patients with chronic eye disease eventually need systemic steroid treatment, even when there are no systemic indications for it. Eye disease often requires much higher doses than systemic disease. Response may be incomplete. Despite aggressive therapy and the resolution of systemic disease blindness may still occur.

Chapter 2 References

Al-Arif L., Goldstein R. A., Affronti L. F., Janicki B. W. and Foellmer J. W. (1980) HLA antigens and sarcoidosis in a North American black population. In *Proceedings of the VIIIth International Conference on Sarcoidosis*, eds. W. J. Williams and B. H. Davies. Cardiff, Alpha Omega, pp. 206–212.

Allen R., Mendelsohn F. A. O., Csicsmann J., Weller R. F., Hurley T. H. and Doyle A. E. (1980) A clinical evaluation of serum angiotensin converting enzyme in sarcoidosis. *Aust. N.Z. J. Med.* **10**, 496–501.

Asdourian G. K., Goldberg M. F. and Busse B. J. (1975) Peripheral retinal neovascularisation in sarcoidosis. *Arch. Ophthalmol.* **93**, 787.

Bersani T. A. and Nichols C. W. (1985) Intralesional triamcinolone for cutaneous palpebral sarcoidosis. *Am. J. Ophthalmol.* **99**, 561–562.

Campo R. V. and Aaberg T. M. (1984) Choroidal granuloma in sarcoidosis. *Am. J. Ophthalmol.* **97**, 419–427.

Crick R. P., Hoyle C. and Smellie, H. (1961) The eyes in sarcoidosis. *Br. J. Ophthalmol.* **45**, 461–481.

Crystal R. G., Gadek J. E., Ferrans V. J., Fulmer J. D., Line B. P. and Hunninghake, G. W. (1981) Interstitial lung disease: current concepts of pathogenesis, staging and therapy. *Am. J. Med.* **70**, 542–568.

Daniele R. P. and Rowlands D. T. (1976) Antibodies to T cells in sarcoidosis. *Ann. N.Y. Acad. Sci.* **278**, 88–100.

Daniele R. P., McMillan L. J., Dauber J. H. and Rossman M. D. (1978) Immune complexes in sarcoidosis. *Chest* **74**, 261–264.

Delaney, P. (1977) Neurologic manifestations in sarcoidosis. *Ann. Intern. Med.* **87**, 336–345.

DeRemee R. A. and Rohrbach M. S. (1980) Serum angiotensin-converting enzyme activity in evaluating the clinical course of sarcoidosis. *Ann. Intern. Med.* **92**, 361–365.

Friedman O. H., Blaugrund S. M. and Siltzbach L. H. (1963) Biopsy of the bronchial wall as an aid in diagnosis of sarcoidosis. *JAMA* **183**, 646–650.

Gumpel J. M., Johns C. J. and Shulman L. E. (1967) The joint disease of sarcoidosis. *Ann. Rheum. Dis.* **26**, 194–205.

Gupta R. C., Keuppers F., DeRemee R. A., Huston K. A. and McDuffie F. C. (1977) Pulmonary and extrapulmonary sarcoidosis in relation to circulating immune complexes. *Am. Rev. Respir. Dis.* **116**, 261–266.

Henkind P. (1982) Sarcoidosis: an expanding ophthalmic horizon. *J. R. Soc. Med.* **75**, 153–159.

Huang C. T., Heurich A. E., Rosen Y., Moon S. and Lyons H. A. (1979) Pulmonary sarcoidosis: roentgenographic, functional, and pathologic correlations. *Respiration* **37**, 337–345.

Hunninghake G. W. and Crystal R. G. (1981a) Pulmonary sarcoidosis – a disorder mediated by excess helper T-lymphocyte activity at sites of disease activity. *N. Engl. J. Med.* **305**, 429–433.

Hunninghake G. W. and Crystal R. G. (1981b) Mechanisms of hypergammaglobulinemia in pulmonary sarcoidosis. *J. Clin. Invest.* **67**, 86–91.

Hunninghake G. W., Gadek J. E., Kawanami O., Ferrans V. J. and Crystal R. G. (1979) Inflammatory and immune processes in the human lung in health and disease: evaluation by bronchoalveolar lavage. *Am. J. Pathol.* **97**, 149–206.

Hunninghake G. W., Keogh B. A., Line B. R., Gadek J. E., Kawanami O., Ferrans V. J. and Crystal R. G. (1980) Pulmonary sarcoidosis: pathogenesis and therapy. In *Basic and Clinical Aspects of Granulomatous Diseases*, eds. D. L. Boros and T. Yoshida. New York, Elsevier, pp. 275–290.

Iwata K., Nanba K., Sobue U. and Abe H. (1976) Ocular sarcoidosis: evaluation of intraocular findings. *Ann. N.Y. Acad. Sci.* **278**, 445–454.

James D. G. and Brett G. Z. (1964) Prevalence of intrathoracic sarcoidosis in Britain. *Acta Med. Scand.* **176** (suppl. 425), 115–117.

James D. G., Neville E., Siltzbach L. E., Turiaf J., Battesti J. P., Sharma O. P., Hosoda Y., Mikami R., Odaka M., Villar T. G., Djuric B., Douglas A. C., Middleton W., Karlish A., Blasi A., Olivieri D. and Press P. (1976a) A worldwide review of sarcoidosis. *Ann. N.Y. Acad. Sci.* **278**, 321–333.

James D. G., Neville E. and Langley D. A. (1966) Ocular sarcoidosis. *Trans. Ophthalmol. Soc. U.K.* **96**, 133–139.

Johns C. J., Zachary J. B. and Ball W. C. (1974) A ten-year study of corticosteroid treatment of pulmonary sarcoidosis. *Johns Hopkins Med. J.* **134**, 271–283.

Kaplan H. (1963) Sarcoid arthritis. A review. *Arch. Intern. Med.* **112**, 924–935.

Karma A. and Laatikainen L. (1981) Fluorescein iris angiography in nodular sarcoid iritis. *Int. Ophthalmol.* **3**, 97–106.

Katz P., Haynes B. F. and Fauci A. S. (1978) Alteration of T-lymphocyte subpopulations in sarcoidosis. *Clin. Immunol. Immunopathol.* **10**, 350–354.

Kirks D. R., McCormick V. D. and Greenspan R. H. (1973) Pulmonary sarcoidosis. Roentgenologic analysis of 150 patients. *Am. J. Radiol.* **117**, 777–786.

Kveim A. En ny og spesifikk kutan-reaksjon ved Boecks sarcoid. (1941) *Nord. Med.* **9**, 169–172.

Lieberman J. (1975) Elevation of serum angiotensin-converting enzyme (ACE) level in sarcoidosis. *Am. J. Med.* **59**, 365–372.

Lieberman J., Nosal A., Schlessner L. A. and Sastre-Foken A. (1979) Serum angiotensin-converting enzyme for diagnosis and therapeutic evaluation of sarcoidosis. *Am. Rev. Resp. Dis.* **120**, 329–335.

Lobo P. I. and Suratt P. M. (1979) Studies on the autoantibody to lymphocytes in sarcoidosis. *J. Clin. Lab. Immunol.* **1**, 283–288.

Mitchell D. M., Rees R. J. W. and Goswami K. K. A. (1976) Transmissible agents from human sarcoid and Crohn's disease tissues. *Lancet* **2**, 761–764.

Mitchell D. M., Mitchell D. N., Collins J. V. and Emerson C. J. (1980) Transbronchial lung biopsy through fibreoptic bronchoscope in diagnosis of sarcoidosis. *Br. Med. J.* **280**, 679–681.

Neville E., Carstairs L. S. and James D. G. (1977) Sarcoidosis of bone. *Q. J. Med.* **46**, 215–227.

Neville E., James D. G., Brewerton D. A., James D. C. O., Cockburn C. and Fenichal B. (1980) HLA antigens and clinical features of sarcoidosis. In *Proceedings of the VIIIth International Conference on Sarcoidosis*, eds. W. J. Williams and B. H. Davies. Cardiff, Alpha Omega, pp. 201–205.

Nosal A., Schleissner L. A., Mishkin F. and Lieberman J. (1979) Angiotensin-1-converting enzyme and gallium scan in noninvasive evaluation of sarcoidosis. *Ann. Intern. Med.* **90**, 328–331.

Obenauf C. D., Shaw H. E., Sydnor C. F. and Klintworth G. K. (1978) Sarcoidosis and its ophthalmic manifestations. *Am. J. Ophthalmol.* **86**, 648–655.

Perkins E. S. (1958) The aetiology and treatment of uveitis. *Trans. Ophthalmol. Soc. U.K.* **78**, 511–522.

Romer F. K. (1980) Angiotensin-converting enzyme in newly detected sarcoidosis. *Acta Med. Scand.* **208**, 437–443.

Romer F. K., Schmidt P. and Geday H. (1980) Angiotensin-converting enzyme in uveitis and sarcoidosis. *Acta Ophthalmol. (Copenh.)* **58**, 243–249.

Rossman M. D., Dauber J. H., Cardillo M. E. and Daniele R. P. (1982) Pulmonary sarcoidosis: correlation of serum angiotensin-converting enzyme with blood and bronchoalveolar lymphocytes. *Am. Rev. Resp. Dis.* **125**, 366–369.

Selroos O. and Sellergren T. L. (1979) Corticosteroid therapy of pulmonary sarcoidosis (a prospective evaluation of alternative day and daily dosage in stage II disease). *Scand. J. Respir. Dis.* **60**, 215–221.

Sharma O. P. and Vita J. B. (1983) Determination of angiotensin-converting enzyme activity in tears. *Arch. Ophthalmol.* **101**, 559–561.

Siltzbach L. E. and Ehrlich J. C. (1954) The Nickerson–Kveim reaction in sarcoidosis. *Am. J. Med.* **16**, 790–803.

Silverstein E., Friedland J. and Ackerman T. (1977) Elevation of granulomatous lymph-node and serum lysozyme in sarcoidosis and correlation with angiotensin-converting enzyme. *Am. J. Clin. Pathol.* **68**, 219–224.

Spalton D. J. and Sanders M. D. (1981) Fundus changes in histologically confirmed sarcoidosis. *Br. J. Ophthalmol.* **65**, 348–358.

Spilberg I., Siltzbach L. E. and McEwen C. E (1969) The arthritis of sarcoidosis. *Arthritis Rheum.* **12**, 126–137.

Weinberg R. S. and Tessler H. H. (1976) Serum lysozyme in sarcoid uveitis. *Am. J. Ophthalmol.* **82**, 105–108.

Weinreb R. N. (1981) An approach to lacrimal gland biopsy in sarcoid. *Invest. Ophthalmol. Vis. Sci. (Suppl.)* **20**, 87.

Weinreb R. N., Yavitz E. Q. and O'Connor G. R. (1981) Lacrimal gland uptake of gallium citrate Ga^{67}. *Am. J. Ophthalmol.* **92**, 16–20.

Weinreb R. N., Sandman R., Ryder M. I. and Friberg T. R. (1985) Angiotensin-converting enzyme activity in human aqueous humor. *Arch. Ophthalmol.* **103**, 34–36.
Yoshida T., Siltzbach L. E., Masih N. and Cohen S. (1979) Serum migration inhibitory activity in patients with sarcoidosis. *Clin. Immunol. Immunopathol.* **13**, 39–46.

Chapter three

Systemic Vasculitis Syndromes

INTRODUCTION

Many clinical syndromes are loosely related under this heading because in all of them the essential pathological process is localized to blood vessels. However, there are wide differences in both the clinical and the histopathological details. Any classification is at best a compromise between these clinical and pathological distinctions. Cupps and Fauci have provided a comprehensive classification which the reader may wish to consult (Cupps and Fauci, 1981).

Significant ocular involvement occurs in only a few of the vasculitides, and this chapter deals only with those conditions:

Behçet's syndrome
Polyarteritis nodosa (systemic necrotizing vasculitis)
Wegener's granulomatosis
Giant cell arteritis
(including polymyalgia rheumatica
and Takayasu's disease)
Cogan's syndrome

From the medical point of view it is important to emphasize at the outset that symptoms of vasculitis commonly occur in other well-defined conditions such as rheumatoid arthritis, systemic lupus erythematosus, and some drug reactions.

BEHÇET'S SYNDROME

In 1937 Behçet, a dermatologist in Istanbul, described a triad of oral and genital ulceration and inflammatory eye lesions (Behçet, 1937). At the time he remarked on the features that this clinical picture shared with other disease entities, and suggested a viral aetiology. It is of interest to note that the diagnosis remains a clinical one, and that much current research is aimed at elucidating the possible role of viruses in its causation.

Diagnostic Criteria

The commonly followed diagnostic criteria base the diagnosis on the presence of a combination of 'major' and 'minor' findings (Mason and Barnes, 1969).

Major findings are:

(1) Buccal ulceration
(2) Genital ulceration
(3) Non-ulcerative skin lesions
(4) Eye lesions

Minor findings are:

(1) Arthritis
(2) Thrombophlebitis
(3) Cardiovascular disease
(4) Gastrointestinal disease
(5) Central nervous system disease
(6) Epididymitis (*see below*)
(7) Renal disease

Mason and Barnes suggested that the syndrome be diagnosed if 3 major, or 2 major plus 2 minor findings are present. There are other systems of diagnostic criteria, but they are fundamentally in agreement with the above (O'Duffy, 1974). Current descriptions of the disease tend, however, to be dominated by Japanese criteria, in view of the high prevalence in Japan (Behçet's Disease Research Committee of Japan, 1974). These criteria are similar to those of Mason and Barnes as regards major findings, but recognize epididymitis as an additional minor finding. From his own experience with patients from Europe and the Middle East, the author is in complete agreement with the Japanese in this regard.

The Japanese classify the disease into 4 types:

1. *Complete Type.* All major findings occur at some time in the disease.
2. *Incomplete Type.* Three major findings occur, or uveitis occurs in association with one other major finding.
3. *Suspect Type.* Two major findings occur.
4. *Possible Type.* One major finding occurs.

In Great Britain and America the diagnosis is not made in the absence of recurrent oral ulceration.

Epidemiology

The disease affects both sexes, most commonly in the third and fourth decades, although there is often a long antecedent history of recurrent

oral aphthous ulceration. In both Britain and Japan men outnumber women when the eyes are involved (Dinning, 1979; Ohno, 1982). Overall, however, the male preponderance observed in Japan for the syndrome in general has disappeared in the past decade (Maeda et al., 1982). Japanese authors are convinced that the incidence of the disease has increased in the last thirty years. It is rare in western Europe and America, but occurs more frequently in the countries around the eastern Mediterranean Sea. In Britain the incidence is approximately 0·5 per 100 000. In Japan the incidence is by far the highest in the world, increasing from south to north, where it is 7·0 to 8·5 per 100 000.

A strong association with the possession of HLA B5 histocompatibility antigen is noted in Japanese patients (Ohno et al., 1973), and in particular with the Bw51 split (Ohno et al., 1978). The latter is also true of Turkish and British patients (Yazici, Chamberlain et al., 1980). In British patients arthritic symptoms appear to be associated with HLA B27 (Lehner and Batchelor, 1979).

One Turkish study found that Behçet's syndrome occurred in 4·3% of the relatives of patients (Dilsen et al., 1982), but the same study failed to show any increase above normal of recurrent oral ulceration in relatives (recurrent oral ulceration occurred in 29·2% of controls).

Clinical Features

It is important to be aware that the reported incidence of different disease features is greatly influenced by the type of clinic from which reports emanate. For example, patients attending rheumatology clinics will present with a different spectrum of features from those attending ophthalmology clinics.

The immediate morbidity of Behçet's syndrome is principally related to the ocular disease, but there is an appreciable mortality from the so-called 'minor' features. Death may occur from the rupture of aneurysms and intestinal ulcers or from central nervous system disease, and has also been reported from the complications of corticosteroid and cytotoxic therapy.

A Major Findings

1 Recurrent Oral Ulceration

Ulcers occur singly or in crops, especially inside the lips, on the tongue or the buccal mucosa, but sometimes also on the palate and fauces. They may occur so frequently and be so severe as almost to incapacitate the patient, but they may also occur only a few times a year and

pass practically unnoticed. They are usually quite painful. They are shallow and yellowish, and vary from a few millimetres across to 10 mm or more. They tend to heal within 10 days and leave varying degrees of scarring, but their sites are often difficult to detect once they are healed. There are no clinical or pathological features by which these ulcers may be characterized. (*Figs.* 50–52.)

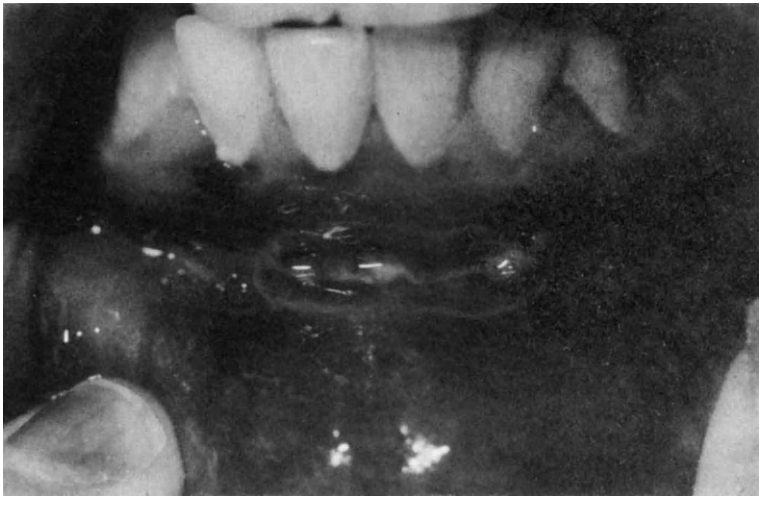


Figure 50 Behçet's syndrome: mouth ulcers.
(Dr Michael Denman.)

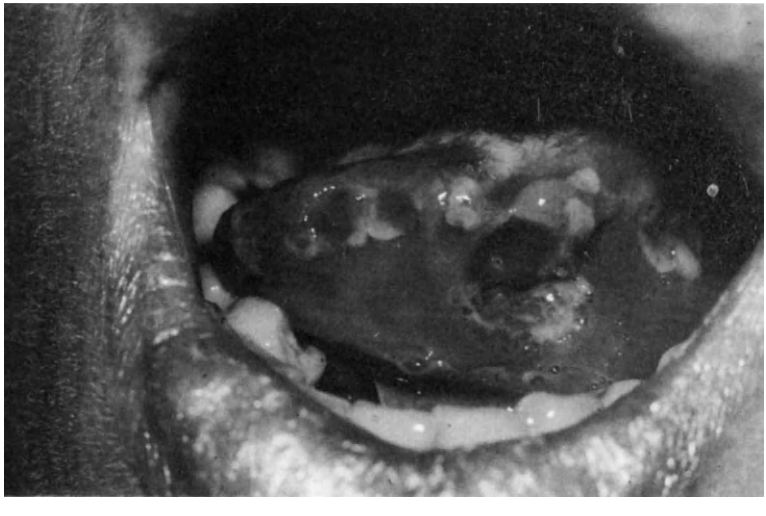


Figure 51 Behçet's syndrome: mouth ulcers.
(Dr Michael Denman.)

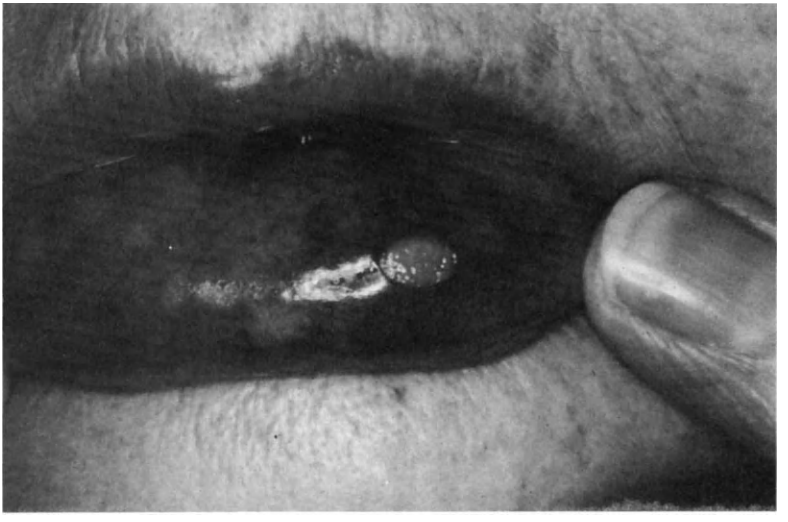


Figure 52 Behçet's syndrome: mouth ulcers. (Dr Colin Barnes.)

Recurrent oral ulcers are very common in the general population and this finding is not such a reliable guide to the diagnosis as the casual reader may be led to imagine.

2 Genital Ulcers

These also tend to occur in a recurrent pattern. They particularly involve the scrotum and vulva, but may be found on the penis, vagina and around the anus. They run a course similar to the oral ulcers, but are deeper and heal with more obvious scarring. More than two-thirds of patients suffer from them. (*Fig.* 53.)

3 Other Skin Lesions

About two-thirds of patients have other skin disease, such as typical erythema nodosum, folliculitis and acneiform lesions, and superficial thrombophlebitis.

In Turkey a great deal of weight is given to the so-called 'pathergy' reaction of the skin in making the diagnosis (Yazici, Tüzün et al., 1980). A positive reaction takes the form of marked redness and swelling at the site of a skin prick or intradermal injection of saline, which develops within 48 hours. In Britain this has not been found a useful test (Davies et al., 1984).

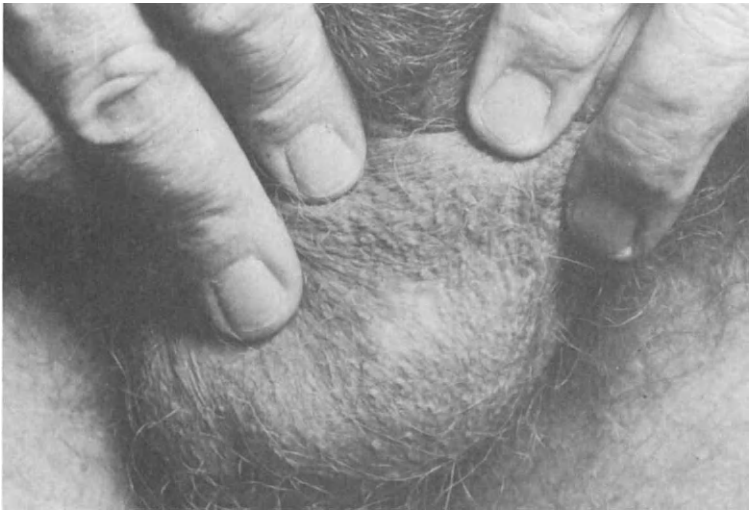


Figure 53 Behçet's syndrome: healing scrotal ulcers. (Dr Colin Barnes.)

4 Ocular Lesions

The presenting ocular symptoms may be the result of an anterior uveitis, posterior segment disease, or panuveitis. Recurrent conjunctivitis is also described, but it is not a serious problem.

The classic picture is that of severe, recurrent, bilateral anterior uveitis with hypopyon (*see Fig.* 18) progressing to extensive synechia formation, pupil occlusion, cataract and glaucoma. In fact, fewer than a third of patients with eye disease ever have hypopyon. In Western countries very few patients are seen without some evidence of posterior segment disease (*Figs.*54, 55). This may reflect the pattern of referral of a rare disease to central clinics, but it is in marked contrast to Japan, where as many as 22% of all cases of uveitis are due to Behçet's syndrome (Fujiwara and Furutani, 1977). Japanese writers divide ocular disease into an iridocyclitis type, and a uveoretinitis type (Mimura et al, 1983), the former having a good prognosis and responding well to local therapy.

The essential feature of the posterior segment disease is progressive obliterative vasculitis which is first clinically detectable in the veins. This may progress by an insidious process of capillary closure in the periphery (*see Fig.* 35). Striking circumferential venous communications may be seen linking adjacent radial venous trunks in the periphery, coursing across large areas of poorly perfused retina. New

vessel formation is seen in fewer than 20% of patients. Small, repeated vitreous haemorrhages are common, and accompany focal retinal inflammation. These foci represent retinitis and focal microscopic vasculitis. The marked venous changes are complicated by sudden occlusion of a branch of a retinal vein in a significant proportion of patients (Bonamour et al., 1972).

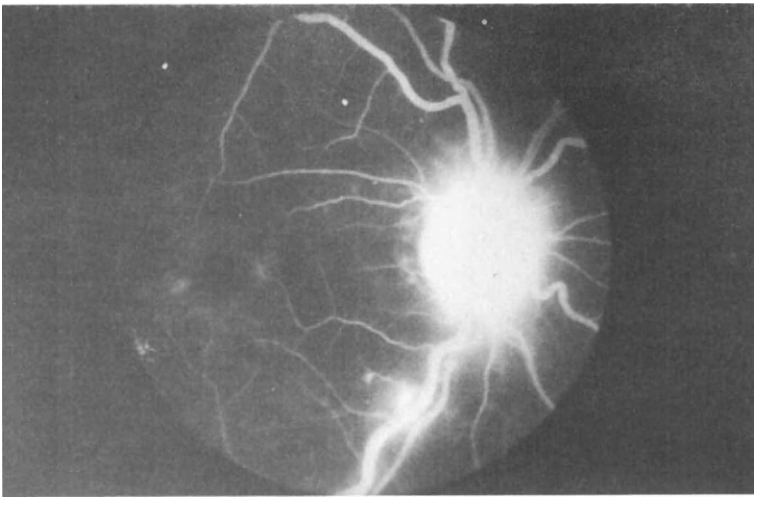


Figure 54 Behçet's syndrome: fluorescein leakage from optic disc, veins and macular region.

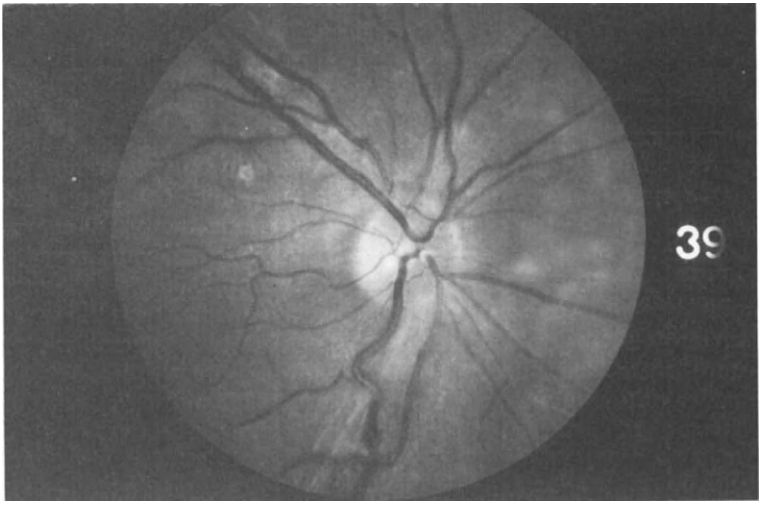


Figure 55 Behçet's syndrome: tortuous retinal veins.

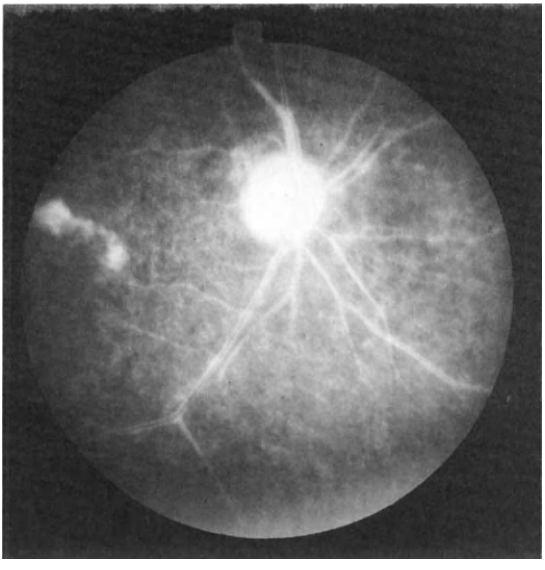


Figure 56 Behçet's syndrome: terminal atrophy of retina and optic nerve. Note avascularity.

However, the most devastating change is due to arterial occlusion leading to large areas of retinal infarction. This is accompanied by intense vitritis. When the vitreous opacity clears, areas of retinal oedema and haemorrhage are seen. In time the oedema resolves and leaves behind large areas of atrophic retina with occluded vessels seen as thin white lines. As the retina is progressively destroyed optic atrophy becomes more apparent (*Fig.* 56). The optic nerve itself may be involved primarily in the process of inflammation and vaso-occlusion.

B Minor Findings

1 Arthritis

Joint symptoms occur in about 60% of patients. The large joints are asymmetrically involved, especially the knees. Synovial biopsy shows signs of acute inflammation, but erosive changes do not occur.

2 and 3 Thrombophlebitis and Cardiovascular Disease

Subcutaneous thrombophlebitis with typical tenderness and swelling is seen in 10–20% of patients, but fewer than 5% of all patients develop

major vessel disease (Urayama et al., 1982). Death may result from the sequelae of large vessel occlusion, particularly of cerebral or limb arteries, and also from the rupture of aneurysms. It is believed that vasculitis of the vasa vasorum of large arteries is the underlying mechanism. Occlusion of large veins such as the superior vena cava may also occur and poses a threat to life (*Fig.* 57). Myocardial disease itself is rare.

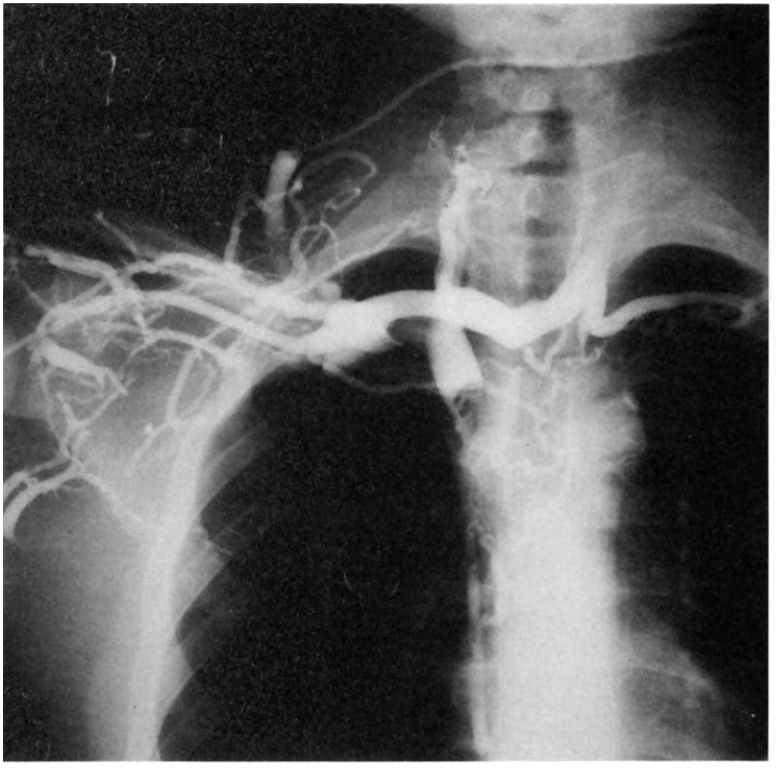


Figure 57 Behçet's syndrome: superior vena caval obstruction.

4 Gastrointestinal Disease

As many as 50% of patients may have mild symptoms of gastrointestinal disease, such as abdominal pain, diarrhoea or constipation. Ulcerative lesions probably occur in fewer than 5% of patients. They tend to involve the terminal ileum and caecum, and may perforate (Baba and Morioka, 1982).

5 Central Nervous System Disease

The brain and spinal cord are sites of potentially fatal disease. All varieties of motor, sensory and neuropsychiatric symptoms have been described, occurring independently or in combination. The commonest complaints are headache, memory impairment and mood changes. Hyperreflexia is often found on examination. The multiplicity and global nature of these symptoms reflects the wide scatter of the lesions, but they tend to be more marked in the brain stem. Occlusion of larger cerebral vessels may lead to hemiplegia. Cerebral or spinal meningitis is not uncommon, and pleocytosis in the cerebrospinal fluid may be the clue to subclinical central nervous system involvement.

Episodes of CNS disease tend to be few and infrequent in individual patients, in contrast to multiple sclerosis. They may thus leave well-localized and unilateral signs.

NMR scans are showing that CNS involvement is much commoner than previously thought, and definite patterns of cerebral change are likely to emerge from current studies.

6 Epididymitis

Epididymitis occurs in a small but significant proportion of men.

7 Renal Disease

Mild signs of renal disease have been described in only a few patients.

Course and Prognosis

The recurrent oral lesions are almost always the first to appear, and they may continue for life. More severe attacks of ulceration may accompany signs of disease exacerbation elsewhere, for example in the eyes or joints, but this is not necessarily so. As time passes additional symptoms may be added to the clinical picture and these also show a variable fluctuation in severity. Without treatment it is unusual for signs of inflammation to subside completely between exacerbations, and a progressive deterioration of function is the result. Over a period of 5–10 years a decrease in the frequency of attacks is often seen. Unfortunately in the eye this is commonly paralleled by complete functional destruction. Inflammatory signs may disappear altogether from eyes with total retinal and optic atrophy. On the other hand there are cases in which a blind eye repeatedly suffers such severe and painful inflammation as to warrant enucleation. Although changes in treatment may have led to an improvement in visual prognosis, about half

the patients with eye disease are blind within five years of the onset of visual symptoms. Nevertheless, the severity of eye disease is quite variable and many patients are notable exceptions to the above statement. In addition, gross asymmetry in the severity of disease in the two eyes is common and excellent sight may be preserved in one eye for ten years or more after the other is completely blind.

Death may occur from rupture of an aneurysm, bulbar palsy, arterial occlusion or perforation of an intestinal ulcer. Patients may present with these grave findings. Venous occlusion is not so serious because recanalization and collateral channels develop.

At the time of diagnosis there is no reliable way of predicting the course, or how the disease will respond to treatment in the long term.

Death from treatment is well documented. The risks of therapy must be outlined to the patient. One patient died from Gram-negative septicaemia while taking high doses of corticosteroids (Chamberlain, 1977) and several deaths from acute leukaemia have been reported in patients taking immunosuppressive drugs for ocular involvement (Bonnet, 1982; Palmer et al., 1984).

Pathology and Immunology

The microscopic pathology is similar in all tissues examined. There is perivascular infiltration with lymphocytes, plasma cells, polymorphs and macrophages, and associated thrombosis in the vessels.

In the oral mucosa the earliest lesion is infiltration of the epithelium with lymphocytes and monocytes, and some proliferation of vascular endothelium (Lehner, 1969). At the stage of actual ulceration the ulcer base is infiltrated with polymorphs and there is a deeper infiltration with lymphocytes (Mamo and Baghdassarian, 1964). Neighbouring vessels show perivascular infiltration with lymphocytes and plasma cells, and capillaries, venules and arterioles are all affected (O'Duffy et al., 1971).

Some workers have reported that cellular infiltration is more marked around the veins in mucocutaneous lesions (France et al., 1951), and around capillaries and venules in the smaller lesions in the brain (Totsuka et al., 1982). Pathological studies on cases of neurological disease show lymphocytic meningeal infiltration and disseminated foci of perivascular lymphocytic and histiocytic infiltration, with multiple small areas of softening, especially in the white matter of the brain stem, and less frequently in the spinal cord, cerebrum and cerebellum (McMenemy and Lawrence, 1957; Totsuka et al., 1982). Thrombotic cerebral arteritis may cause large areas of cerebral infarction. It is suspected that in the larger cerebral vessels and similar vessels elsewhere the process commences as inflammation of the vasa vasorum.

Similar pathology is seen in gastrointestinal ulcers. Some workers believe that ulceration is secondary to obliterative arteritis and phlebitis in the gut wall (Baba and Morioka, 1982) while others believe that the vascular changes are secondary to the ulcerative inflammation (Fukuda et al., 1980).

Pathological examination of enucleated eyes usually adds little to what can be inferred from clinical observation because most specimens represent end stage disease. In a few cases of early disease sparse round cell infiltration has been described in the retina, choroid and anterior chamber angle, and later histiocytic infiltration around retinal vessels (Shikano, 1966).

In a few cases in which such parameters have been studied, raised plasma fibrinogen levels, diminished fibrinolysis and hypercoagulability of the blood have been found in the active phase of the disease.

The observed abnormalities in many parameters of immunological function have led to the proposal that Behçet's syndrome has an immunogenetic basis. Despite this it is not possible to construct a scheme of pathological events to account for the disease manifestations. Attempts to construct a comprehensive aetiopathological model from data gathered from many sources are inhibited by the fact that the stage or activity of the disease may have a profound effect on laboratory results, and also because many different tests of doubtful comparability are being used to evaluate the same parameters in different laboratories.

During active disease the ESR and serum levels of IgG, IgM and IgA are all raised. There is usually a marked neutrophil leucocytosis. Circulating immune complexes are found in about 60% of patients (Levinsky and Lehner, 1978). In quiescent phases, whether spontaneous or induced by treatment, these findings revert towards normal, sometimes completely. Immune complexes are mainly of the IgG type and are found more commonly when there is associated joint disease (Hashimoto et al., 1982).

The finding of antibodies against human oral mucosa (Shimizu et al., 1965; Lehner, 1967) indicates an autoimmune element in pathogenesis.

It is generally accepted that neutrophil chemotaxis is increased (Matsumura and Mizushima, 1975; Fordham et al., 1982). This is the basis for the popularity of colchicine therapy in Japan. It has not yet been determined beyond doubt that the reason for the alteration in leucocyte behaviour does not reside in the serum, and the subject is still a matter of dispute. Abdalla and Lehner found that polymorphs from patients with Behçet's syndrome (and, to a less extent, those from people who suffer simply from recurrent oral ulceration) show a *depressed* response to chemotactic stimuli (Abdalla and Lehner, 1979). They postulate that cold-precipitable IgA immune complexes, which

they have demonstrated, may block the chemotactic receptors on polymorphs. The resultant reduction of polymorph migration may then lead to reduced phagocytosis of IgG immune complexes, the persistence of which may lead to tissue damage. Defective polymorph phagocytosis has been demonstrated in patients with Behçet's syndrome (Wilton and Lehner, 1979) but this is not necessarily due to the mechanism proposed above.

The results of many studies of cellular immunity are quite ambiguous, but in one study in which care was taken to correlate the findings with the activity of the disease it was found that suppressor T-cell activity was reduced immediately before a flare-up of disease, but not during the flare-up or in quiescent periods (Sakane et al., 1982).

Treatment

Mild Disease

Patients with mild disease are often adequately managed simply by local treatment of the oral ulcers with preparations such as hydrocortisone in Orabase (Squibb) (carmellose sodium). Minor episodes of phlebitis, arthritis or orchitis may not need specific treatment. However, mouth ulcers may be disablingly severe, but usually respond well to systemic corticosteroid treatment in modest doses. Non-steroidal anti-inflammatory drugs may be useful in managing joint symptoms.

Ocular and CNS Disease

When intraocular or central nervous system disease is present aggressive treatment with systemic corticosteroids and immunosuppressives is indicated. If ocular disease is the only serious manifestation of the syndrome it may be possible to manage the acute episode with locally applied steroids and mydriatics (including orbital depot steroid injections) while establishing an immunosuppressive regime. In this way the patient may be spared the added burden of systemic steroid therapy. Although one can expect to wait up to three months for the usual immunosuppressive regimes to take effect in reducing the frequency and severity of attacks of ocular inflammation, patients usually experience amelioration of ulcerative symptoms within a few weeks.

Steroids and immunosuppressives are usually also used in patients with major thrombotic disease, but it is by no means clear to what degree this is due to inflammation or to blood flow and coagulation disorders *per se*. Various fibrinolytic and anticoagulant regimes are therefore also used in this situation.

There are no masked trials of alternative treatment regimes in this

disease and the natural history of untreated disease is not recorded in any but a few cases described in the years following the description of the disease.

Until the 1970s systemic corticosteroid therapy was the only treatment which appeared to ameliorate the disease. There is general agreement that high doses of corticosteroids will dampen acute inflammatory episodes but will not prevent their recurrence, or obviously influence the progressively worsening course of the disease. (Indeed, Japanese workers now believe that treatment with high doses of systemic steroids makes the prognosis worse (Mimura, 1982) but the data presented do not entirely justify this conclusion. The assertion that any particular manipulation makes any disease worse cannot be made unless the natural history of untreated disease in a comparable population is known). This, together with the problems resulting from the long-term use of systemic steroids, led to the trial of cytotoxic drugs. Cytotoxic agents seem to be able to substitute in part for steroids, and it was felt that their immune-modifying effects might be helpful in a disease in which immunogenetic mechanisms were suspected. The very toxic drugs such as 6-mercaptopurine and methotrexate were quickly abandoned in favour of the nitrogen mustards cyclophosphamide (Martenet, 1981) and chlorambucil (Godfrey et al., 1974). Azathioprine was found to be ineffective (Martenet, 1976).

In clinical practice in Europe and America patients tend to be treated first with high doses of oral steroids, and cytotoxic drugs are added later. Steroid dose is then gradually reduced. However, it is often possible to manage patients with cytotoxic (immunosuppressive) treatment alone if local (e.g. ocular) complications can be managed by local treatment, as mentioned earlier. The suppressant effects of these drugs only appears after 2–3 months of therapy and flare-up of ocular disease is not uncommon in this early period. Failure to appreciate this has led in the past to patients being taken off treatment after only a few weeks in the mistaken belief that a flare-up of disease in the early stage signified treatment failure.

For the purpose of prolonged immunosuppression it is difficult to choose between chlorambucil (starting dose 0·1–0·15 mg/kg/day) and cyclophosphamide (starting dose 1·5–2·0 mg/kg/day) on the grounds of clinical response or danger from side effects. Therapy is continued for one to two years and the patient must be closely observed for side effects. (For a full discussion of the use of these drugs in uveitis *see* Dinning, 1986.) Patients treated with these drugs must accept the likelihood of sterility, especially men. The side effects of chlorambucil appear to have been studied more thoroughly than those of cyclophosphamide. Continuous chlorambucil therapy causes cumulative chromosomal damage in man (Palmer et al., 1984). It has long been known that the damage persists after the drug is withdrawn (Lawler and Lele,

1972; Reeves et al., 1985). It is reasonable to presume that this effect is related to the induction of malignancy. Indefinite continuous or intermittent therapy with these agents is therefore out of the question when they are given for non-life-threatening conditions. Deaths from acute leukaemia are well documented in patients taking nitrogen mustards for non-malignant conditions.

The foregoing comments may well be rendered superfluous by the impact of the cyclosporins in the management of Behçet's syndrome. The initial experience with cyclosporin-A is encouraging (Nussenblatt et al., 1983) and the results of masked randomized trials are eagerly awaited. However, there are many complications of therapy with this drug, the most worrying being interstitial renal fibrosis (Myers et al., 1984). It may be that if used in much lower doses than those used to date (for example, 4 mg/kg/day), in combination with modest doses of corticosteroids, these effects may be avoided without loss of the beneficial effects. Like the cytotoxic agents, it can only be used in centres where meticulous clinical surveillance is possible. It has also proved very difficult to stop therapy without provoking relapse of eye disease (Graham et al., 1985). New cyclosporins are in development, and it is hoped that they may have fewer side effects.

Until the important question as to whether cyclosporin-associated renal damage is progressive or not can be settled, the author believes that the most reasonable treatment for severe ocular disease is chlorambucil. One can expect to achieve relief from the frequent episodes of retinal vasculitis for up to four to five years after the first 3 months of an 18-month course. Inflammation does tend to break out again, and it is not feasible to contemplate more than two courses of such toxic therapy. Despite quiescence of the eye disease, there may be a slowly progressive closure of the retinal capillary bed. Many patients, despite well-preserved visual acuity, develop gross peripheral retinal ischaemia over many years.

Other Treatments

In Japan there is much enthusiasm for the use of colchicine in low doses (1–2 mg/day). It was found to be as effective as cyclophosphamide in an open study (Hijakata and Masuda, 1978). In Turkey a double-blind study failed to show any beneficial effect in eye disease but suggested that it might be useful in arthralgia and erythema nodosum (Aktulga et al., 1980).

In very severe episodes patients may be managed by plasmapheresis, antilymphocytic globulin and intravenous pulses of methylprednisolone in the initial 1–2 week period, after which a programme of prolonged immunosuppression is established, as previously discussed.

Aetiology

Behçet himself suggested that the disease might be caused by a virus. There have been sporadic reports of virus isolation from patients, but these have never been confirmed. The impossibility of pathological differentiation between the oral ulcers of Behçet's syndrome and the common aphthous ulcers of unaffected persons, and the increased incidence of herpetiform buccal ulceration in Behçet's syndrome has kept alive the notion that Behçet's syndrome might be a severe manifestation in predisposed individuals to an otherwise trivial viral infection which is known to persist once it is established. There is evidence that lymphocytes of patients may be persistently infected with virus in that they do not support the growth of Herpes simplex virus as do normal cells (Denman et al., 1980). This is associated with chromosomal alterations which could be virus-induced. More recently, greater hybridization of Herpes simplex virus I DNA and the complementary RNA in mononuclear cells has been found in Behçet's syndrome, suggesting that at least part of the HSV I genome may be present and transcribed in peripheral blood mononuclear cells from patients, especially those with ocular and arthritic disease (Eglin et al., 1982). Thus the possibility of a viral aetiology is still very much alive.

POLYARTERITIS NODOSA

Many of the vasculitic diseases now recognized as distinct clinical entities have been extracted over a period of time from a body of conditions grouped under this heading. Although further subgroups will undoubtedly continue to be separated from it as powers of discrimination improve, the term 'polyarteritis (or periarteritis) nodosa' is now given to a disease picture which is itself reasonably well defined by clinical and pathological criteria. Confusion may still result from the fact that the typical clinical findings of polyarteritis nodosa may occur in collagen diseases such as rheumatoid arthritis and systemic lupus erythematosus.

Clinical Features

Polyarteritis nodosa may occur at any age, but principally affects people in the fifth and sixth decades, men twice as commonly as women.

The degree of dissemination of the arteritic lesions is very variable and so presentation may be with signs and symptoms of involvement of a particular organ system, such as renal disease, polyneuritis or

myocardial infarction, or alternatively with indications of diffuse disease such as fever, weight loss, muscle pains and anaemia.

The most serious aspect of the disease is renal polyarteritis. This gives rise to glomerulitis and secondary hypertension which is itself a major cause of death. Other patients die from infarction in other organs such as the heart. Coronary artery disease is particularly common in children.

Recurrent abdominal pain is an important presenting symptom. Gastrointestinal lesions may lead to ulceration or perforation of the bowel.

Muscle and joint pain is common. Nervous system disease becomes manifest late in the course. Involvement of the vasa nervorum produces multiple mononeuropathy.

Purpura, urticarial lesions and subcutaneous nodules are often seen, and biopsy of a nodule may assist in the diagnosis.

Ocular Disease

Fundus changes of hypertension are common. A proportion of patients show signs of vaso-occlusive disease such as central retinal artery occlusion (Schroeder et al., 1976; Solomon and Solomon, 1978). Optic atrophy may result from vaso-occlusive disease in the ciliary vessels, central retinal vessels or the vessels of the optic nerve. Direct signs of inflammation are rarely seen in the eyes, but uveitis is described, both with and without retinal vasculitis (Sheehan et al., 1958). Transient focal retinal detachments have been seen (Herson and Sampson, 1949) and exudative retinal detachment is reported in the presence of non-granulomatous uveitis and granulomatous scleritis (Kielar, 1976). Recently immune complexes have been demonstrated within small and medium-sized arterioles in avascular conjunctival lesions (Purcell et al., 1984). Aneurysms of retinal vessels are rare. (*Figs.* 58, 59.)

Laboratory Investigations

Anaemia and polymorphonuclear leucocytosis are usually present. Eosinophilia is common, especially when there is pulmonary disease. Many patients have raised ESR and levels of plasma immunoglobulins. However, as with giant cell arteritis (q.v.) the ESR may be normal. Renal and hepatic angiography reveals multiple arterial aneurysms. Tissue biopsy shows the typical histopathological features described *below*. Biopsy of the appropriate organs is performed on suspicion of significant disease. The results are crucial to therapy and prognosis.

Biopsy of the liver and kidney carries a greater risk of bleeding than usual, because of the aneurysms. Unfortunately biopsy of tender muscle is often negative. As with sarcoidosis, biopsy of clinically uninvolved tissue is unhelpful.

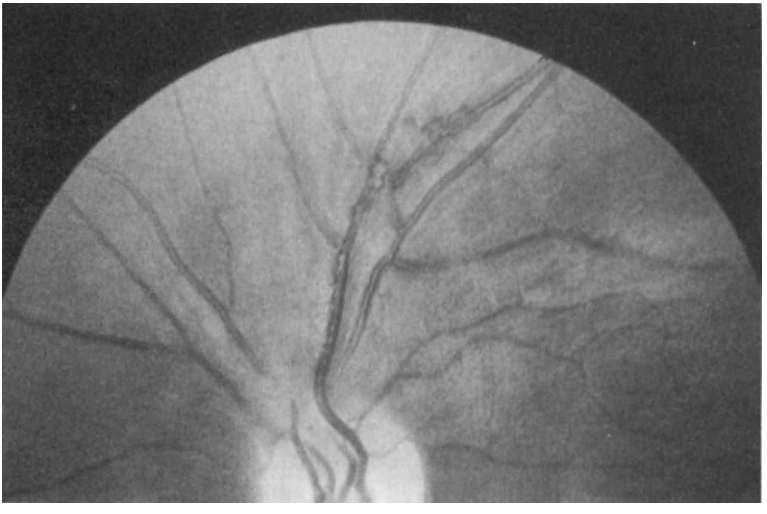


Figure 58 Polyarteritis nodosa: retinal vascular disease.

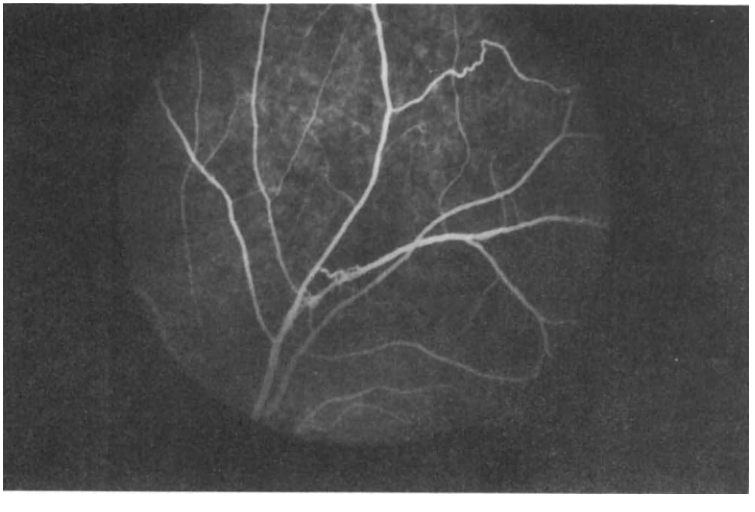


Figure 59 Polyarteritis nodosa: retinal vascular disease (retinal angiogram).

Histopathology

Small and medium-sized muscular arteries show necrosis of the media with fibrinoid change, especially at sites of branching or bifurcation. The initial infiltration is by neutrophils and eosinophils, but later macrophages and fibroblasts are seen. Giant cells are absent. Thrombosis occurs in the involved vessels and granulation tissue replaces the areas of fibrinoid necrosis. The vessel intima proliferates and is replaced by scar tissue. In addition there is periarterial fibrosis. The obstruction of local blood flow leads to progressive distal infarction. Destruction of the media and elastic tissue in the vessel walls leads to aneurysmal dilatation in the healing stages. Subcutaneous aneurysms may be palpable. Lesions are found in all stages of evolution. Acute vascular accidents may therefore occur at any time, from infarction, or from haemorrhage from an aneurysm.

In the eye, retinal vascular changes may be absent altogether (*but see* Kielar, 1976, whose case showed widespread perivasculitis in the eye involving intrascleral, iris, ciliary body and retinal vessels). The choroidal vessels appear to bear the brunt of inflammation in most reported cases and show grossly thickened, hyalinized walls with fibrinoid changes and endothelial proliferation, accompanied by lymphocytic and mononuclear cell infiltration (Goldstein and Wexler, 1929; Goldsmith, 1946).

Aetiology

The cause is unknown. Reference to the suggestion that a particular disease may represent an abnormal immunological response to a virus or viral component will be found in other places in this chapter. There is actually some evidence that this might be true of polyarteritis nodosa. Gocke and coworkers found that 4 of 11 biopsy-proven cases of polyarteritis nodosa had liver involvement, and 3 of these patients had circulating immune complexes containing hepatitis-B antigen. They also had hepatitis-B antigen, IgM and complement localized to the sites of tissue damage (Gocke et al., 1970). Other studies have confirmed this observation (Michalak, 1978). Immune complexes seem to have a primary role in causing acute vascular damage in this disease. However enthusiasm for hepatitis-B antigen as the trigger for the vasculitis does not run high. Although patients with polyarteritis nodosa and hepatitis-B antigen-antibody complexes do have evidence of liver disease, many patients with chronic hepatitis have such complexes in their vessel walls and do not have vasculitis. Christian and Sergent discuss the possible role of viral infection in vasculitis syndromes and draw the analogy between the human disease and equine viral arteritis (Christian and Sergent, 1976).

Treatment

It has been customary to begin treatment with moderate to high doses of oral prednisolone (60–100 mg/day for an adult). This is gradually reduced as the disease comes under control, but may need to be continued indefinitely. It is not clear whether or not steroids influence survival because there is evidence of progression of the pathological process despite control of acute symptoms (Report to the Medical Research Council by the Collagen Diseases and Hypersensitivity Panel, 1960). Many cases do not even respond in the short term to steroids. In these patients the use of cytotoxic agents in combination with steroids has brought about a dramatic improvement (Lieb et al., 1979). Azathioprine and cyclophosphamide have both been used but cyclophosphamide (1–2 mg/kg/day) combined with prednisolone is currently the regime of choice (Fauci et al., 1978; Scott et al., 1982). The most remarkable effect of such therapy is the resolution of all the aneurysms seen on pretreatment angiography.

Prognosis

Those patients with disease confined to skin and muscle arteries have always had a reasonable prognosis, but the prognosis for patients with more generalized disease was very poor. More than half of untreated patients died within 9 months of diagnosis but corticosteroids improved short-term survival (Report to the Medical Research Council by the Collagen Diseases and Hypersensitivity Panel, 1960). The combined use of cytotoxic drugs with steroids has changed the prognosis altogether, and the 5-year survival with combined therapy has been estimated at 80% (Lieb et al., 1979). Another undoubtedly important influence on prognosis is the care with which associated hypertension is controlled.

WEGENER'S GRANULOMATOSIS

This disease was first described by Klinger, who regarded it as a variant of polyarteritis nodosa (Klinger, 1931). A few years later Wegener described 5 cases and suggested that they represented a definite clinical entity (Wegener, 1936).

Clinical Features

The criteria for diagnosis are those laid down by Godman and Churg (1954):

1. Necrotizing granulomatous lesions in the upper or lower respiratory tract, or both.
2. Generalized focal necrotizing vasculitis involving arteries and veins, almost always in the lungs, and widely disseminated in other sites.
3. Glomerulitis characterized by necrosis and thrombosis of loops or lobes of the capillary tufts, capsular adhesions, and evolution as a granulomatous lesion.

Patients usually present in the fourth and fifth decades, and men outnumber women 3 to 2. Almost all patients have facial pain and nasal discharge. Most have fever and weight loss. Lower respiratory tract disease may be asymptomatic, but cough and chest pain are common, and haemoptysis may occur. Eustachian tube blockage is followed by otitis media. About 50% of patients have arthralgia. There may be signs of ocular disease at presentation.

The upper respiratory tract disease progresses to nasal ulceration and septal infarction but the palate is rarely involved and destruction of surface tissues does not occur. This is in contrast to malignant midline granuloma (*see below*).

Renal disease occurs in about 80% of patients, and once red cells and casts appear in the urine the disease is usually rapidly progressive. Unlike the renal disease of polyarteritis nodosa it does not usually give rise to hypertension.

Various signs of cutaneous vasculitis are common. This may take the form of purpura or petechial haemorrhages, papules, vesicles and ulcers, or nodules.

A proportion of patients develop cranial neuritis, mononeuritis multiplex, and signs of cerebral vasculitis.

Ocular Findings

About 40% of patients have ocular symptoms (Walton, 1958; Fauci and Wolff, 1973).

The orbit may be involved in contiguity with disease in the upper respiratory tract, resulting in painful proptosis, lid oedema, conjunctival chemosis, restriction of eye movement, and retinal venous congestion. Such events are usually unilateral. A recent review of the Mayo Clinic experience with Wegener's granulomatosis draws attention to the fact that orbital disease may have an explosive onset (Liesegang et al., 1983).

Involvement of the tissues of the eye itself also occurs, with or without orbital disease. The commonest ocular complaint is a non-specific conjunctivitis (Straatsma, 1957; Liesegang et al., 1983), often with subconjunctival haemorrhages. Next in frequency is episcleritis and scleritis (diffuse, nodular or necrotizing) and this frequently

correlates in severity with the severity of systemic signs and symptoms. Peripheral corneal disease with infiltration, ulceration and sometimes perforation also occurs, and scleritis may accompany this.

Visual loss can occur from optic nerve ischaemia in association with compressive inflammatory orbital disease, but isolated cases of optic nerve ischaemia have been reported as a result of ciliary vessel and vasa nervorum vasculitis, or retinal artery thrombosis.

Intraocular disease is rare. Occasional reports occur of retinal artery narrowing and cottonwool spots in the absence of hypertension (Straatsma, 1957), venous tortuosity, choroidal thickening and folding, and cystic macular oedema (Liesegang et al., 1983), and anterior or posterior uveitis or choroidoretinitis (Coutu et al., 1975; Liesegang et al., 1983) which in one case was complicated by neovascular glaucoma. In one series of 18 patients with severe renal disease a surprisingly high incidence of ocular findings was reported. Seven had conjunctivitis, 8 had episcleritis, 10 had retinal vasculitis and 2 had panuveitis (Pinching et al., 1983).

Clinical and Laboratory Investigation

There are no specific biochemical tests. Most patients have anaemia and leucocytosis and an ESR of greater than 100 mm in the first hour. Elevated levels of immunoglobulins and rheumatoid factor tend to be correlated with the severity of renal involvement. Antinuclear antibodies and LE cells are not found.

An association has been found with HLA B-8 (Katz et al., 1979) but there are no clinical characteristics which enable a distinction to be made between HLA B-8-positive and negative patients, and Wegener's granulomatosis has not been reported in relatives.

Blood, protein and casts are found in the urine.

Chest X-ray findings may be minimal, but there are commonly multiple nodules or cavitating infiltrates in both lung fields, and sometimes signs of destruction of large areas of lung, such as masses and bronchopulmonary fistulae.

Biopsy of affected tissue shows the characteristic changes described below.

Histopathology

Diseased tissue in the upper respiratory tract, orbit, lung or kidney shows vasculitis of small arteries and veins with granuloma formation, thrombosis and necrosis. In the acute stages fibrinoid necrosis is seen in the vessel walls. Infiltration is first with neutrophils, which are

replaced by monocytes. Granulomas occur within the vessel walls as well as adjacent to and separate from them, and contain typical multinucleate giant cells. Renal biopsy shows focal and segmental glomerulonephritis, but *rarely* necrotizing vasculitis of renal arterioles, or granulomas. The renal lesion progresses rapidly to glomerular fibrosis and renal failure.

The pulmonary pathology has been interpreted as representing repeated waves of peripheral organization of the necrotic zones and subsequent extensions of necrosis into the fibrosed areas (Godman and Churg, 1954).

In any individual patient biopsies may show vascular lesions in all stages of evolution.

Differential Diagnosis

(1) Goodpasture's syndrome
(2) Churg–Strauss syndrome (allergic angiitis and granulomatosis)
(3) Lymphomatoid granulomatosis
(4) Malignant midline granuloma
(5) Polyarteritis nodosa

1 Goodpasture's Syndrome

This is a rapidly progressive glomerulonephritis with linear deposition of anti-basement membrane antibody along glomerular capillaries, often accompanied by the presence of antibodies against pulmonary alveolar basement membrane. Lung damage from the latter gives rise to haemoptysis. Renal biopsy may be the only way to make the distinction from Wegener's granulomatosis. Ocular disease does not occur.

2 Churg–Strauss Syndrome

In 1951 Churg and Strauss described 13 patients suffering from fever, severe asthma or other pulmonary symptoms, eosinophilia and symptoms of widespread vascular disease (Churg and Strauss, 1951).

Histological study shows inflammation of medium-sized muscular arteries, arterioles and venules with an intense infiltrate of eosinophils, which undergoes necrosis. There is fibrinoid necrosis of collagen and granulomatous proliferation of epithelioid and giant cells, granulomas being both related to the vessels and in extravascular sites. Biopsy of cutaneous nodules allows differentiation from the disease it most closely resembles, polyarteritis nodosa, by revealing the extravascular site of granuloma formation and the giant cells. The disease is very

rare. Ocular involvement has not been reported. The prognosis is better than for Wegener's granulomatosis or polyarteritis nodosa.

3 Lymphomatoid Granulomatosis

This rare condition differs from Wegener's granulomatosis in that the renal lesions consist of nodular interstitial infiltration with normal and atypical forms of lymphoid cells, rather than a glomerulonephritis (Liebow et al., 1972). A significant proportion of cases evolve into lymphomas and it is uncertain whether it is primarily a vasculitis or a lymphoma.

Bilateral retinitis with vitritis has been described in this condition (Haynes et al., 1977).

The conditions most likely to be confused with Wegener's granulomatosis are malignant midline granuloma and polyarteritis nodosa.

4 Malignant Midline Granuloma

Midline granuloma is a localized condition but has only recently been differentiated from Wegener's granulomatosis (Fauci et al., 1976). It only affects the upper respiratory tract and the eye is involved by spread of disease into the orbit. A similar local reaction may be seen when necrosis and granulomatous inflammation occur in relation to a midline nasopharyngeal neoplasm, and when fungal infection such as mucormycosis, blastomycosis or coccidioidomycosis causes extensive destruction.

Central facial structures are totally destroyed. A large open cavity may result, extending from the floor of the mouth to the base of the brain before the patient dies of systemic infection, haemorrhage or meningitis. Long-term remission has been achieved with high-dose local irradiation (Fauci et al., 1976), but no other treatment is of any use.

5 Polyarteritis Nodosa (q.v.)

The vasculitis of polyarteritis nodosa usually involves bifurcations of medium-sized muscular arteries, and necrotizing granulomatous reaction is not typically seen. Pulmonary vessels are only rarely involved. Renal disease in polyarteritis nodosa usually results in hypertension.

Aetiology

The cause remains a mystery. Involvement of the respiratory tract invites the hypothesis that the trigger is an inhaled allergen, but none

has been specifically implicated. It has also been suggested that the pathological changes result from a granulomatous reaction to immune complexes deposited in the tissue. The association with HLA-B8 indicates a possible autoimmune basis, since this histocompatibility antigen is found in association with some autoimmune diseases (Graves' disease and possibly SLE). There have been disappointingly few recent advances to take any of these ideas out of the realm of speculation.

Treatment

The response to corticosteroid therapy is unpredictable although sloughing of large areas of tissue is probably prevented (Blatt et al., 1959). Various cytotoxic drugs have been tried, but cyclophosphamide is clearly the drug of choice and has transformed the outlook for the patient (Novack and Pearson, 1971). It is given in a dose of 1–2 mg/kg/day and should be continued for at least a year. If there is severe ocular or central nervous system disease at presentation systemic corticosteroids are also indicated until the condition is brought under control. Less severe local ocular complications may respond to local steroid therapy.

Fulminating disease still has a high early mortality (Pinching et al., 1983). The best therapy in such cases may be a combination of high-dose corticosteroids or plasma exchange combined with cyclophosphamide (*Ibid.*)

Prognosis

The disease is rapidly fatal if untreated, one series reporting an average course of 5 months (Walton, 1958) and another an 82% death rate within one year of presentation (Fauci and Wolff, 1973). An encouraging prognosis can now be given with the treatment described above. Many cases have been reported of long-term remission which has continued after stopping treatment.

GIANT CELL ARTERITIS

Giant cell arteritis involves mainly medium and large muscular arteries, especially the branches of the carotid. The widespread nature of vessel involvement has long been recognized (Roux, 1954; Whitfield et al., 1963) but use of the words 'cranial' or 'temporal' arteritis persists because initial symptoms are commonly related to the scalp and temples.

Epidemiology

The disease is rare in people under 50 years of age. The mean age of onset is 70. Most series show that it is 2 to 4 times commoner in women than men. Although most patients are Caucasian it does affect people of all races.

The prevalence in the population over 50 years of age is now between 1 and 1·5 per 1000. It appears to have been rising, but this may be at least in part due to a better awareness of the diagnosis, particularly since the risk of blindness was fully appreciated. The annual incidence rises with age from 1·4 per 100 000 in the sixth decade to 29·6 per 100 000 in the eighth (Huston et al., 1978).

Clinical Features

The disease usually begins with systemic symptoms of fever, malaise, anorexia and weight loss, accompanied by a continuous temporal headache. The headache is severe, subject to momentary sharp exacerbations, and often radiates to the forehead or occiput. Paraesthesia on touching the scalp or combing the hair is common. The temporal arteries may be tender and palpably thickened, or completely pulseless and impalpable. In severe cases the skin in the area of distribution of the temporal artery blood supply may be reddened or even ulcerated.

It may present with visual loss, pains in limb muscles and jaws, arthritis, or signs of coronary or cerebral vascular disease or aortic aneurysm, but these are usually later developments. Facial artery ischaemia may produce pain on chewing and this symptom is very suggestive of the diagnosis.

A so-called 'occult' form of the disease occurs which presents with sudden blindness in an eye, without headache, vessel tenderness or constitutional symptoms. The ESR is high and temporal artery biopsy confirms the diagnosis. It may even be more common than classic disease (Cullen, 1967).

Ocular Disease

In selected series of cases ocular complications have been reported in well over 80% of patients (Whitfield et al., 1963) but the true prevalence is probably much lower. In the large retrospective study of Huston and coworkers 40% of patients had visual complaints of one sort or another, and almost 20% suffered permanent partial or complete visual loss (Huston et al., 1978).

Visual loss is usually sudden and permanent. Amaurosis fugax is the

exception rather than the rule (Whitfield, 1963; Cullen and Coliero, 1976). The commonest cause of visual loss is ischaemic optic neuropathy. Central retinal artery occlusion is less common. The two eyes may be affected simultaneously or the second eye may go blind within hours to days of the first. Delayed involvement of the second eye has even been reported in patients having appropriate treatment. Diplopia and ptosis are sometimes seen and cortical blindness is by no means rare.

Oedema of the optic disc, congestion of the disc vessels, and peripapillary haemorrhages may be seen in the acute phase, but within a few days the fundus looks unremarkable. Disc pallor develops later as the optic nerve atrophies. When the central retinal artery is occluded the whole fundus appears pale, except for the macula which is prominent and pink ('cherry red spot'). Retinal vessels are narrow and there may be signs of sluggish circulation in the form of 'cattle trucking' of blood columns. After a few days the retinal oedema clears and the circulation may not appear obviously abnormal. Once again, optic atrophy follows. Occlusion of a branch of the retinal artery results in partial loss of vision and a corresponding field defect, but central vision is usually significantly impaired if a temporal branch of the retinal artery is occluded.

Laboratory Findings

There is usually a mild normochromic, normocytic anaemia. Plasma IgG and fibrinogen levels are raised. The ESR is usually above 50 mm in the first hour, but it is well recognized that the ESR may be normal in biopsy-proven cases. No specific immunological abnormalities have been identified.

Pathology

Medium and large muscular arteries are affected by patchy inflammation. There are zones of infiltration with histiocytes, lymphocytes and giant cells in the media and intima, and the internal limiting membrane is destroyed (Fauchald et al., 1972). It has been postulated that the disease is due to a cell mediated immune response against the elastic tissue of the internal limiting membrane, but histological evidence has been presented that the initial lesion is degeneration of the smooth muscle cells of the media (Reinecke and Kuwabara, 1969). Reinecke and Kuwabara envisage the process as primary swelling and degeneration of smooth muscle cells, with mural inflammatory infiltration and thrombosis in the lumen. This phase is succeeded by one in which the

characteristic infiltration with histiocytes, lymphocytes and giant cells appears, the vessel walls thicken and the elastic fibres fragment, and intimal fibrosis appears. Finally there is a repair stage in which inflammatory cells disappear, intimal and medial fibrosis progresses, and thrombus becomes organized.

Intervening segments of affected vessels are normal. Thus, temporal artery biopsy may be negative, and it should be done wherever possible in areas where the vessel is tender or thickened, or in several sites.

Diagnosis

The diagnosis is a clinical one but it is supported by the findings of a high ESR and a positive artery biopsy. However, a negative biopsy and even a normal ESR do not exclude the diagnosis. It is essential to appreciate this and to be prepared to treat the patient solely on the basis of the clinical impression. On presentation, blood should be drawn for ESR, and temporal artery biopsy performed if possible, because a positive result will confirm the diagnosis. Treatment should be started immediately, without awaiting biopsy results. The diagnosis will be supported by the almost universal and rapid relief of symptoms.

Treatment

Prednisolone in doses of 40–80 mg/day should be continued until the patient is symptom-free and the ESR is returning towards normal. This may take a month or more, but in most patients the dose of steroids can be reduced after a few weeks and by two or three months a maintenance dose of about 10 mg/day can be established. This generally needs to be continued for two years, but many patients need maintenance treatment for much longer. Relapses are usually the result of too rapid reduction in steroid dose but they have been reported in patients taking quite high doses of steroids. Relapses have included the occurrence of ocular disease in previously uninvolved eyes.

In making adjustments to therapy one would in practice be guided more by the clinical well-being of patients once they had responded to treatment, rather than moderate abnormalities of the ESR. Only patients themselves can monitor the *disease*. There are, for example, no clinical signs of impending blindness in the asymptomatic patient. The arterial occlusion is effectively instantaneous. *Any* blurring of vision, or recurrence of headache or myalgia demands immediate attention from the physician. Patients can never truly be discharged.

There is no fast rule about how long to continue treatment. Graham and coworkers have reported the success of a regime they have used for

many years, which aims to tail off treatment after about six months (Graham et al., 1981). Once the initial attack has been controlled they reduce steroid dosage to the minimum needed to alleviate symptoms. They have very little delayed visual loss with this approach, using symptoms rather than ESR to monitor therapy levels. Clinicians should not pursue the goal of a 'normal' ESR by ever-increasing doses of steroids in these patients, who are in an age group especially at risk of osteoporosis.

Prognosis

The prognosis for untreated disease is poor, death occurring from coronary artery or aortic disease, or from cerebral disease.

Most patients respond well to treatment and remain well when treatment is eventually discontinued. Relapses can be expected in about 25% of patients, usually when treatment is being withdrawn (Fauchald et al., 1972; Huston et al., 1978). It is of interest that biopsies have shown that active arteritis can be found long after clinical recovery (Fauchald et al., 1972).

Treatment arrests transient amaurosis and some visual improvement may occur when visual loss has been incomplete. Total visual loss does not recover but prompt treatment almost always prevents the disease from involving the second eye.

Polymyalgia Rheumatica

The term 'polymyalgia rheumatica' is used in two ways. It is used to describe the symptoms of limb girdle muscle pain and stiffness. In this sense it occurs in almost 50% of patients suffering from giant cell arteritis (Huston et al., 1978). In the second place it is used to denote a syndrome in which the above symptoms occur with varying degrees of fever, weight loss and malaise in elderly Caucasians (as in giant cell arteritis) but in which muscle or arterial biopsies are normal. Although it is reasonable to preserve this second use of the term, it is impossible to regard the syndrome as entirely separate from giant cell arteritis. The relationship of the two conditions is fully discussed by Healey and Wilske (1978).

As with giant cell arteritis, the annual incidence increases with age and is about 1/1000 in the eighth decade (Chuang et al., 1982). The ESR is usually markedly raised but there are no pathological or electromyographical changes. About 15% of patients eventually develop the full picture of giant cell arteritis, and visual symptoms may occur. However, it must be appreciated that visual symptoms can

occur in patients who have no signs of temporal artery disease.

In contrast with giant cell arteritis it is a relatively benign condition with little or no effect on survival. Lower doses of steroids than one would use for giant cell arteritis, and for shorter periods, are very effective in treatment, and milder cases respond to aspirin or non-steroidal antiinflammatory drugs. Relapses and recurrences do occur but more than 80% of patients recover fully and remain well after treatment.

The cause is unknown. Hepatitis-B surface antibody was found in 9 of a group of 12 patients (Bacon et al., 1975) and this led to the suggestion that the condition might represent an abnormal immunological response to infection in the elderly. However, hepatitis-B surface antigen was not found, and unlike the situation with polyarteritis nodosa (Gocke et al., 1970) grounds for implicating hepatitis-B virus specifically are insubstantial.

Takayasu's or Pulseless Disease

This rare condition was thought to be confined to Oriental women, but has now been recognized worldwide. The gross pathology resembles a localized form of polyarteritis nodosa in its progression from acute arteritis to thrombosis, occlusion and aneurysm formation, but it affects large elastic arteries such as the aorta and its major branches. In recent years it has been realized that the pulmonary artery is also frequently involved. All layers of the arterial wall are infiltrated with mononuclear and giant cells.

There tends to be a delay of many years between the onset of symptoms and diagnosis. The initial symptoms are those of generalized inflammatory disease such as intermittent fever, malaise and joint and muscle pain. Later, symptoms of ischaemia occur in areas supplied by affected vessels, and from accompanying hypertension. At this stage patients may complain of visual symptoms (transient blurring or visual field loss), fainting attacks and chest pain. Men are rarely affected. The average age at diagnosis is 30 years.

Although the condition had been described well before 1906 when Takayasu published his paper (Caccamise and Okuda, 1954), he first drew attention to the ocular changes. The literature contains occasional mention of inflammatory eye lesions such as episcleritis and iritis but the common eye changes are purely those of hypertensive retinopathy. Hypertension is secondary to renal artery stenosis. In a series of 54 cases (Ishikawa, 1978) only one patient had retinal changes described as typical of this condition, namely arteriovenous anastomoses and preretinal haemorrhages, and this patient had bilateral occlusion both of the carotid and vertebral arteries.

Histological examination of the eye shows a non-specific picture of ischaemic retinal and choroidal disease, with neovascularization (Font and Naumann, 1969).

Clinical Findings

Pulses will be absent in affected regions and bruits may be heard at the root of the neck. The ESR and plasma immunoglobulin levels are usually raised but blood tests are generally uninformative. The most useful investigation is arteriography, which reveals narrowing, occlusion and aneurysm formation in large arteries and helps to estimate the degree of collateral blood flow.

Syphilitic aortitis should be excluded.

Treatment

Corticosteroids are usually helpful in the acute phase of the disease, particularly if given early. It is not clear whether or not they influence the prognosis for life. In progressive disease cyclophosphamide is added (Shelhamer et al., 1985). Anticoagulants, antiplatelet agents and vasodilators may be added to the therapeutic regime. Treatment of hypertension and ischaemic or congestive heart disease is usually also necessary (Ishikawa, 1978).

Prognosis

Five-year survival of treated cases is better than 80%. Congestive cardiac failure and cerebrovascular accident are the usual causes of death.

COGAN'S SYNDROME

(syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms)

This syndrome affects young adults. There is an abrupt onset of vertigo, tinnitus and deafness, pain and redness of the eyes and blurred vision. Four cases were reported by Cogan in 1945 and a long-term follow-up including the same patients was published in 1959 (Cogan, 1945; Norton and Cogan, 1959). Some of the early patients eventually developed signs of cardiovascular disease (Cogan and Dickersin, 1964) and in a more recent survey of the topic it was reported that about 10% of patients develop aortic incompetence from acute aortitis (Haynes et al., 1980). In all, 21% of patients develop signs of more widespread vasculitis and these have a worse prognosis overall. They

also develop eye disease other than the keratitis. Scleritis, choroiditis, uveitis, retinal haemorrhages, retinal arterial occlusion and papill-oedema have been described.

In some cases the onset of the disease has been associated with upper respiratory tract infection and this has led to the suggestion that it represents a hypersensitivity response to an infectious agent or to drugs given at the time of the respiratory infection.

The prognosis for vision is good but deafness is usually permanent.

The eye disease responds well to local treatment with steroids and mydriatics. Haynes and his fellow workers have the impression that treatment with systemic steroids within the first two weeks from the onset of hearing loss may improve the prognosis for hearing, but this is uncertain because of the 5 patients in their series whose hearing improved 4 did so spontaneously. They suggest prednisone 2 mg/kg/day for two weeks and a tapered reduction after that (Haynes et al., 1980).

Chapter 3 References

Behçet's Syndrome

Abdalla Y. H. and Lehner T. (1979) The effect of immune complexes on chemotaxis in Behçet's syndrome and recurrent oral ulcers. In *Behçet's Syndrome*, eds. T. Lehner and C. G. Barnes. London, Academic Press, pp. 55–66.

Aktulga E., Altaç M., Müftüoglu A., Özyazgan Y., Pazarli H., Tüzün Y., Yalçin B., Yazici H. and Yurdakal S. (1980) A double blind study of colchicine in Behçet's disease. *Haematologica (Pavia)* **65**, 399–402.

Baba S. and Morioka S. (1982) Treatment of intestinal Behçet's disease. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 559–570.

Behçet H. (1937) Über rezidivierende, aphthöse, durch ein Virus verursachte Geschwüre am Mund, am Auge und an den Genitalien. *Dermatol. Wochenschr.* **105**, 1152–1157.

Behçet's Disease Research Committee of Japan (1974) Behçet's disease; Guide to diagnosis of Behçet's disease. *Jpn. J. Ophthalmol.* **18**, 291–294.

Bonamour G., Grange J. and Bonnet M. (1972) Retinal vein involvement in Behçet's disease. In *Behçet's Disease*, eds. N. Dilsen, M. Koniçe and C. Övül. Amsterdam, Excerpta Medica, pp. 142–144.

Bonnet M. (1982) Immunosuppressive therapy of Behçet's syndrome: long term follow-up evaluation. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 487–498.

Chamberlain M. A. (1977) Behçet's syndrome in 34 patients in Yorkshire. *Ann. Rheum. Dis.* **36**, 491–499.

Davies P. G., Fordham J. N., Kirwan J. R., Barnes C. G. and Dinning W. J. (1984) Pathergy test and Behçet's syndrome in Britain. *Ann. Rheum. Dis.* **43**, 70–73.

Denman A. M., Fialkow P. J., Pelton B. K., Salo A. C., Appleford D. J. and Gilchrist C. (1980) Lymphocyte abnormalities in Behçet's syndrome. *Clin. Exp. Immunol.* **42**, 175–185.

Dilsen N., Koniçe M., Övül C. and Aral O. (1982) A preliminary family study on Behçet's disease in Turkey. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 103–111.

Dinning W. J. (1979) Behçet's Disease and the eye; epidemiological considerations. In *Behçet's Syndrome*, eds. T. Lehner and C. G. Barnes. London, Academic Press, pp. 177–181.

Dinning W. J. (1986) Therapy-Selected Topics. In *Uveitis, Pathophysiology and Therapy*, 2nd ed., eds. E. Kraus-Mackiw and G. R. O'Connor. New York, Thieme, pp. 204–226.

Eglin R. P., Lehner T. and Subak-Sharpe J. H. (1982) Detection of RNA complementary to Herpes simplex virus in mononuclear cells from patients with Behçet's syndrome and recurrent oral ulcers. *Lancet* **2**, 1356–1361.

Fordham J. N., Davies P. G., Kirk A. and Currey H. L. F. (1982) Polymorphonuclear function in Behçet's syndrome. *Ann. Rheum. Dis.* **41**, 421–425.

France R., Buchanan R., Wilson M. and Sheldon M. (1951) Relapsing iritis with recurrent ulcers of the mouth and genitalia (Behçet's syndrome). *Medicine (Baltimore)* **30**, 335–355.

Fujiwara H. and Furutani A. (1977) A statistical survey of uveitis. *Folia Ophthal. Jap.* **28**, 91–95.

Fukuda Y., Watanabe I., Hayashi H. and Kuwabara N. (1980) Pathological studies on Behçet's disease. *Ryumachi.* **20**, 268–275.

Godfrey W. A., Epstein W. V., O'Connor G. R., Kimura S. J., Hogan M. J. and Nozic R. A. (1974) The use of chlorambucil in intractable idiopathic uveitis. *Am. J. Ophthalmol.* **78**, 415–428.

Graham E., Sanders M. D., James D. G., Hamblin A., Kasp-Grochowska E. and Dumonde D. E. (1985) Cyclosporin A in the treatment of posterior uveitis. *Trans. Ophthalmol. Soc. U.K.* **104**, 146–151.

Hashimoto T., Yanagida T., Okamoto S. and Tatsuichi T. (1982) Immunochemical properties of circulating immune complexes in Behçet's disease. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 391–403.

Hijakata K. and Masuda K. (1978) Visual prognosis in Behçet's disease: effects of cyclophosphamide and colchicine. *Jap. J. Ophthalmol.* **22**, 506–519.

Lawler S. D. and Lele K. P. (1972) Chromosome damage induced by chlorambucil in chronic lymphocytic leukaemia. *Scand. J. Haematol.* **9**, 603–612.

Lehner T. (1967) Behçet's syndrome and autoimmunity. *Br. Med. J.* **1**, 465–467.

Lehner T. (1969) Pathology of recurrent oral ulceration and oral ulceration in Behçet's syndrome: light, electron and fluorescence microscopy. *J. Pathol.* **97**, 481–494.

Lehner T. and Batchelor J. R. (1979) Classification and an immunogenetic basis of Behçet's syndrome. In *Behçet's Syndrome*, eds. T. Lehner and C. G. Barnes. London, Academic Press, pp. 13–32.

Levinsky R. and Lehner T. (1978) Circulating soluble immune complexes in recurrent oral ulceration and Behçet's syndrome. *Clin. Exp. Immunol.* **32**, 193–198.

McMenemey W. and Lawrence B. (1957) Encephalopathy in Behçet's disease. *Lancet* **2**, 353–358.

Maeda K., Agata T. and Nakae K. (1982) Recent trends of Behçet's disease in Japan and some of its epidemiological features. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 15–24.

Mamo J. and Baghdassarian A. (1964) Behçet's disease. *Arch. Ophthalmol.* **71**, 4–14.

Martenet A.-C. (1976) Résultats de l'immunodépression par cytostatiques en ophthalmologie. *Ophthalmologica* **172**, 106–115.

Martenet A.-C. (1981) Therapie der endogenen Uveitis: immunosuppression. *Ber. Dtsch. Ophthalmol. Ges.* **78**, 223–228.

Mason R. M. and Barnes C. G. (1969) Behçet's syndrome with arthritis. *Ann. Rheum. Dis.* **28**, 95–103.

Matsumura N. and Mizushima Y. (1975) Leukocyte movement and colchicine treatment in Behçet's disease. *Lancet* **2**, 813.

Mimura Y. (1982) Treatment of ocular lesions in Behçet's disease. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 499–512.

Mimura Y., Miyaura T. and Mizuno K. (1983) Indication of corticosteroid, cyclophosphamide and colchicine therapies in ocular lesions of Behçet's disease. *Acta XXIV International Congress of Ophthalmology*, ed. P. Henkind. Philadelphia, Lippincott, pp. 826–829.

Myers B., Ross J., Newton L., Leutscher J. and Perlroth M. (1984) Cyclosporin-associated chronic nephropathy. *N. Eng. J. Med.* **311**, 699–705.

Nussenblatt R. B., Palestine A. G. and Chan C.-C. (1983) Cyclosporin-A therapy in the treatment of intraocular inflammatory disease resistant to systemic corticosteroids and cytotoxic agents. *Am. J. Ophthalmol.* **96**, 275–282.

O'Duffy J. D. (1974) Suggested criteria for diagnosis of Behçet's disease. *J. Rheumatol.* **1**, (Suppl. 1), 18.

O'Duffy J. D., Carney J. A. and Deodhar S. (1971) Behçet's disease. Report of 10 cases, 3 with new manifestations. *Ann. Intern. Med.* **75**, 561–570.

Ohno S. (1982) Clinical and immunological studies on ocular lesions in Behçet's disease. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 127–136.

Ohno S., Aoki K., Sugiura S., Nakayama E., Itakura K. and Aizawa M. (1973) HL-A5 and Behçet's disease. *Lancet* **2**, 1383–1384.

Ohno S., Asanuma T., Sugiura S., Wakisaka A., Aizawa M. and Itakura K. (1978) HLA-Bw51 and Behçet's disease. *JAMA* **240**, 529.

Palmer R. G., Doré C. J. and Denman A. M. (1984) Chlorambucil-induced chromosome damage to human lymphocytes is dose-dependent and cumulative. *Lancet* **1**, 246–249.

Reeves B. R., Casey G., Harris H. and Dinning W. J. (1985) Longterm cytogenetic follow-up study of patients with uveitis treated with chlorambucil. *Carcinogenesis* **6**, 1615–1619.

Sakane T., Kotani H., Honda M. and Taniguchi Y. (1982) Aberration of suppressor T-cell function in patients with Behçet's disease. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 377–389.

Shikano S. (1966) Ocular pathology of Behçet's syndrome. In *International Symposium on Behçet's Disease, Rome*, eds. M. Monacelli and P. Nazzaro. Basel/New York, Karger, pp. 111–136.

Shimizu Y., Katsuta Y. and Oshima Y. (1965) Immunological studies on Behçet's syndrome. *Ann. Rheum. Dis.* **24**, 494–500.

Totsuka S., Hattori T., Yazaki M. and Nagao K. (1982) Clinicopathology of neuro-Behçet's disease. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 183–196.

Urayama A., Sakuragi S., Sakai F., Tanaka Y. and Koseki T. (1982) Angio-Behçet syndrome. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 171–176.

Urayama A., Takahashi N. and Sakai F. (1982) The position of ocular symptoms in Behçet's disease. In *Behçet's Disease*, ed. G. Inaba. Univ. Tokyo Press, pp. 153–160.

Wilton J. M. A. and Lehner T. (1979) Defective polymorphonuclear leukocyte phagocytosis in patients with Behçet's syndrome and recurrent oral ulcers. In *Behçet's Syndrome*, eds. T. Lehner and C. G. Barnes. London, Academic Press, pp. 67–75.

Yazici H., Chamberlain M. A., Schreuder I., D'Amaro J. and Müftüoglu A. (1980a) HLA antigens in Behçet's disease: a reappraisal by a comparative study of Turkish and British patients. *Ann. Rheum. Dis.* **39**, 344–348.

Yazici H., Tüzün Y., Pazarli H., Yalçin B., Yurdakul S. and Müftüoglu A. (1980b) The combined use of HLA-B5 and pathergy test as diagnostic markers of Behçet's disease in Turkey. *J. Rheumatol.* **7**, 206–210.

Polyarteritis

Christian C. L. and Sergent J. S. (1976) Vasculitis syndromes: clinical and experimental models. *Am. J. Med.* **61**, 385–392.

Cupps T. R. and Fauci A. S. (1981) *The Vasculitides*. Philadelphia, Saunders, p. 2.

Fauci A. S., Doppman J. L. and Wolff S. M. (1978) Cyclophosphamide-induced remissions in advanced polyarteritis nodosa. *Am. J. Med.* **64**, 890–894.

Gocke D. J., Hsu K., Morgan C., Bombardieri S., Lockshin M. and Christian C. L. (1970) Association between polyarteritis and Australia antigen. *Lancet* **2**, 1149–1153.

Goldsmith J. (1946) Periarteritis nodosa with involvement of the choroidal and retinal arteries. *Am. J. Ophthalmol.* **29**, 435–446.

Goldstein I. and Wexler D. (1929) The ocular pathology of periarteritis nodosa. *Arch. Ophthalmol.* **2**, 288–299.

Herson R. N. and Sampson R. (1949) The ocular manifestations of polyarteritis nodosa. *Q. J. Med.* **18**, 123–132.

Kielar R. A. (1976) Exudative retinal detachment and scleritis in polyarteritis. *Am. J. Ophthalmol.* **82**, 694–698.

Lieb E. S., Restivo C. and Paulus H. E. (1979) Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. *Am. J. Med.* **67**, 941–947.

Michalak T. (1978) Immune complexes of hepatitis B surface antigen in the pathogenesis of periarteritis nodosa. A study of seven necropsy cases. *Am. J. Pathol.* **90**, 619–632.

Purcell J. J., Birkenkamp R. and Tsai C. C. (1984) Conjunctival lesions in periarteritis nodosa. *Arch. Ophthalmol.* **102**, 736–738.

Report to the Medical Research Council by the Collagen Diseases and Hypersensitivity Panel (1960) Treatment of polyarteritis nodosa with cortisone: results after three years. *Br. Med. J.* **1**, 1399–1400.

Schroeder W., Kunert H. and Müller-Jensen A. (1976) Early neuro-ophthalmological symptoms of periarteritis nodosa (case report). *Klin. Monatsbl. Augenheilkd.* **168**, 794–798.

Scott D. G. I., Bacon P. A., Elliott P. J., Tribe C. R. and Wallington T. B. (1982) Systemic vasculitis in a district general hospital 1972–1980: clinical and laboratory features, classification and prognosis of 80 cases. *Q. J. Med.* **203**, 292–311.

Sheehan B., Harriman D. G. F. and Bradshaw J. P. P. (1958) Polyarteritis nodosa with ophthalmic and neurological complications. *Arch. Ophthalmol.* **60**, 537–547.

Solomon S. M. and Solomon J. H. (1978) Bilateral central artery occlusion in polyarteritis nodosa. *Ann. Ophthalmol.* **10**, 567–569.

Wegener's Granulomatosis

Blatt I. M., Seltzer H. S., Rubin P., Furstenburg A. C., Maxwell J. H. and Schull W. J. (1959) Fatal granulomatosis of the respiratory tract (lethal midline granuloma–Wegener's granulomatosis). *Arch. Otolaryngol.* **70**, 707–757.

Churg J. and Strauss L. (1951) Allergic granulomatosis, allergic angiitis, periarteritis nodosa. *Am. J. Pathol.* **27**, 277–301.

Coutu R. E., Klein M., Lessel S., Friedman E. and Snider G. L. (1975) Limited form of Wegener's granulomatosis. Eye involvement as a major sign. *JAMA* **233**, 868–871.

Fauci A. S. and Wolff S. M. (1973) Wegener's granulomatosis: studies in eighteen patients and a review of the literature. *Medicine (Baltimore)* **52**, 535–561.

Fauci A. S., Johnson R. E. and Wolff S. M. (1976) Radiation therapy of midline granuloma. *Ann. Intern. Med.* **84**, 140–147.

Godman G. C. and Churg J. (1954) Wegener's granulomatosis. Pathology and review of the literature. *Arch. Pathol.* **58**, 533–553.

Haynes B. F., Fishman M. C., Fauci A. S. and Wolff S. M. (1977) The ocular manifestations of Wegener's granulomatosis. Fifteen years' experience and review of the literature. *Am. J. Med.* **63**, 131–140.

Katz P., Alling D. W., Haynes B. F. and Fauci A. S. (1979) Association of Wegener's granulomatosis with HLA B-8. *Clin. Immunol. Immunopathol.* **14**, 268–270.

Klinger H. (1931) Grenzformen der Periarteritis Nodosa. *Frankf. Z. Pathol.* **42**, 455–480.

Liebow A. A., Carrington C. R. B. and Friedman P. J. (1972) Lymphomatoid granulomatosis. *Hum. Pathol.* **3**, 457–558.

Liesegang T. J., Bullen C. L., McDonald T. J. and DeRemee R. A. (1983) Ophthalmic Wegener's granulomatosis. *Acta XXIV International Congress of Ophthalmology*, ed. P. Henkind. Philadelphia, Lippincott, pp. 830–833.

Novack S. N. and Pearson C. M. (1971) Cyclophosphamide therapy in Wegener's granulomatosis. *N. Engl. J. Med.* **284**, 938–942.

Pinching A. T., Lockwood C. M., Pussel B. A., Rees A. J., Sweny P., Evans D. J., Bowley N. and Peters D. K. (1983) Wegener's granulomatosis: observations on 18 patients with severe renal disease. *Q. J. Med.* **52**, 435–460.

Straatsma B. R. (1957) Ocular manifestations of Wegener's granulomatosis. *Am. J. Ophthalmol.* **44**, 789–799.

Walton E. W. (1958) Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br. Med. J.* **2**, 265–270.

Wegener F. (1936) Über generalisierte, septische Gefasserkrankungen. *Verh. Dtsch. Ges. Pathol.* **29**, 202–210.

Giant Cell Arteritis and Cogan's Syndrome

Bacon P. A., Doherty S. M. and Zuckerman A. J. (1975) Hepatitis B antibody in polymyalgia rheumatica. *Lancet* **2**, 476–478.

Caccamise W. C. and Okuda K. (1954) Takayasu's or pulseless disease. *Am. J. Ophthalmol.* **37**, 784–786.

Chuang T.-Y., Hunder G. G., Ilstrup D. M. and Kurland L. T. (1982) Polymyalgia rheumatica. A 10 year epidemiologic and clinical study. *Ann. Intern. Med.* **97**, 672–680.

Cogan D. G. (1945) Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. *Arch. Ophthalmol.* **33**, 144–149.

Cogan D. G. and Dickersin G. R. (1964) Nonsyphilitic interstitial keratitis with vestibuloauditory symptoms. A case with fatal aortitis. *Arch. Ophthalmol.* **71**, 172–175.

Cullen J. F. (1967) Occult temporal arteritis. A common cause of blindness in old age. *Br. J. Ophthalmol.* **51**, 513–525.

Cullen J. F. and Coleiro J. A. (1976) Ophthalmic complications of giant cell arteritis. *Surv. Ophthalmol.* **20**, 247–260.

Fauchald P., Rygvold O. and Oystese B. (1972) Temporal arteritis and polymyalgia rheumatica. Clinical and biopsy findings. *Ann. Intern. Med.* **77**, 845–852.

Font R. L. and Naumann G. (1969) Ocular histopathology in pulseless disease. *Arch. Ophthalmol.* **82**, 784–788.

Gocke D. J., Hsu K., Morgan C., Bombardieri S., Lockshin M. and Christian C. L. (1970) Association between polyarteritis and Australia antigen. *Lancet* **2**, 1149–1153.

Graham E., Holland A., Avery A. and Ross Russell R. W. (1981) Prognosis in giant cell arteritis. *Br. Med. J.* **282**, 269–271.

Haynes B. F., Kaiser-Kupfer M. I., Mason P. and Fauci A. S. (1980) Cogan syndrome: studies in 13 patients, long-term follow-up, and a review of the literature. *Medicine* **59**, 426–441.

Healey L. A. and Wilske K. R. (1978) *The Systemic Manifestations of Temporal Arteritis*. New York, Grune and Stratton, pp. 67–77.

Huston K. A., Hunder G. C., Lie J. T., Kennedy R. H. and Elveback L. R. (1978) Temporal arteritis. A 25-year epidemiological, clinical and pathological study. *Ann. Intern. Med.* **88**, 162–167.

Ishikawa K. (1978) Natural history and classification of occlusive thromboaortopathy (Takayasu's disease). *Circulation* **57**, 27–35.

Norton E. W. D. and Cogan D. G. (1959) Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. *Arch. Ophthalmol.* **61**, 695–697.

Reinecke R. D. and Kuwabara T. (1969) Temporal arteritis. I. Smooth muscle involvement. *Arch. Ophthalmol.* **82**, 446–453.

Roux J.-L. (1954) Le syndrome de l'artérite temporale. *Helvetica Medica Acta (Suppl. 34)*, 1–82.

Shelhamer J. H., Volkman D. J., Parrillo J. E., Lawley T. J., Johnson M. R. and Fauci A. S. (1985) Takayasu's arteritis and its therapy. *Ann. Intern. Med.* **103**, 121–126.

Whitfield A. G., Bateman M. and Cooke W. T. (1963) Temporal arteritis. *Br. J. Ophthalmol.* **47**, 555–566.

Chapter four

Systemic Lupus Erythematosus and Scleroderma

SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction

Systemic lupus erythematosus (SLE) is regarded as the classical spontaneous autoimmune disease. The term 'collagen disease' was coined for SLE and scleroderma following the hypothesis that they were systemic diseases of the connective tissue 'system' (Klemperer et al., 1942). This notion has always been speculative, and the term is falling into disuse. The cause remains entirely unknown. There are still problems in diagnosis, especially in differentiating some cases from rheumatoid arthritis. Clinically distinct varieties of the disease have long been recognized. More subtypes are being identified. A more refined classification is likely to permit a better understanding of the pathogenesis of the disease.

Diagnosis

The Revised Criteria of the American Rheumatism Association are widely accepted (Tan et al., 1982). The diagnosis can be made if 4 of the criteria in *Table* 2 are met, either serially or simultaneously.

Epidemiology

There has probably been an improvement in case recognition, making it difficult to interpret the available figures. The annual incidence is probably about 1–2 per 100 000 (Siegel et al., 1970). In the United States it is 3 times commoner in black women than in others. About 90% of patients are women.

Familial Disease

The physical and laboratory abnormalities found in patients with SLE

occur more commonly in their relatives than in others (Leonhardt, 1964). However, the laboratory attributes of familial cases are no different overall from those of non-familial cases (Arnett and Shulman, 1976). The uncertain incidence of familial disease has been estimated from 0·5 to 5%. There is a high concordance of disease expression between pairs of identical twins and between parents and their offspring (Arnett and Shulman, 1976).

The histocompatibility antigen HLA 8 is found more frequently than normal in Caucasians with SLE (Grumet et al., 1971), and HLA 1 in Blacks. HLA 1 also seems to be associated with onset of disease at an early age (Goldberg et al., 1976). There is also an increased association of the antigens HLA DRw2 and 3 (Gibofsky et al., 1978; Reinertsen et al., 1978). It is interesting that in many of the recently recognized subgroups of SLE there is a strong association of the HLA DRw3 phenotype and anti-Ro antibodies (a soluble cytoplasmic antigen/RNA protein conjugate) (*see below*). This subject has recently been extensively reviewed (Hochberg et al., 1985).

Table 2 Criteria for SLE diagnosis

	Symptom	*Characteristics*
1	Malar rash	a flat or raised erythematous rash over the malar eminences – the 'butterfly rash'
2	Discoid rash	raised erythematous patches with keratotic scales and follicular plugging
3	Photosensitivity	
4	Oral ulcers	usually painless
5	Arthritis	non-erosive, involving 2 or more peripheral joints
6	Serositis	pleuritis or pericarditis
7	Renal disease	persistent proteinuria or casts
8	Neurological disease	seizures or psychosis that are not complications of drug treatment or metabolic disease
9	Haematological disease	haemolytic anaemia, leucopaenia, lymphopaenia, thrombocytopaenia
10	Immunological disease	positive LE cell preparation, or antibody to native DNA, or antibody to Sm nuclear antigen, or false positive serological tests for syphilis
11	Antinuclear antibody	

Clinical Features

Onset

Symptoms usually begin between the ages of 15 and 25. The onset resembles rheumatoid arthritis, with fatigue, fever, weight loss, joint pain and swelling, and myalgia. However, erosive arthritis is rare and

although joint deformities can occur the pathology is not that of rheumatoid arthritis.

Skin

Skin disease occurs in 85% of patients.

(1) The typical *butterfly rash* is present in half the patients at diagnosis. It consists of redness and slight swelling of the skin across the cheeks and the bridge of the nose. It does not produce scarring. (*Fig.* 60.)

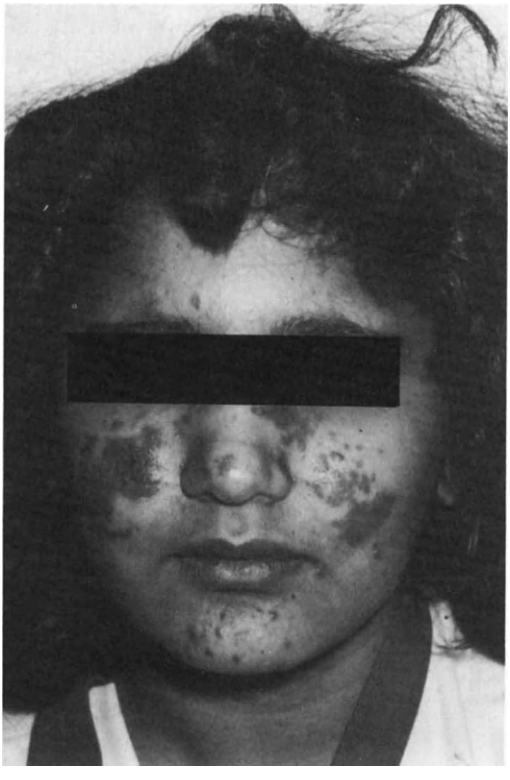


Figure 60 SLE: facial rash.
(Dr Michael Denman.)

(2) A non-specific *erythematous maculopapular* rash may occur anywhere on the body.

(3) *Discoid lesions* occur in 20% of patients and may be the only manifestation of disease for many years. They may be single or multiple. They are raised, well demarcated papules on the 'butterfly' area of the face, or other areas of the head. Less commonly, lesions are found on the upper chest, back and arms. They usually extend slowly, the central area fading as the plaque enlarges. Histologically there is blood vessel dilatation, hyperkeratosis, acanthosis of the prickle cell layer and necrosis of the basal layer. The upper dermis is markedly infiltrated with lymphocytes. Immunoglobulin is deposited at the dermoepidermal junction more consistently and intensively in lesional skin than in other dermatoses (Burnham et al., 1963), and in generalised disease it can also be found in apparently unaffected skin (Cormane, 1964). Atrophy finally leads to marked scarring. Similar lesions occur in subacute cutaneous lupus (q.v.) but do not lead to scarring.

(4) *Cutaneous vasculitis* is common, particularly on the extensor surfaces of the forearms, and on the finger tips. Splinter haemorrhages occur also in the finger tips and nails and in the toes. In the skin of the nail fold the subpapillary plexus of vessels is prominent, with patchy areas of apparent capillary loss (Maricq and LeRoy, 1973). Relapsing panniculitis, purpura, livido reticularis and urticaria are also seen. Alopecia is also common, but the hair regrows except at the sites of discoid lesions.

Many of these skin lesions are sensitive to sunlight. Exposure to the sun often activates systemic disease as well.

Painless mouth ulcers are common.

Renal Disease

More than half the patients have protein, blood and casts in the urine. Many clinicians have the impression that if renal disease is absent when the diagnosis is made, adequate initial treatment may prevent its later appearance.

The overall prognosis depends upon the type of renal involvement, being worse in the proliferative types of lupus nephritis, and better in the membranous and mesangial types.

Proliferative lupus nephritis may be focal, in which there is only segmental proliferation of glomerular tufts, or diffuse, in which there is proliferation of the whole of the tuft. Deposits of immunoglobulin and C3 are found along the glomerular capillary loops. In diffuse disease deposits also occur in the tubular basement membrane, in peritubular capillary walls and in the renal interstitium. The nephrotic syndrome develops when more than 50% of the glomeruli are involved.

In *membranous lupus nephritis* immunoglobulin is found along all basement membranes in subepithelial and subendothelial locations. Proteinuria results, sometimes with haematuria, and the nephrotic syndrome may occur.

In *mesangial disease* immunoglobulin and C3 are found in mesangial structures and sometimes in capillary walls, but the glomeruli are normal and significant proteinuria or haematuria do not occur.

Four distinct patterns of immunofluorescent glomerular staining from immunoglobulin deposition have been described which correlate with the type of renal disease present (Agnello et al., 1973).

When proliferative disease goes into remission the affected glomeruli become sclerosed. In active disease there are widespread histological signs of inflammation, including endothelial proliferation and thrombosis in the glomerular capillaries, acute lesions of the tubular endothelium, inflammatory cell infiltration of the interstitium, and necrotizing angiitis. Fibrinoid necrosis of the capillary walls and occlusion of the vessels give rise to the so-called 'wire loop' changes in the glomeruli.

Disease of Blood Vessels

The vascular disease has already been mentioned in the kidneys, skin and other organ systems. Raynaud's phenomenon occurs in about 20% of patients (cf. scleroderma). Inflammation of small vessels with necrosis and thrombosis is a common pathology in affected organs, but with the exception of mesenteric vessels, large vessel occlusion is rare.

Heart

Most patients with active systemic disease have T wave abnormalities on the ECG. Pericarditis is common but not usually symptomatic. Myocardial disease is less common. Verrucous endocarditis (Libman–Sacks) may occur on the mitral and tricuspid valves.

Lungs

Pleuritis is similarly common, but parenchymal disease of the lung is not, except in older patients. These may suffer acute pneumonitis, or a diffuse interstitial inflammation, giving rise to restrictive lung disease (scleroderma lung).

Central Nervous System

Neurological disease is also the result of vasculitis. A peripheral sensory neuropathy may occur. Microinfarcts in the cerebrum lead to

an organic brain syndrome. Cerebral lupus may present with psychosis, and fits may occur, even at the onset of the disease. Deposits of IgG have been found in the choroid plexus.

Ocular Disease

Eye disease is uncommon. This is a point worthy of emphasis because it is fashionable to ascribe many cases of uveitis to the deposition of immune complexes. The rarity of uveitis in SLE which is accepted as an immune complex-mediated disease is distinctly at variance with such a suggestion. Interestingly, ocular deposition of immunoglobulin has been found in the choriocapillaris and basement membrane of the ciliary processes in a patient who had transient subretinal oedema (Aronson et al., 1979).

In a review of 61 cases only one had transient signs of uveitis (Gold et al., 1972). Evidence of iridocyclitis was found in one case at autopsy examination (Clifton and Greer, 1955).

On the other hand, retinal vasculitis is well documented, although it is by no means so frequently seen as one might expect. The routine performance of fluorescent fundus angiography in SLE would probably reveal signs of vascular leakage in some ophthalmoscopically normal cases (Lanham et al., 1982). Apart from changes of hypertension the findings are those of retinal ischaemia on the basis of retinal vasculitis. Multiple 'cottonwool spots' (q.v.) are reported by most writers (Lanham et al., 1982; Wong et al., 1981), and signs of retinal vascular occlusion, from capillary non-perfusion only seen on fundus angiography (Gold et al., 1977) to obvious major arterial and venous occlusion (Coppeto and Lessell, 1977; Wong et al., 1981). Optic nerve vasculitis may proceed to atrophy (Lanham et al., 1982). The presence of cottonwool spots appears to correlate with disease activity but it has not been possible to relate ocular changes to central nervous system disease. However, a case has recently been reported in which vasculitis with fibrinoid necrosis was found in some meningeal and choroidal vessels, together with amorphous hyaline material occluding some retinal vessels, without signs of vasculitis (Graham et al., 1985).

Sjögren's syndrome also occurs, but not so consistently as in rheumatoid arthritis.

Haematological Disease

Anaemia, mild leucopaenia, lymphopaenia and thrombocytopaenia are common. About one-third of the cases of anaemia are haemolytic. Serological tests for syphilis give persistently positive results in over 10% of patients. Most have a raised ESR, and the LE cell phenomenon is found in about 90%. *The LE cell* (Hargraves et al., 1948) is a

neutrophil which has ingested nuclear material from damaged white cells, complexed with complement and antinuclear antibody. The material is contained in a large vacuole in the cytoplasm. It thus indirectly indicates the presence of the antinuclear antibody, but direct tests for this are more sensitive and detect antinuclear antibodies in almost all patients (Burnham et al., 1966).

Other Systems

All types of hepatitis have been described.

Pathology

The early change common to all lesions is a vasculitis of small arteries. Segments of the vessel walls become necrotic and take on a 'fibrinoid' appearance. The fibrinoid has been found to consist of immune complexes of DNA and anti-DNA immunoglobulin and complement.

Other pathological features have already been mentioned.

Subgroups of SLE

1 Discoid Lupus

The skin lesions have already been described. They may remain the only sign of disease for many years.

2 Subacute Cutaneous Lupus

In this condition the skin lesions are diffuse but not scarring. There is a high incidence of antinuclear and anticytoplasmic antibodies and immune complexes in the blood (Sontheimer et al., 1982).

3 ANA-negative SLE

Antinuclear antibodies are not detected in about 5% of patients, but they do have anticytoplasmic antibodies. The histology of the skin disease is said to be characteristic of this subgroup, but no difference is found in the nature and incidence of systemic disease (Maddison et al., 1981).

4 Homozygous C2 Deficiency Lupus

One-third of patients with this deficiency have discoid lupus, with or without systemic disease (Provost et al., 1983).

5 Neonatal Lupus

This is a rare condition and is believed to be the result of transplacental passage of a maternal factor. There is transient lupus-type dermatitis and systemic and haematological abnormalities. It resolves in 6–15 months. The mothers are usually asymptomatic but are HLA DRw3 positive and many have definite SLE or related disease such as rheumatoid arthritis (Watson et al., 1984).

6 Lupus in the Elderly

Elderly patients with SLE tend to suffer less joint disease and more lung disease than younger patients. They have anticytoplasmic antibodies rarely found in normal elderly people (Catoggio et al., 1984).

The presence of anticytoplasmic Ro (SSA) antibodies is strongly associated with the HLA Drw3 phenotype (Catoggio et al., 1984). Both these 'markers' are found in most of the more recently described subsets of disease, and in these the typical anti-native DNA antibodies are less frequently found than in classic SLE. This is no doubt in part due to the fact that much of the work comes from the same laboratory, but it is important to realize that it is not yet possible to define disease subgroups on the basis of laboratory markers alone.

Drug-induced Lupus

Many drugs are known to induce the disease. Most studied are the related drugs hydralazine, procainamide and isoniazid. Toxicity to hydralazine appears to arise more commonly in those who are slow acetylators of the drug. They are related to the appearance of antinuclear antibodies in the blood (Perry et al., 1970). Patients who develop lupus erythematosus while taking the drug show immunological reactions to it, and antibodies to native DNA appear, as in the idiopathic disease (Hahn et al., 1972). Anticonvulsants, phenothiazines, sulphonamides and some antibiotics may cause it. The drug-induced disease tends to take a mild form, without renal or nervous system involvement.

Triggering Factors

Most types of lupus erythematosus may be triggered by exposure to sunlight. The disease is likely to be much worse in pregnancy and the puerperium. Pregnancy is usually discouraged, but it is generally felt that termination in a pregnant patient may be just as dangerous as

allowing the pregnancy to continue. The stresses of infection, surgery and strong emotion often induce flares of activity. Sulphonamides should never be given to patients with SLE.

Animal Models

A spontaneous disease akin to human SLE occurs in several mouse strains, particularly the NZB/NZW hybrid. Eye changes like Sjögren's syndrome have been described in these mice, including infiltration of the lacrimal glands with mononuclear cells (Kessler et al., 1971).

Parallels with human disease, and the pathogenetic significance of the findings in the murine model have recently been discussed by Steinberg and others (Steinberg et al., 1984). It appears that an endogenous trigger permits the expression of a genetic predisposition to excessive B-cell activation. Susceptible mouse strains differ in disease particulars, such as age at onset, and males are less susceptible than females. Male hormones protect females and castration increases male susceptibility. In the NZB/NZW hybrid female hormone administration accelerates the disease process. In certain strains early thymectomy delays the onset of disease.

A remarkable finding in murine disease is that possession of a single gene (xid) prevents the development of the lupus syndrome and autoimmune disease in general, probably by inhibiting the development of a subset of splenic B-cells which are responsible for much of the spontaneous autoantibody production in these mice.

SLE also occurs in dogs. Here it also appears to be a multifactorial condition (Lewis and Schwartz, 1971).

Aetiology

The cause of this disease remains unknown. There is undoubtedly a genetic predisposition as indicated by family studies and HLA associations. There is little to support the infective hypothesis. Genetic analysis suggests that a trigger factor, possibly a virus, is transmitted vertically in susceptible dogs (Lewis and Schwartz, 1971), and in the murine model of SLE (Phillips, 1975).

It is suggested that there is excessive proliferation of lymphocytic stem cells as a result of defective immunoregulation by T-cells. Affected laboratory mice do show polyclonal B-cell activation and, while this is not necessarily true of man, a wide variety of autoantibodies is produced, and the subgroups of disease probably depend at least to a degree upon the preponderating autoantibodies. Despite the leucopaenia, increased numbers of immunoglobulin-secreting cells are found in the blood of patients with active disease (Blaese et al., 1980). B-

lymphocytes sensitive to native DNA have been demonstrated in the blood both of normal persons and patients with SLE (Bankhurst and Williams, 1975). This suggests that the increase in immunoglobulin-secreting cells and in immunoglobulin results from expansion of pre-existing cell subsets, independently of the participation of DNA-specific T-lymphocytes. The functional activity of other cell types is also disturbed. For example, NK cell activity is reduced (Goto et al., 1980; Sibbitt et al., 1983) and this may be due to a specific antibody in the serum to NK cells.

The wide variety of antibodies found in the serum includes antibodies against clotting factors and platelets. Antibodies against RNA are present in 50% of cases and have been seen as evidence for infection with an RNA virus (Agnello et al., 1973). Anti-double stranded (native) DNA antibodies are more specific for SLE than anti-single stranded (denatured) DNA antibodies, and are found in highest concentrations in acute disease. When they were first demonstrated in company with DNA in the serum of some patients with SLE (Tan et al., 1966) the suggestion naturally arose that DNA and anti-DNA antibodies could form immune complexes *in vivo* and produce the manifestations of disease.

Laboratory Indices of Disease Activity

The ESR, measures of the serum levels of anti-DNA antibodies, IgG, IgM, and circulating immune complexes, and peripheral lymphocyte counts have all been found helpful in assessing activity (Blaese et al., 1980; Morrow et al., 1982). C-reactive protein levels have not been found to be useful (Bertouch, 1983). However, there is no general agreement upon the extent to which the results of such investigations should guide the modulation of therapy, in contrast to the clinical findings.

Prognosis

The prognosis depends upon the presence and severity of renal and central nervous system disease, and the responsiveness to initial treatment. Renal failure with diffuse proliferative glomerulonephritis and heavy proteinuria carries a poor prognosis. Nephritis may progress rapidly over 1–2 years and is responsible for half the deaths. Since the advent of corticosteroid therapy the prognosis in the early years of the disease has greatly improved (Ropes, 1976). Patients are now surviving much longer and a brighter prognosis can be given. Infection was also a common cause of death, even in patients with only mild renal disease.

Better control of hypertension has improved the outlook for patients with severe disease.

In general, a good response to steroid treatment can be expected. Long and repeated periods of spontaneous remission are also common. Patients who get the disease later in life also have a better prognosis.

There is no general agreement about the relationship of laboratory measures to prognosis, although persistently high levels of antibodies to DNA and low levels of complement are unfavourable signs. However, other clinical factors such as response to steroids seem generally more important.

Treatment

Mild disease may require no systemic treatment, but the avoidance of all known triggering factors is important for all patients. Aspirin and the non-steroidal antiinflammatory drugs may be sufficient to control joint symptoms. Low doses of corticosteroids may be necessary for mildly symptomatic disease. Severe disease, particularly when there is haemolytic anaemia or central nervous system involvement, may require high doses of corticosteroids (> 60 mg/day prednisolone) for long periods. Such patients usually improve within 48 hours although their levels of circulating immune complexes remain high for a month and take six months or more to fall to near normal (Boyd et al., 1983). Discoid skin lesions may respond to topical steroids. Hydroxychloroquine (200 mg/day) is particularly useful in the control of discoid lupus, but it should probably be stopped after a total dose of 450 g in view of the potential for ocular toxicity. Antimalarials also relieve joint pain.

Azathioprine has been advocated for patients with a poor prognosis (1–2 mg/kg/day) (Ginzler et al., 1975) but cyclophosphamide (100–150 mg/day) seems to be superior (Steinberg and Decker, 1974). In the long-term control of lupus nephritis it appears to be slightly superior to corticosteroids, but not in terms of slowing the deterioration of renal function (Carette et al., 1983).

Other measures in patients with severe disease unresponsive to steroids and cytotoxic agents, such as plasmapheresis, are only helpful in the short term (Verrier-Jones et al., 1979).

SCLERODERMA

Introduction

The term scleroderma embraces another cluster of diseases which, like systemic lupus erythematosus, are believed to be mediated by way of

immune complex deposition. Other similarities with SLE include the characteristic vascular pathology of intimal proliferation, fibrinoid necrosis and small vessel obliteration. Symptomatically there is also a considerable overlap with SLE, and also with rheumatoid arthritis. The main difference from SLE is the widespread fibrosis in many organs, particularly the skin.

Clinical Features

It is mainly a disease of women in the fourth decade, clinically presenting with Raynaud's phenomenon, and swelling and pigmentation of the face, hands and feet. Occasionally it presents with polyarthritis, myositis, or the consequences of severe hypertension. The skin swelling quickly progresses to atrophy and subcutaneous fibrosis. In diffuse disease the fibrosis affects all organs.

Skin

Raynaud's phenomenon occurs in 90% of all patients. Cold hypersensitivity may be present years before any other manifestations of scleroderma occur (Birnstingl, 1971).

There are generalized, localized or linear areas of tight and thickened skin, mainly of the head and extremities, with loss of the hair and nails. It becomes bound to underlying structures and interferes with mobility. After many years the skin may soften. (*Figs.* 61, 62.)

The skin of the nailfolds shows grossly dilated capillary loops, and in the presence of systemic disease there are also areas of avascularity (Maricq et al., 1976).

Gastrointestinal Tract

Oesophageal hypomotility from fibrosis is found in 90% of patients but only a proportion of them have dysphagia. Involvement of the upper small intestine may produce malabsorption.

Lungs

Pleural effusion is common. Pulmonary hypertension and diffuse interstitial pulmonary fibrosis is a major cause of death (Pisko et al., 1979).

Kidneys

Uraemia, proteinuria and hypertension due to raised plasma renin

occur in about half the patients. Renal disease is a major cause of death (Oliver and Cannon, 1977). Unlike SLE, the main change is progressive fibrosis of the interlobular arteries (Sinclair et al., 1976).

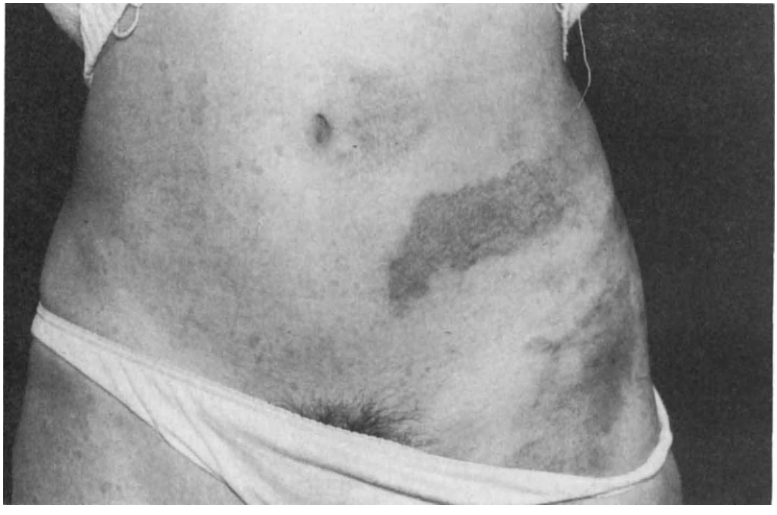


Figure 61 Linear scleroderma.
(Dr Michael Denman.)

Musculoskeletal System

Seronegative arthropathy is common. It is less severe and less often erosive than rheumatoid arthritis (Baron et al., 1982).

After many years the distal tufts of the fingers may become resorbed.

Generalized muscle atrophy is common. Some patients have myositis and the symptoms of polymyalgia.

Heart

Pericarditis with fibrosis may occur. Myocarditis is also occasionally found.

Eyes

Tightness of the eyelids sometimes leads to corneal exposure. Reduced tear production also causes dryness and irritation (Horan, 1969). Minor changes are often seen in the conjunctival vessels (West and Barnett, 1979). Iris changes suggestive of atrophy have been described

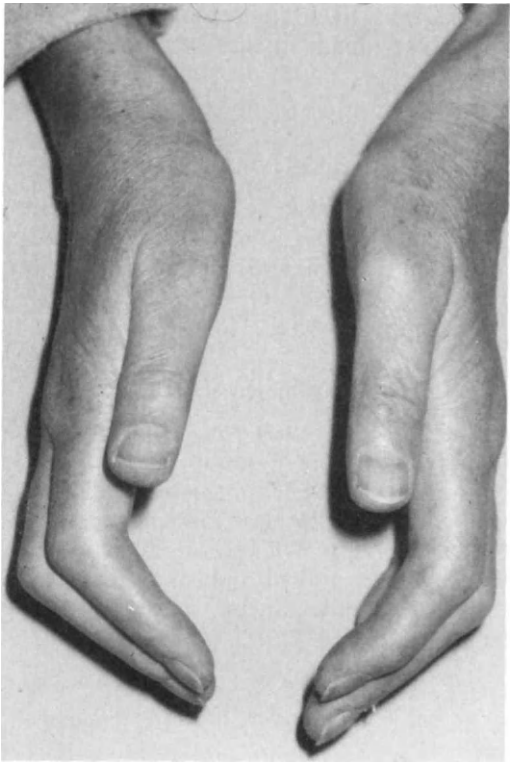


Figure 62 Hands in scleroderma.
(Dr Michael Denman.)

(Manschott, 1965; West and Barnett, 1979), and retinal exudates in a patient with ocular symptoms (Manschott, 1965).

Clinical Types

Patients may be placed into 3 rather ill-defined categories:

(1) *Cutaneous scleroderma*, in which skin disease is unaccompanied by systemic findings.

(2) *Diffuse generalized scleroderma*, with chronic skin and systemic disease. This is the commonest type.

(3) *CREST syndrome*. The letters stand for calcinosis, Raynaud's phenomenon, oesophageal hypomotility, sclerodactyly, and telangiectasia. Apart from the upper gastrointestinal tract the disease is superficial.

Patients presenting with the more localized types of disease unfortunately tend to develop systemic disease eventually.

Serological Changes

A variety of antinuclear antibodies are found in the majority of patients (Rothfield and Rodnan, 1968; Tan et al., 1980). Rheumatoid factors and anti-smooth muscle antibodies are also common.

Pathogenesis

It has been suggested that the initial event may be vascular endothelial cell damage, possibly as a result of immune complex deposition, or by way of some unknown but specific injurious agent. This then induces the collagen production and fibrosis (Fleischmajer, 1977; Kahaleh et al., 1979; LeRoy et al., 1982). The initial infiltration of lymphocytes, plasma cells, macrophages and fibroblasts occurs around the blood vessels of the dermis and subcutaneous tissues, and of other affected organs (Fleischmajer et al., 1977).

Treatment

The general treatment of Raynaud's phenomenon includes the avoidance of exposure to cold, and the use of sympatholytic drugs, such as guanethidine and phenoxybenzamine (Porter et al., 1975).

Physiotherapy is important for the maintenance of mobility. Drug therapy has little effect on the skin, but massage and movement may be beneficial.

Hypertension should be treated aggressively with renin/angiotensin antagonists such as captopril and enalapril. Dialysis is sometimes required in severe renal disease.

At present a possible role for D-penicillamine treatment is being investigated (Steen et al., 1985).

Prognosis

The prognosis is good so long as disease remains localized, but with widespread systemic disease survival figures as low as 20% at ten years have been given. Older patients have a poorer prognosis.

Chapter 4 References

Systemic Lupus Erythematosus

Agnello V., Koffler D. and Kunkel, H. G. (1973) Immune complex systems in the nephritis of systemic lupus erythematosus. *Kidney Int.* **3**, 90–99.

Arnett F. C. and Shulman L. E. (1976) Studies in familial systemic lupus erythematosus. *Medicine* **55**, 313–322.

Aronson A. J., Ordonez N. G., Diddie K. R. and Ernest J. T. (1979) Immune complex deposition in the eye in systemic lupus erythematosus. *Arch. Intern. Med.* **139**, 1312–1313.

Bankhurst A. D. and Williams R. C. (1975) Identification of DNA binding lymphocytes in patients with systemic lupus erythematosus. *J. Clin. Invest.* **56**, 1378–1385.

Bertouch J. V., Roberts-Thompson P. J., Feng P. H. and Bradley J. (1983) C-reactive protein and serological indices of disease activity in systemic lupus erythematosus. *Ann. Rheum. Dis.* **42**, 655–658.

Blaese R. M., Grayson J. and Steinberg A. D. (1980) Increased immunoglobulin-secreting cells in the blood of patients with active systemic lupus erythematosus. *Am. J. Med.* **69**, 345–350.

Boyd R. E., Birchmore D. A., Kaiser D. L., Young A. C. and Davis J. S. (1983) Acute effects of steroids on immune complex profile of patients with systemic lupus erythematosus. *Arthritis Rheum.* **26**, 637–655.

Burnham T. K., Neblett T. R. and Fine G. (1963) The application of the fluorescent antibody technique to the investigation of lupus erythematosus and various dermatoses. *J. Invest. Dermatol.* **41**, 451–456.

Burnham T. K., Fine G. and Neblett T. R. (1966) The immunofluorescent tumor imprint technique. II. The frequency of antinuclear factors in connective tissue diseases and dermatoses. *Ann. Intern. Med.* **65**, 9–19.

Carette S., Klippel J. H., Decker J. L., Austin H. A., Plotz P. H., Steinberg A. D. and Balow J. E. (1983) Controlled studies of oral immunosuppressive drugs in lupus nephritis. A long-term follow up. *Ann. Intern. Med.* **99**, 1–8.

Catoggio L. G., Skinner R. P., Smith G. and Maddison P. J. (1984) Systemic lupus erythematosus in the elderly: clinical and serological characteristics. *J. Rheumatol.* **11**, 175–181.

Clifton F. and Greer C. H. (1955) Ocular changes in acute systemic lupus erythematosus. *Br. J. Ophthalmol.* **39**, 1–10.

Coppeto J. and Lessel S. (1977) Retinopathy in systemic lupus erythematosus. *Arch. Ophthalmol.* **95**, 794–797.

Cormane R. H. (1964) 'Bound' globulin in the skin of patients with chronic discoid lupus erythematosus and systemic lupus erythematosus. *Lancet* **1**, 534–535.

Gibofsky A., Winchester R. J., Patarroyo M., Fotino M. and Kunkel H. G. (1978) Disease associations of the Ia-like human alloantigens. Contrasting patterns in rheumatoid arthritis and systemic lupus erythematosus. *J. Exp. Med.* **148**, 1728–1732.

Ginzler E., Sharon E., Diamond H. and Kaplan D. (1975) Long-term maintenance therapy with azathioprine in systemic lupus erythematosus. *Arthritis Rheum.* **18**, 27–34.

Gold D. H., Morris D. A. and Henkind P. (1972) Ocular findings in systemic lupus erythematosus. *Br. J. Ophthalmol.* **56**, 800–804.

Gold D. H., Feiner L. and Henkind P. (1977) Retinal arterial occlusive disease in systemic lupus erythematosus. *Arch. Ophthalmol.* **95**, 1580–1585.

Goldberg M. A., Arnett F. C., Bias W. B. and Shulman L. E. (1976) Histocompatibility antigens in systemic lupus erythematosus. *Arthritis Rheum.* **19**, 129–132.

Goto M., Tanimoto K. and Horiuchi Y. (1980) Natural cell-mediated cytotoxicity in systemic lupus erythematosus. *Arthritis Rheum.* **23**, 1274–1281.

Graham E., Spalton D. J., Barnard R. O., Garner A. and Ross Russell R. W. (1985) Cerebral and retinal vascular changes in systemic lupus erythematosus. *Ophthalmology* **92**, 444–448.

Grumet E. C., Coukell A. and Bodmer J. G. (1971) Histocompatibility (HL-A) antigens associated with systemic lupus erythematosus. A possible genetic predisposition to disease. *N. Engl. J. Med.* **285**, 193–196.

Hahn B. H., Sharp G. C., Irvin W. S., Kantor O. S., Gardner C. A., Bagby M. K., Perry H. M. and Osterland C. K. (1972) Immune responses to hydralazine and nuclear antigens in hydralazine-induced lupus erythematosus. *Ann. Intern. Med.* **76**, 365–374.

Hargraves M. M., Richmond H. and Morton R. (1948) Presentation of two bone marrow elements: the 'tart' cell and the 'LE' cell. *Proc. Mayo Clin.* **23**, 25–28,

Hochberg M. C., Boyd R. E., Ahearn J. M., Arnett F. C., Bias W. B., Provost T. T. and Stevens M. B. (1985) Systemic lupus erythematosus: a review of clinico-laboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. *Medicine* **64**, 285–295.

Kessler H. S., Cubberly M. and Manski W. (1971) Eye changes in autoimmune NZB and NZB/NZW mice. *Arch. Ophthalmol.* **85**, 211–219. 1979.

Klemperer P., Pollack A. D. and Baehr G. (1942) Diffuse collagen disease. Acute disseminated lupus erythematosus and diffuse scleroderma. *JAMA* **119**, 331–332.

Lanham J. G., Barrie T., Kohner E. M. and Hughes G. V. R. (1982) SLE retinopathy evaluation by fluorescein angiography. *Ann. Rheum. Dis.* **41**, 473–478.

Leonhardt T. (1964) Family studies in systemic lupus erythematosus. *Acta Med. Scand. (Suppl.)* **416**, 1–156.

Lewis R. M. and Schwartz R. S. (1971) Canine systemic lupus erythematosus: genetic analysis of an established breeding colony. *J. Exp. Med.* **134**, 417–438.

Maddison P. J., Provost T. T. and Reichlin M. (1981) Serological findings in patients with 'ANA negative' systemic lupus erythematosus. *Medicine* **60**, 87–94.

Maricq H. R. and LeRoy E. C. (1973) Patterns of finger capillary abnormalities in connective tissue disease by 'wide-field' microscopy. *Arthritis Rheum.* **16**, 619–628.

Morrow W. J. H., Isenberg D. A., Todd-Pok Ropek A., Parry H. F. and Snaith M. L. (1982) Useful laboratory measurements in the management of systemic lupus erythematosus. *Q. J. Med.* **51**, 125–138.

Perry H. M., Tan E. M., Carmody S. and Sakamoto A. (1970) Relationship of acetyltransferase activity to antinuclear antibodies and toxic symptoms in hypertensive patients treated with hydralazine. *J. Lab. Clin. Med.* **76**, 114–125.

Phillips P. E. (1975) The virus hypothesis in systemic lupus erythematosus. *Ann. Intern. Med.* **83**, 709–715.

Provost T. T., Arnett F. C. and Reichlin M. (1983) Homozygous C2 deficiency lupus erythematosus and anti-Ro (SSA) antibodies. *Arthritis Rheum.* **26**, 1279–1282.

Reinertsen J. L., Klippel J. H., Johnson A. H., Steinberg A. D., Decker J. L. and Mann D. L. (1978) B-lymphocyte alloantigens associated with systemic lupus erythematosus. *N. Engl. J. Med.* **299**, 515–518.

Ropes M. W. (1976) *Systemic Lupus Erythematosus*. Cambridge, Mass., Harvard, p. 96.

Sibbitt W. L., Likar L., Spellman C. W. and Bankhurst A. D. (1983) Impaired natural killer cell function in systemic lupus erythematosus. Relationship to interleukin-2 production. *Arthritis Rheum.* **26**, 1316–1320.

Siegel M., Holley H. L. and Lee S. L. (1970) Epidemiologic studies on systemic lupus erythematosus: comparative data from New York City and Jefferson County, Alabama, 1956–1965. *Arthritis Rheum.* **13**, 802–811.

Sontheimer D. R., Maddison P. J., Reichlin M., Jordan R. E., Stastny P. and Gilliam J. N. (1982) Serologic and HLA associations in subacute cutaneous lupus erythematosus, a clinical subset of lupus erythematosus. *Ann. Intern. Med.* **97**, 664–671.

Steinberg A. D. and Decker J. L. (1974) A double-blind controlled trial comparing cyclophosphamide, azathioprine, and placebo in the treatment of lupus glomerulonephritis. *Arthritis Rheum.* **17**, 923–937.

Steinberg A. D., Raveché E. S., Laskin C. A., Smith H. R., Santoro T., Miller M. L. and Plotz P. H. (1984) Systemic lupus erythematosus: insights from animal models. *Ann. Intern. Med.* **100**, 714–727.

Tan E. M., Schur P. H., Carr R. I. and Kunkel H. G. (1966) Deoxyribonucleic acid (DNA) and antibodies to DNA in the serum of patients with systemic lupus erythematosus. *J. Clin. Invest.* **45**, 1732–1740.

Tan E. M., Cohen A. S., Fries J. F., Masi A. T., McShane D. J., Rothfield N. F., Schaller J. G., Talal N. and Winchester R. J. (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* **25**, 1271–1277.

Verrier-Jones J., Cumming R. H., Bacon P. A., Evers J., Frazer I. D., Bothamley J., Tribe C. R., Davis P. and Hughes G. V. R. (1979) Evidence for a therapeutic effect of plasmapheresis in patients with systemic lupus erythematosus. *Q. J. Med.* **48**, 555–576.

Watson R. M., Lane A. T., Barnett N. K., Bias W. B., Arnett F. C. and Provost T. T. (1984) Neonatal lupus erythematosus: a clinical, serological and immunogenetic study with review of the literature. *Medicine* **63**, 362–378.

Wong K., Ai E., Jones J. V. and Young D. (1981) Visual loss as the initial symptom of systemic lupus erythematosus. *Am. J. Ophthalmol.* **92**, 238–244.

Scleroderma

Baron P., Lee P. and Keystone E. C. (1982) The articular manifestations of progressive systemic sclerosis (scleroderma). *Ann. Rheum. Dis.* **41**, 147–152.

Birnstingl M. (1971) The Raynaud syndrome. *Postgrad. Med. J.* **47**, 297–310.

Fleischmajer R. (1977) The pathophysiology of scleroderma. *Int. J. Dermatol.* **16**, 310–318.

Fleischmajer R., Perlish J. S. and West W. P. (1977) Ultrastructure of cutaneous cellular infiltrates in scleroderma. *Arch. Dermatol.* **113**, 1661–1666.

Horan E. C. (1969) Ophthalmic manifestations of progressive systemic sclerosis. *Br. J. Ophthalmol.* **53**, 388–392.

Kahaleh M. B., Sherer G. K. and LeRoy E. C. (1979) Endothelial injury in scleroderma. *J. Exp. Med.* **149**, 1326–1335.

LeRoy E. C., Mercurio S. and Sherer G. K. (1982) Replication and phenotypic expression of control and scleroderma human fibroblasts: responses to growth factors. *Proc. Natl. Acad. Sci. USA.* **79**, 1286–1290.

Manschott W. A. (1965) Generalized scleroderma with ocular symptoms. *Ophthalmologica* **149**, 131–137.

Maricq H. R., Spencer-Green G. and LeRoy E. C. (1976) Skin capillary abnormalities as indicators of organ involvement in scleroderma (systemic sclerosis), Raynaud's syndrome and dermatomyositis. *Am. J. Med.* **61**, 862–870.

Oliver J. A. and Cannon P. J. (1977) The kidney in scleroderma. *Nephron* **18**, 141–150.

Pisko E., Gallup K., Turner R., Parker M., Nomeir A.-M., Box J., Davis J., Box P. and Rothberger H. (1979) Cardiopulmonary manifestations of progressive systemic sclerosis. *Arthritis Rheum.* **22**, 518–523.

Porter J. M., Snider R. L., Bardana E. J., Rösch J. and Eidemiller L. R. (1975) The diagnosis and treatment of Raynaud's phenomenon. *Surgery* **77**, 11–23.

Rothfield N. F. and Rodnan G. P. (1968) Serum antinuclear antibodies in progressive systemic sclerosis (scleroderma). *Arthritis Rheum.* **11**, 607–617.

Sinclair R. A., Antonovych T. T. and Mostofi F. K. (1976) Renal proliferative arteriopathies and associated glomerular changes. A light and electron microscopic study. *Hum. Pathol.* **7**, 565–588.

Steen V. D., Owens G. R., Redmond C., Rodnan G. P. and Medsger T. A. (1985) The effects of D-penicillamine on pulmonary findings in systemic sclerosis. *Arthritis Rheum.* **28**, 882–888.

Tan E. M., Rodnan G. P., Garcia I., Moroi Y., Fritzler M. J. and Peebles C. (1980) Diversity of antinuclear antibodies in progressive systemic sclerosis. Anti-centromere antibody and its relationship to CREST syndrome. *Arthritis Rheum.* **23**, 617–625.

West R. H. and Barnett A. J. (1979) Ocular involvement in scleroderma. *Br. J. Ophthalmol.* **63**, 845–847.

Chapter five

The Eye and Joint Disease

INTRODUCTION

In one large series of 1927 cases of uveitis seen over a 10 year period (Kimura et al., 1967) 10% were associated with some sort of joint disease. In another large series, signs of ankylosing spondylitis were found in 12·5% of cases of acute anterior uveitis (Perkins 1961).

Ocular inflammation occurs in several chronic joint diseases. Each of the three major groups of joint disease to be discussed tends to have its own pattern of ocular involvement. It is therefore important not to draw loose conceptual relationships between the eye and the joint. Advances in understanding are likely to be made only if common factors are sought within each disease complex. It is reasonable to assume a common pathogenesis for the ocular and joint inflammation within each complex, but there is little understanding of the factors determining why in these diseases, which probably influence all body systems, the joints and the eyes should manifest the most significant clinical disease.

Anatomical and histological analogies cannot be drawn on the basis of present knowledge, nor can functional ones. For example, in rheumatoid arthritis any tissue properties which might be uniquely shared between the sclera and synovium are at present unrecognized. With the exception of the nodules the histology is different. Most experts agree that immune complex mediation is important in rheumatoid arthritis, but in glomerulonephritis, in which the case for immune complex induction is much firmer, eye disease does not occur.

This chapter will deal with three clinical disease groupings:

(1) *Rheumatoid arthritis*, which tends to be associated with scleritis and keratoconjunctivitis sicca.

(2) *Juvenile chronic polyarthritis*, which may be accompanied by a chronic anterior or panuveitis.

(3) *The adult seronegative arthritides*, which tend to be associated with conjunctivitis and acute anterior uveitis.

The pattern of eye disease found with inflammatory bowel disease resembles that of the seronegative arthritides.

An opportunity is taken to discuss the relevance of HLA-B27 and the role of infection before the section dealing with Reiter's syndrome and ankylosing spondylitis.

SJÖGREN'S SYNDROME

Introduction

Sjögren's syndrome is not a single disease. The term embraces three broad clinical groupings but within these there is considerable individual variation. The essential findings are keratoconjunctivitis sicca (KCS) and xerostomia. These may or may not be associated with changes outside the salivary and lacrimal glands.

Divisions

1 Sicca Syndrome

In British literature the finding of dry eyes and mouth unaccompanied by any systemic change at all is accorded this title.

2 Primary Sjögren's Syndrome

A wide variety of extraglandular manifestations occur but none is typical of the classic connective tissue diseases (Moutsopoulos et al., 1979b).

3 Secondary Sjögren's Syndrome

Dry eyes and mouth occur in typical connective tissue diseases such as rheumatoid arthritis, SLE and scleroderma. Sjögren himself first recognized the clinical association of dry eyes and mouth with symptoms of joint disease (Sjögren, 1933). Until recently most descriptions have referred to what is now described as secondary Sjögren's syndrome. In rheumatoid arthritis and SLE, keratoconjunctivitis sicca is the most common of all ocular complications.

The primary and secondary syndromes have many features in common including age at onset of symptoms, immunoglobulin and rheumatoid factor levels and histopathology. However, whereas patients with secondary Sjögren's syndrome tend to possess HLA haplotypes associated with their connective disease component—for example HLA Dw4 in rheumatoid arthritis—the primary syndrome appears to be associated with HLA Dw3 (Moutsopoulos et al., 1979a; Manthorpe et al.,

1981). In addition, antibodies to salivary duct epithelium tend to be found in the serum in the secondary syndrome and not in the primary (Bloch et al., 1965; MacSween et al., 1967).

Prevalence

In rheumatoid arthritis in general 25–50% of patients fulfil the criteria of Sjögren's syndrome. Signs of KCS are more common than those of xerostomia (Whaley et al., 1973). When specifically sought in other diseases with autoimmune components such as systemic lupus erythematosus and primary biliary cirrhosis most patients may be found to have it (Alarcón-Segovia et al., 1973, 1974).

Both primary and secondary disease affect the elderly, and the secondary syndrome particularly affects women. The peak onset is at the menopause.

In considerations of prevalence of the *disease* it is important to realize that dryness of the mouth and eyes are quite common in the healthy elderly (Whaley et al., 1972). In addition the tear production is reduced by many drugs, such as the anticholinergics and tricyclic antidepressants.

Clinical Features

Primary Disease

The primary disease usually presents with symptoms of dryness of the eyes or mouth. It evolves over a period of 10 years or so. All exocrine glands are involved and there are glandular and extraglandular manifestations. Lacrimal and salivary gland enlargment may be unilateral and even intermittent. Other organs also become enlarged, with functional impairment. Recurrent pneumonia and pleurisy may result from bronchial gland impairment and extraglandular infiltration (Constantopoulos et al., 1985). Renal tubular acidosis, renal tubular atrophy and fibrosis, and nephrocalcinosis also occur (Talal et al., 1968). Gastritis and pancreatitis are seen and polymyositis is common. Vasculitis affects fewer than 10% of patients and causes skin ulceration and peripheral neuropathy. Purpura and Raynaud's phenomenon may also form part of the picture. A type of arthritis has been described in the primary syndrome. Clinical or biochemical evidence of liver disease is found in up to 10% of patients. Hypothyroidism has been reported in a similar proportion of patients (Fox et al., 1984), and the similarity between the histological response in Sjögren's syndrome and Hashimoto's thyroiditis has long been recognized (Bunim, 1961).

Secondary Disease

Disease secondary to other conditions has a similar pattern. Salivary gland swelling, lymphadenopathy, splenomegaly, myositis, Raynaud's phenomenon, purpura and renal involvement tend to be less marked than in the primary disease (Pavlidis et al., 1982).

Lymphoma in Sjögren's Syndrome

The terminal expression of the disease is the development of lymphoreticular neoplasms. The overall risk for this is more than 40 times what is expected in the normal population (Kassan et al., 1978). The distinction of pseudolymphomatous infiltration from true lymphoma is often difficult. Several histological types of lymphoma have been described (Bloch et al., 1965; Kassan et al., 1978) but in the primary disease these appear to be due to a monoclonal B-lymphocytic process, usually of the IgM class, giving rise to B-cell lymphomas or Waldenström's macroglobulinaemia (Faguet et al., 1978; Zulman et al., 1978).

Keratoconjunctivitis Sicca

Patients complain of burning, itching or a feeling of grittiness in the eyes. They may have difficulty keeping the eyes open. Symptoms are worse in dry or smoky environments. In severe cases the eyes are red, photophobic and obviously uncomfortable. In mild cases close examination may be necessary to reveal evidence of dryness, which appears in the form of fine grey spots on the corneal epithelium, especially in the interpalpebral strip. These spots are tiny areas of epithelial damage or absence. They enlarge and coalesce as dryness worsens. Superficial corneal vascularization may develop and frank corneal ulceration sometimes occurs. In advanced disease shrinkage of the conjunctiva may become evident. The eye is also much more prone to infection.

Strands of mucus are frequently found attached to the cornea or lying in the lower fornices of the conjunctiva. A filamentary keratitis may be seen in which strands of mucus and rolled-up diseased epithelium are adherent to the cornea. This is a particularly painful condition because blinking moves the filaments, tugging on the epithelial attachments and tending to strip off further epithelium. It is not clear whether the mucus manifestations are the result simply of an increase in mucus secretion (or an abnormal mucus) or to mucus precipitation because of the disturbed balance of components in the tear film resulting from a fall in the watery component.

Pathology and Immunopathology

In the exocrine glands there is an infiltration around the ducts and in the acini consisting predominantly of lymphocytes, variable numbers of plasma cells and occasional reticulum cells. The secretory epithelium degenerates, and the ducts become filled with inspissated material. Irregular dilatation of the ducts occurs (sialectasia), and polymorphs and eosinophils may be found around these areas, as they are prone to infection. Eventually the gland is destroyed and replaced partly by fatty tissue but principally by fibrosis.

Because of the risks of complications it is not customary to biopsy major salivary or lacrimal glands. However, excellent histological information can be obtained from labial salivary gland biopsy (Chisholm and Mason, 1968; Tarpley et al., 1974).

Labial gland biopsies have shown increased T- and B-lymphocytes in the tissues in both primary and secondary disease (Fox et al., 1982; Kilpi et al., 1983). B-cells are sometimes increased in the peripheral blood (Talal et al., 1974). The T-cells in the gland are helper cells (Fox et al., 1982), presumably encouraging the local B-cell hyperactivity, which accounts for the increased immunoglobulin synthesis observed in tissue culture of salivary gland lymphoid cells in Sjögren's syndrome (Talal et al., 1970). It has been suggested that at the time lymphoid neoplasms develop the polyclonal B-cell activation has become a monoclonal one (Zulman et al., 1978).

Investigation

The signs of corneal and conjunctival dryness can easily be accentuated by staining with Rose Bengal dye. This is taken up by the tiny spots of disordered epithelium, which appear dark blue when viewed with red-free light.

Schirmer's test of tear production (Schirmer, 1903) is still the most helpful investigation. However, it may be badly performed, and the results must be interpreted with the patient's age in mind. A standard strip of filter paper 40 mm long and 5 mm wide is folded 5 mm from one end so that this can be inserted in the lower conjunctival fornix. The eyes are then closed and the strip is left in place for 5 minutes. Normally more than 10 mm of the strip beyond the fold is wetted by tears. It is customary to perform the test before any other interference with the eyes, so as to obtain baseline results. Some workers advocate the prior use of local anaesthetic drops, on the grounds that the above method of performance causes reflex tear production from the irritation of the strip, and thus does not give basal measurements.

However, they in turn ignore the fact that all local anaesthetic drops are initially irritant. The important point is that one should select one method and adhere to it so that results will be reasonably reproducible. An assessment of tear flow on stimulation can be obtained by performing the test after the brief inhalation of 10% ammonia solution held 15 cm from the nose.

There are other more sophisticated tests, such as observation of the time the tear film takes to break up when the eye is held open, but in clinical practice they have not proved very useful because of the difficulty of standardizing important factors such as the humidity of the room, air flow and temperature.

Assessment of salivary flow is difficult and can only be done reliably under conditions of maximal stimulation. Formal measurement of parotid flow shows a decrease in about 60% of patients (Pavlidis et al., 1982). In practice the absence of pooling of saliva in the floor of the mouth is taken as a gross sign of reduced production.

Parotid sialography shows gross distortion and dilatation of the ducts (sialectasis).

Salivary gland uptake of radioactive technetium pertechnetate ($^{99}Tc^{m}$ pertechnetate) is reduced in the primary form of the syndrome (Stephen et al., 1971).

Histological findings on biopsy of labial salivary glands have already been mentioned (*see* Pathology and Immunopathology).

Haematological studies show a mild anaemia and leucopenia in about a third of patients. The ESR is elevated, as are immunoglobulin levels. There may be hyperviscosity because of cryoglobulins and IgG-antiIgG immune complexes (Lawley et al., 1979). Highest levels of immunoglobulins and rheumatoid factors tend to be found in the primary syndrome (Bloch et al., 1965). The rheumatoid factors in disease secondary to rheumatoid arthritis are the same as those normally found in rheumatoid arthritis, but in the primary syndrome they are directed against different antigenic determinants on the IgG molecule. Patients with the primary syndrome also have more non-specific autoimmune antibodies but do not as a rule have high levels of antibodies against salivary epithelium. This is the reverse of the secondary syndrome.

Treatment

The Mouth

Treatment of the dry mouth can be very difficult but most patients control their symptoms by taking oral fluids frequently. Oral candidiasis may be a problem requiring special measures.

The Eyes

Most patients respond well to local treatment for dry eyes (Whaley et al., 1973). Many tear substitutes are available, but additional measures may be required to control the mucus-associated problems and any secondary infection. Artificial tears represent attempts to combine the qualities of normal tears with powers of constituting an intact film over the cornea and conjunctiva. Newer preparations require less frequent application than the older ones such as hypromellose. Some suitable tear substitutes are:

g. hypromellose 0·5% or 1%
g. BJ6
Tears Naturale (Alcon)
Liquifilm Tears (Allergan)
Lacri-Lube (Allergan)

Acetylcysteine drops, 5% or 10%, are used as a mucolytic.

The frequency of application depends on the severity of the dryness and the needs of the patient to remain comfortable. Drops may need to be used every hour or even more frequently.

Conservation of the tears that are produced can be attempted in severe cases by occluding the lacrimal puncta by cautery. However, before this is done the efficacy of punctal occlusion should be tested by the temporary insertion of gelatin rods into the lacrimal canaliculi.

Complications require treatment on their own merits. The lymphomas sometimes respond well to steroids and cyclophosphamide.

RHEUMATOID ARTHRITIS

Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disease in which all organs of the body may be affected, but disease of the joints and surrounding tissues produces the dominant clinical signs and symptoms and is responsible for most of the morbidity of this condition.

Diagnosis

Despite the importance of various laboratory investigations in this disease the diagnosis is a clinical one. In use are two groups of diagnostic criteria. The clinical spectrum of the disease is well illustrated by listing these criteria.

The criteria of the American Rheumatism Association (the ARA Criteria) (Ropes et al., 1958), are the following eleven:

(1) Morning stiffness.

(2) Pain on motion or tenderness in at least one joint (observed by a physician).

(3) Swelling (soft tissue thickening or fluid, not bony overgrowth alone) in at least one joint (observed by a physician).

(4) Swelling (observed by a physician) of at least one other joint (any interval free of joint symptoms between the two joint involvements may not be more than 3 months).

(5) Symmetrical joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body (unilateral involvement of midphalangeal, metacarpophalangeal or metatarsophalangeal joints is acceptable without absolute symmetry). Terminal phalangeal joint involvement will not satisfy this criterion.

(6) Subcutaneous nodules (observed by a physician) over bony prominences, on extensor surfaces or in juxta-articular regions.

(7) X-ray changes typical of rheumatoid arthritis (which must include at least bony decalcification localized to or greatest around the involved joints and not just degenerative changes). Degenerative changes do not exclude patients from any group classified as rheumatoid arthritis.

(8) Positive agglutination test – demonstration of the 'rheumatoid factor' by any method which, in two laboratories, has been positive in not over 5% of normal controls – or positive streptococcal agglutination test.

(9) Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).

(10) Characteristic histologic changes in synovial membrane with three or more of the following: marked villous hypertrophy; proliferation of superficial synovial cells often with palisading; marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with tendency to form 'lymphoid nodules'; deposition of compact fibrin, either on surface or interstitially; foci of cell necrosis.

(11) Characteristic histologic changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

In criteria 1 to 5 the joint signs and symptoms must be continuous for at least 6 weeks.

The diagnosis is 'Classical' if 7, 'Definite' if 5, and 'Probable' if 3 criteria are present.

There is a long list of *exclusions* in the diagnostic criteria because many other generalized diseases may produce a clinical picture resembling rheumatoid arthritis in one of its many guises. These include the rash of lupus erythematosus, the presence of LE cells in the blood, histological evidence of periarteritis nodosa, signs and symptoms of dermatomyositis or scleroderma, rheumatic fever, gout, acute

infectious arthritides, tuberculous arthritis, Reiter's syndrome, neuropathic arthritis, shoulder–hand syndrome, hypertrophic pulmonary osteoarthropathy, alkaptonuria, sarcoidosis, multiple myeloma and leukaemia.

These criteria appear to admit a large number of patients with disease of mild degree which goes into remission after a few years (O'Sullivan and Cathcart, 1972).

The other group of criteria, the so-called 'New York Criteria', were proposed at the Third International Symposium of Population Studies of the Rheumatic Diseases in New York in 1966 (Bennett and Burch, 1967). They are more stringent than the ARA criteria. When they are applied they tend to identify patients whose disease persists. They are as follows:

(1) A history of pain in three or more limb joints.
(2) Involvement by swelling, limitation of motion, subluxation or ankylosis of at least 3 limb joints, *including* at least one hand, wrist or foot joint and symmetry of one joint pair, and excluding the distal interphalangeal joints, the 5th proximal interphalangeal joints, the 1st carpometacarpal joints, the 1st metatarsophalangeal joints and the hips.
(3) X-ray features of grade 2 erosive arthritis.
(4) Positive serological reaction for rheumatoid factor.

Epidemiology

The prevalence of rheumatoid arthritis is variously estimated between 1/100 and 1/1000 of the adult population, depending upon the stringency of the criteria used for diagnosis. It affects women 2–3 times more commonly than men.

Population surveys aimed at identifying environmental risk factors are difficult to interpret (Lawrence, 1970). In Sweden it does appear to be more common in persons engaged in heavy outdoor work (Hellgren, 1970). The view is widely held that the onset of symptoms and of exacerbations are commoner in the colder months of the year.

Evidence for an association with genetic factors is quite firm. The disease has been found more frequently than expected in the female relatives of patients (Siegel et al., 1965) and there is aggregation of severe seropositive disease in families and in monozygous twins (Lawrence, 1970).

The B-cell alloantigens HLA Dw4 and Ia4 are found with higher frequency in patients than in controls (McMichael et al., 1977; Stastny, 1978, 1983). This is in contrast with juvenile chronic polyarthritis in which the frequency of HLA Dw4 is diminished (Stastny and Fink, 1979).

It has not been possible to establish a direct link between HLA Dw4 and the rheumatoid factors (Engleman et al., 1978). Classic rheumatoid arthritis does occur in patients who are seronegative, at least to conventional testing. The D locus genes are believed to be linked to the immune response genes, and so a genetic predisposition and the capacity to make rheumatoid factors can at most be only contributing factors to the aetiology and pathogenesis of the disease. This field is in a state of rapid evolution. Information is appearing concerning individual susceptibility to certain disease features, including susceptibility to toxic drug reactions. The interested reader is advised to consult current issues of the journal *Transplantation Proceedings* (New York, Grune & Stratton), in which much of the latest work is published.

Clinical Features

Most cases present with a gradual onset of polyarthritis, and many patients are able to recall antecedent systemic symptoms such as fatigue, malaise and myalgia. Joint disease may present with stiffness in the mornings, rather than actual pain. Prodromal symptoms are most common in the shoulders, wrists and metacarpophalangeal joints (Jacoby et al., 1973).

The joints most commonly affected in established disease are those of the wrists and hands (except the distal interphalangeal joints), but approximately half those affected also suffer arthritis of the knees, ankles and shoulders. Joint involvement tends to be symmetrical.

Stiffness and pain is eventually accompanied by swelling of the affected joints, due to accumulation of fluid within the joint space and also in the surrounding soft tissues. Joints feel warm and are tender. Adjacent muscles soon become atrophic and movement is guarded. Muscle pain may accompany or precede joint pain.

The ESR is elevated, often to more than 100 mm in the first hour, and there is a mild normochromic anaemia and leucocytosis. Tests are usually positive for rheumatoid factor and negative for ANA. In the serum alpha-2 and gamma globulins are elevated. Joint fluid is straw-coloured and contains fibrin and polymorphs.

Once the disease is established a variety of joint deformities develops. The most obvious is the ulnar deviation of the metacarpophalangeal joints. Involvement of the joints of the cervical spine, knees and ankles is less obvious. Muscle weakness, partly from disuse, partly from tendon destruction by inflammation, and also possibly from myositis adds to the deformity. (*Figs.* 63, 64.)

Although those who apply very stringent criteria for diagnosis would dispute the statement, many patients suspected of having rheumatoid arthritis stop having symptoms after a year or two.

Remission occurs in all affected joints and leaves no sequelae. Perhaps as many as 50% of patients enjoy remissions varying from several months to many years in duration. Many of these patients need only symptomatic therapy and physiotherapy.

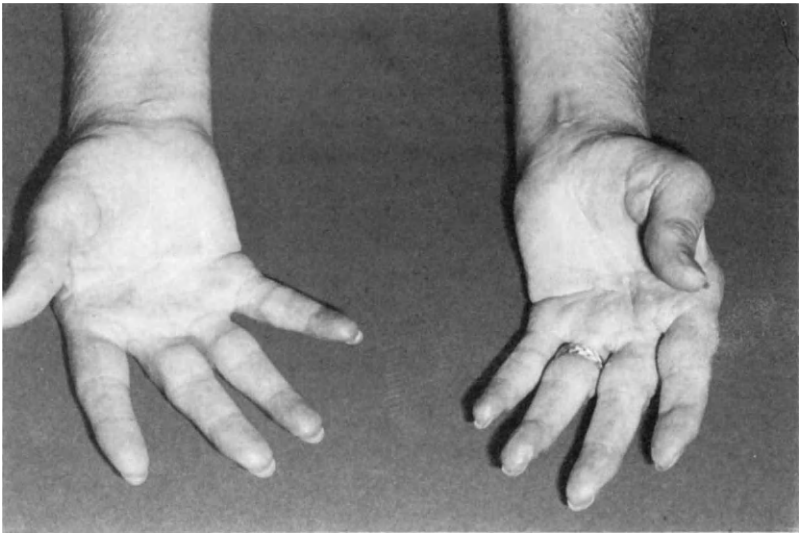


Figure 63 Rheumatoid arthritis: ulnar deviation deformity of hands. (Dr Michael Denman.)

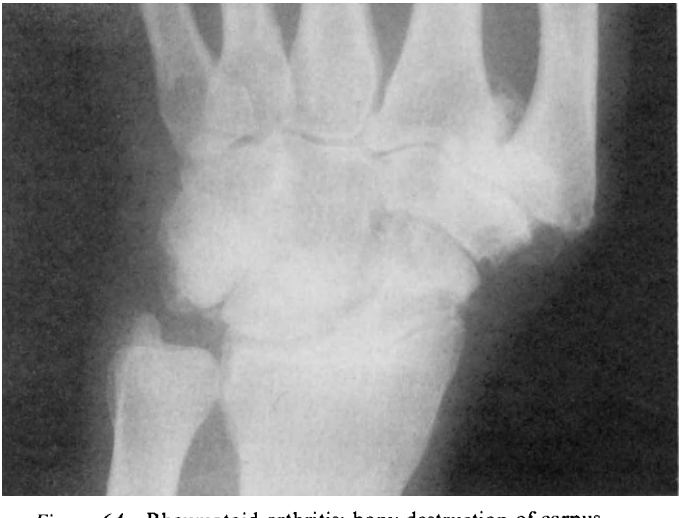


Figure 64 Rheumatoid arthritis: bony destruction of carpus. (Dr Michael Denman.)

The remainder progress with varying rapidity towards a state of destructive disease with great physical disability. Most respond to therapy but few escape some of the burden compounded of joint pain and reduced mobility, the anxiety and frustration of the social and economic consequences, and the side effects of therapy.

Clinical Variants

Palindromic Rheumatism

This is probably an unusual presentation of a mild form of rheumatoid arthritis. There is pain in one or two joints lasting at most a few days, and associated with histological signs of acute inflammation (Hench and Rosenberg, 1944). About half the patients develop low-grade rheumatoid arthritis (Williams et al., 1971).

Still's Disease in the Adult

Some adults in the third or fourth decade present with a pauciarticular arthritis which is clinically and serologically typical of Still's disease (Bywaters, 1971).

Felty's Syndrome

This consists of severe seropositive rheumatoid arthritis accompanied by otherwise unexplained splenomegaly. Sjögren's syndrome is common and scleritis has been described (Barnes et al., 1971). Titres of rheumatoid factor are usually high, and ANA is also present.

Extra-articular Disease

Extra-articular disease is in general commoner in patients with high levels of rheumatoid factors, soluble immune complexes and persistent severe joint disease (Hart, 1969; Gordon et al., 1973).

Skin

Subcutaneous nodules occur in about a third of patients. They are found particularly on the extensor surface of the arms but occur at other pressure points including the bridge of the nose in those who wear spectacles. Another major skin lesion is due to arteritis of the digital arteries. This results in tiny infarcts in the nailfold and finger tips, and sometimes ulceration and gangrene of the skin. A purpuric type of lesion in the dependent areas also occurs as a result of necrotizing vasculitis of the skin. (*Figs.* 65, 66.)

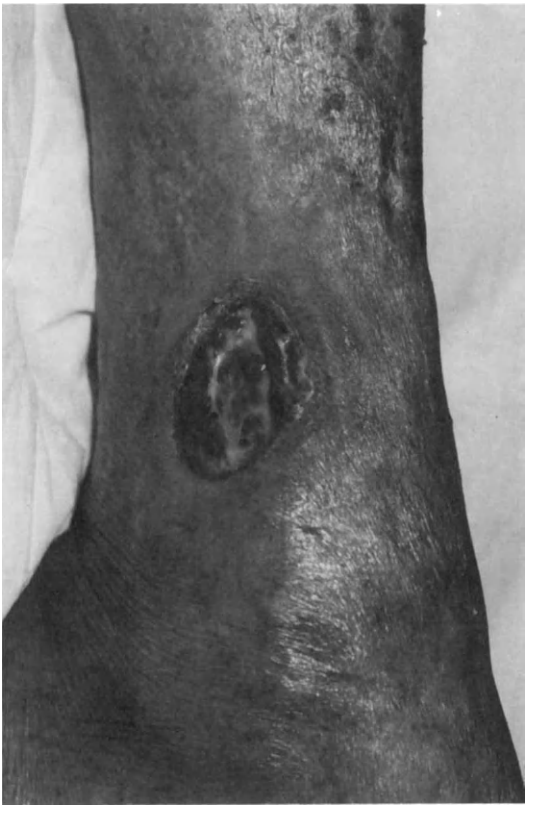


Figure 65 Rheumatoid arthritis: vasculitic skin ulcer. (Dr Michael Denman.)

Lungs

Asymptomatic pulmonary disease is common, especially inflammation of the pleura. Diffuse fibrosis or nodular infiltration of the lungs may also occur and be clinically apparent.

Heart

Pericarditis and myocarditis, like lung disease, are relatively common findings at autopsy, but are rarely symptomatic.

Vasculitis

Vasculitis is common to the pathology of most of the disease manifestations. Apart from the complications already mentioned it may give rise to peripheral neuropathy and occasionally to ischaemic disease of the viscera.

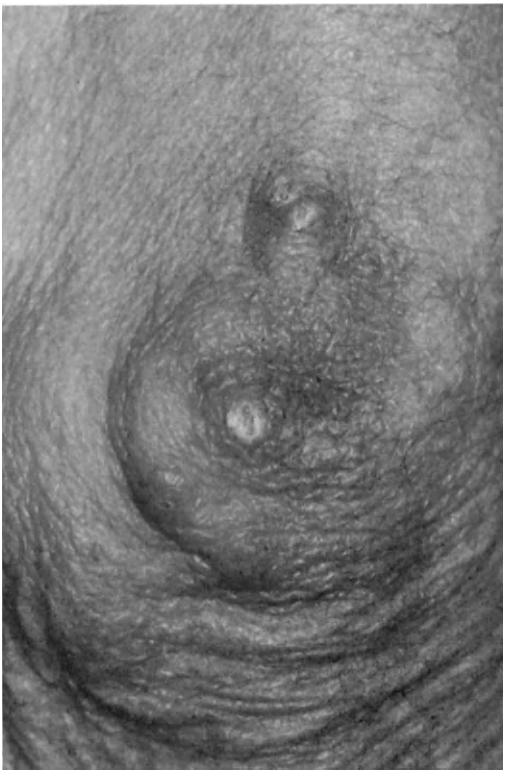


Figure 66 Rheumatoid arthritis: skin nodules. (Dr Michael Denman.)

Sjögren's Syndrome

See above.

Eyes

The principal ocular changes associated with rheumatoid arthritis are dryness of the eyes (keratoconjunctivitis sicca), episcleritis and scleritis.

Keratoconjunctivitis sicca

This is fully discussed in the chapter on Sjögren's syndrome. It occurs in up to 50% of patients with rheumatoid arthritis, particularly women. It is often stated that its incidence increases with age and the severity of the joint disease but this is difficult to substantiate.

Episcleritis and Scleritis

These are regarded as the classic inflammatory eye diseases associated with rheumatoid arthritis but they are both in fact uncommon. In a series of 4210 patients seen in Glasgow the incidence of episcleritis was reported as 0·17%, and scleritis as 0·67% (McGavin et al., 1976). Even if one allowed for the higher figures that would result from a whole of life survey, the incidence would still be low. McGavin and coworkers found that one-third of the patients who presented with scleritis and 5·7% of those presenting with episcleritis had rheumatoid arthritis, but lower figures are reported from other workers (Watson and Hayreh, 1976). A less frequent association is also recognized with other connective tissue diseases, particularly SLE, polyarteritis nodosa, relapsing polychondritis and Wegener's granulomatosis.

Watson and Hayreh have used a simple classification of these conditions which is of great practical help (Watson and Hayreh, 1976). They have pointed out how accurate observation can distinguish scleritis from episcleritis, and have made the important point that while some degree of episcleritis always accompanies underlying scleritis, episcleritis *per se* is never seen to progress to scleritis. The two conditions may coexist. Attention to the proper classification of the condition is crucial for the correct management.

Episcleritis

Episcleritis occurs in sudden attacks. The peak incidence is in the fourth decade and women are affected twice as commonly as men. Affected patients with rheumatoid arthritis seem to be almost exclusively female. Attacks last 7–10 days and may recur for years at 1–3 monthly intervals. Recurrences need not affect the same site or the same eye. Inflammation is usually localized to one part of the interpalpebral area but may be generalized. The eye becomes rapidly red and then tender over 24 hours. Sight is rarely affected, and the symptoms are of discomfort rather than pain. In rare severe cases the lids may be swollen.

Diagnosis depends upon the recognition that there are three layers of vessels superficial to the relatively avascular sclera: (1) the deep episcleral plexus on the surface of the sclera, whose vessels run an irregular and crossing course; (2) the episcleral plexus proper, whose vessels are straight and radial; and (3) the conjunctival plexus.

In simple episcleritis the episcleral vessels are congested and the episclera and overlying conjunctiva are oedematous. The congested vessels can be moved on the underlying sclera, which retains its usual smooth contour. It may sometimes be necessary to constrict the episcleral vessels with 0·1% adrenaline or 10% phenylephrine drops in order to see the deep episcleral vessels and the surface of the sclera to

be sure that the episcleritis is not simply secondary to underlying scleritis. Most episcleritis is 'simple' and the swelling diffuse and salmon-pink in colour. Some cases are 'nodular', the swelling consisting of one or more nodules 2–3 mm in diameter, and being more bluish-red in colour. These nodules can still be moved a little on the underlying sclera. They tend to persist rather longer than the changes of 'simple' episcleritis.

Sometimes the cornea adjacent to a patch of episcleritis becomes oedematous, but permanent changes are rare.

Most cases require no treatment (Watson et al., 1973), but oxyphenbutazone 10% ointment is the drug of choice. Steroid ointment may be used if oxyphenbutazone is ineffective. If systemic therapy is required oxyphenbutazone was recommended, starting at 600 mg/day for 7 days and then 400 mg/day for 14 days more, but because of the high incidence of bone marrow depression and death from this drug it has been withdrawn from routine availability. Indomethacin 100 mg/day for 7 days, then 75 mg/day for a further 14 days is a suitable alternative.

During attacks the episcleral tissues show infiltration with lymphocytes and occasional eosinophils and mast cells.

Scleritis

Most cases of scleritis involve the anterior part of the sclera. Watson and Hayreh have classified this as diffuse, nodular or necrotizing, the last occurring with or without inflammation. Diffuse and nodular types are equally common and affect women more commonly than men. Necrotizing disease is rarer and mainly affects women. It is associated with severe rheumatoid disease and a high mortality. The onset is in the fourth to sixth decades. Diffuse disease is usually bilateral, but nodular and posterior scleritis is usually unilateral. The suggested classification is not exclusive since, for example, posterior scleritis is not uncommon with diffuse anterior disease.

Pain and redness with a bluish tint comes on gradually over 10 days or so. Involved sclera is very tender, particularly the nodules. The eye waters and is photophobic. The pain is most severe around the eye rather than in it, is worse at night, and tends to be resistant to analgesics. Untreated attacks last several months. Episodes recur for many years but it does seem that prompt treatment of the first attack reduces the incidence of recurrence. This may also reduce the chance of non-necrotizing disease progressing to necrotizing disease, which may never fully resolve.

Diffuse Anterior Scleritis

This may involve small or large areas of sclera. All three plexuses of

vessels are congested and the deep episcleral plexus can be seen to be raised on the swollen sclera. Over the affected area vessels eventually appear, which follow an abnormally tortuous course. On resolution the affected sclera looks slightly bluish, not because of thinning but because of alterations in the arrangement of scleral collagen fibres. Some of the abnormal vessels also remain in evidence. Recurrences occur at the same, adjacent or totally separate areas. In half the cases both eyes become affected.

Nodular Anterior Scleritis

Part of the inflamed sclera is more elevated in one or more nodules of an intense bluish redness. Nodules are extremely tender, immobile, and the episcleral tissues can be moved slightly over them. Most occur in the interpalpebral area a few millimetres from the limbus. They may become confluent, and when this occurs with nodules which are especially close to the limbus there is a significant incidence of secondary glaucoma. (*Fig.* 67.)

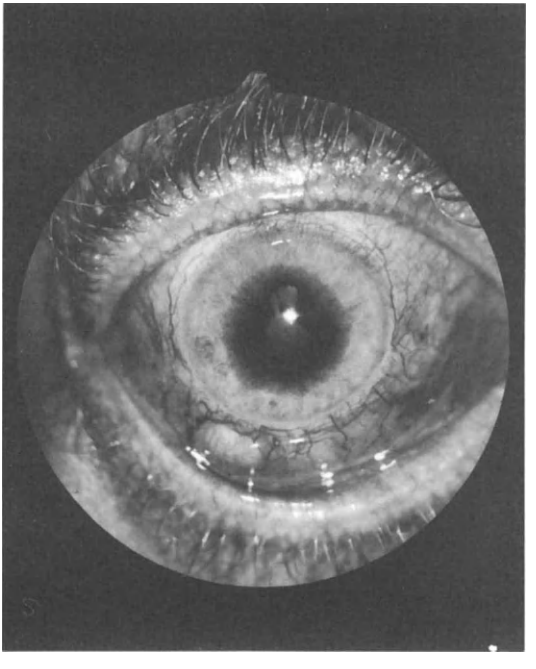


Figure 67 Rheumatoid arthritis: nodular scleritis and uveitis.

Necrotizing Anterior Scleritis (*Fig.* 5)

The clinical picture in necrotizing scleritis consists usually of one or more pale areas of necrosis surrounded by areas of active scleritis. If untreated it tends to progress circumferentially around the globe, the sclera remaining translucent and thinned, and granulation tissue replacing the necrotic sclera. However, there may be large areas where the choroid appears only to be covered by conjunctiva. In the absence of trauma perforation is rare. Necrotizing scleritis is particularly painful except when there are no signs of surrounding inflammation. The latter condition is known as 'scleromalacia perforans'.

Whenever necrosis occurs, including necrosis of a nodule, the overlying episclera becomes avascular.

Posterior Scleritis

Even though this condition is uncommon it is probably often missed. Pain is severe and as with anterior scleritis tends to be referred to the structures around the eye. Visual acuity is affected by virtue of associated changes in the retina and choroid. Oedema of the optic disc and macula, detachment of the retina and choroid, and choroidal granulomas are all described, and if the involved sclera is relatively forward avascular choroidal detachments may occur with shallowing of the anterior chamber and angle closure glaucoma (Cleary et al., 1975; Quinlan and Hitchings, 1978). All patients have posterior or panuveitis. There is usually some limitation of movement and proptosis of the affected eye, and conjunctival chemosis.

Treatment usually brings about a rapid resolution of all the signs and symptoms except for the retinal and choroidal complications. These are slow to settle and leave subretinal fibrotic scars and some disturbance of the retinal pigment epithelium.

Complications of Scleritis

KERATITIS Several forms of keratitis are described. The first is *stromal keratitis*, in which the superficial and mid-stroma becomes involved with a dense white infiltration in both central and peripheral areas. These infiltrates may be surrounded by 'precipitin rings'. They coalesce if the condition is allowed to progress. Vascularization occurs from the periphery and the cornea may become grossly opaque. *Sclerosing keratitis* may appear *de novo* or may evolve from stromal keratitis. The cornea adjacent to areas of scleritis becomes swollen and gradually opacifies. Vascularization follows. Unlike stromal keratitis the opacity does not disappear with treatment, and extends further with recurrences of scleritis. *Peripheral corneal guttering* occasionally appears

and the gutter need not be adjacent to the area of scleritis. It may extend around the circumference of the cornea, but is rarely a severe problem in management, except when it occurs in necrotizing disease. In this case the degree of thinning may require grafting. Another rare event in patients with necrotizing disease is a rapid thinning of the corneal stroma (keratolysis), and this also requires grafting.

UVEITIS Mild uveitis occurs in almost 50% of patients (Wilhelmus et al., 1981). It is usually an anterior uveitis, but posterior uveitis always occurs with posterior scleritis, and all patients with scleromalacia perforans have uveitis.

CATARACT Cataract is unusual, and tends only to occur in severe necrotizing or long-lasting disease.

Pathology of Scleritis

The pathological appearances are not specific. In diffuse disease there is an intense infiltration of lymphoid cells. Nodules are the same as other nodules seen elsewhere in rheumatoid arthritis (Mundy et al., 1951), with a granulomatous inflammatory reaction, central necrosis, a palisade of epithelioid and giant cells, and lymphocytes and plasma cells on the outside. In necrotizing disease mast cells are prominent in the infiltration, and degeneration of the scleral collagen matrix may be an early event mediated by fibroblastic cells (Young and Watson, 1984).

Treatment of Scleritis

Treatment needs to be sustained, usually for a minimum of 6 months, and some patients require treatment for the rest of their lives.

Symptomatic relief is often achieved by the use of local oxyphenbutazone 10% ointment (which is not felt to carry the risk of systemic therapy with this drug, and is still freely available), or prednisolone 0·5% or betamethasone 0·1% ointment.

These are insufficient to arrest the inflammation, which requires systemic therapy. Oxyphenbutazone is no longer freely available because of its serious side effects. An alternative is indomethacin, starting with 100 mg/day until the pain has gone and inflammation begins to subside, then reducing to 75 mg/day. Many other of the newer non-steroidal antiinflammatory agents are probably equally effective. If these drugs fail, recourse is had to prednisolone therapy, starting with 80–100 mg/day and gradually reducing the dose as the condition responds. High-dose steroid therapy appears to be obligatory in necrotizing disease. Azathioprine, starting at 100 mg/day, may

be added and may be found helpful in patients who cannot tolerate high steroid dosage. The final regime for recalcitrant cases is a combination of cyclophosphamide, 100 mg/day, with prednisolone in doses of about 60 mg/day.

Seropositivity – the Rheumatoid Factors

Rheumatoid factors are autoantibodies to antigenic determinants on the Fc portion of immunoglobulin G (IgG) molecules. The factors themselves are of IgM, IgG and IgA classes of immunoglobulin but it is customary only to estimate the IgM rheumatoid factors in most laboratories. They are efficient agglutinators of antigen-coated particles. This property is employed in the tests commonly used to detect them, for example agglutination of human IgG-coated latex or bentonite particles, and red cells coated with rabbit IgG in the classic Rose–Waaler reaction. Precipitation, complement, fixation and radioimmunoassays are now also widely used in the detection of rheumatoid factors.

Rheumatoid factors are not specific to rheumatoid arthritis. They occur in low titres in other rheumatological diseases and in viral infections, chronic inflammatory diseases, and neoplasia after irradiation or chemotherapy, and in some individuals with no apparent disease at all. More than 70% of patients with rheumatoid arthritis have positive latex agglutination tests at a serum dilution which excludes 95% of the normal population. Repeated testing of the so-called 'seronegative' patients reveals conversion to seropositivity in time in many cases, and those who remain seronegative usually have mild disease.

It is not clear what causes patients to begin producing rheumatoid factors, nor what is their precise role in the pathogenesis of the disease. Much of the relevant literature demonstrates clearly that IgG, IgM and IgA are produced by the involved synovial tissue (Smiley et al., 1968; Luthra et al., 1975). Similar findings have been made in culture of salivary gland lymphoid cells in Sjögren's syndrome, especially when it occurs in rheumatoid arthritis (Talal et al., 1970). However, not all this immunoglobulin is rheumatoid factor.

These immunoglobulins tend to form complexes with IgG, and also self-associating complexes. Levels of immune complexes are generally higher in synovial fluid than in the peripheral blood (Luthra et al., 1975) and the nature of the complexes may also differ in the two sites (Winchester et al., 1971), and serum also contains different classes of complexes (Nineham et al., 1978). Serum levels of circulating immune complexes are higher in patients with severe active synovitis and especially if vasculitis is present, but may be normal in patients with

uncomplicated disease (Nineham et al., 1978; Kammer et al., 1980). Raised levels tend to be associated with low complement levels and so the conclusion has been drawn that the tissue damage in rheumatoid arthritis proceeds through the consequences of immune complex deposition and complement activation. Indeed, it is regarded as a prototype immune complex mediated disease. Complement-fixing complexes of IgG rheumatoid factor have been found in plasma cells of rheumatoid synovium (Munthe and Natvig, 1972). IgM anti-IgG cryoglobulins have been found in patients with rheumatoid vasculitis and a fall in levels correlated with response to therapy (Weisman and Zvaifler, 1975).

Whatever the precise role of the rheumatoid factors proves to be, seropositive patients seem to have a worse course, with more complications and impairment of functional capacity than seronegative patients (Cats and Hazevoet, 1970). Nodules occur much more commonly in seropositive patients. The correlation of the presence of circulating immune complexes with the severity of the disease and the presence of vasculitis has already been mentioned. Self-associating IgG rheumatoid factors have been held responsible for the hyperviscosity syndrome in rheumatoid arthritis (Pope et al., 1975), and it is possible that other findings in the disease may depend upon the presence of specific types of immune complex.

Histopathology

Joint Lesions

The earliest changes are probably reversible within the first few weeks of their onset. Although the available studies are few and can be criticized as perhaps representing changes of early arthritis in general rather than rheumatoid arthritis in particular, it does appear that the initial response is an inflammatory infiltration of the subepithelial layers of the synovium by lymphocytes and plasma cells, giant cells appearing soon after (Kulka et al., 1955; Schumacher et al., 1972).

The next feature is a proliferation of the synovium itself, in which the surface loses its smoothness and becomes hypertrophied into microvilli and villi. The proliferative reaction involves all zones of the synovium, which also becomes infiltrated by lymphoid cells, including lymphocytes, plasma cells, plasmablasts and undifferentiated blast cells. As the picture develops it becomes more apparent that the lymphoid cells are concentrated in a perivascular distribution (Kobayashi and Ziff, 1973). Most of the lymphocytes, both in synovium and joint fluid, are T-cells (Sheldon et al., 1974; Loewi et al., 1975; Bankhurst et al., 1976), but there is no disturbance of T- and B-cell percentages in the peripheral blood (Sheldon et al., 1974). There is

an increase in interstitial fluid and fluid also accumulates in the joint space. A striking and early feature of the proliferation is an increase in subsynovial blood vessels. All these changes are present within 3–4 weeks of the onset of symptoms.

Destructive changes begin at the edge of the joint. Proliferating synovium, containing by this stage phagocytic and fibroblast-like cells, often erodes subchondral bone more than the overlying cartilage. Bone and cartilage erosion appears to occur largely by extracellular enzymic destruction, but fragments of collagen are sometimes found in the cells of the invading fibrovascular tissue (pannus), suggesting a direct cellular phagocytic component in the destruction.

Lymphoid cells in the pannus tend to form follicles and multinucleated cells are prominent in these areas.

Erosion extends not only into the joint surface but also the surrounding capsular ligaments, leading to weakening and instability. Added to the inflammatory damage is that of increased physical trauma secondary to joint instability, which varies in severity depending on the joint. The physical properties of the cartilage also change, making it less able to withstand the stresses of use.

The end stage represents the consequences of progressively reduced movement and muscle atrophy, progressive loss of bone and cartilage, and fibrosis from repeated trauma to the joint. Ankylosis is occasionally seen, and there is a diminution of inflammatory signs and a loss of cellularity and vascularity of the tissues.

Nodules

Subcutaneous nodules are most often found over pressure points. They display a combination of cellular proliferation and vasculitis (Bennett et al., 1940). There is central necrosis surrounded by a zone of cells interspersed with collagen fibres and arranged radially, and peripherally a zone of dense connective tissue. The necrotic centre contains collagen and dense filamentous material which gives rise to the 'fibrinoid' appearance on light microscopy (Cochrane et al., 1964). There is a large amount of intercellular fluid in these nodules and it is thought that rapid changes in this component are responsible for the fact that nodules can appear and enlarge very rapidly.

The pathology of nodules in the sclera and in tendons is the same as described above.

Vasculitis

The vasculitis of rheumatoid arthritis is believed to be mediated by immune complex deposition in the vessel walls, which leads to complement activation and the attraction of polymorphs into the tissue. The

latter release enzymes which produce tissue damage. It has been suggested that the neutropenia found in rheumatoid arthritis may be due to the death of neutrophils after they have engulfed phagocytosable immune complexes formed by the reaction of IgG rheumatoid factors with IgM factors (Theofilopoulos et al., 1974; Ziff, 1977).

The arteritis is commonly a granulomatous process, with periarterial infiltration of lymphocytes and histiocytes which may form palisades as in rheumatoid nodules. In association with high circulating levels of rheumatoid factors and digital arteritis the picture of an obliterative endarteritis may be seen, and in the severest forms of generalized disease a necrotizing arteritis occurs, indistinguishable from polyarteritis nodosa (Solkoloff and Bunim, 1957).

Immunopathology

The cause of rheumatoid arthritis is unknown. It has been suggested that infective agents may cause it, but this is based upon little other than the fact that particular organisms can cause serological and histological changes similar to those found in rheumatoid arthritis. Antibodies with activity against common viruses are synthesized in the joints but this is probably the result of polyclonal B-cell activation (Mims et al., 1985). Viral *antigen* has not been found in the joints. Analogies have been drawn with rheumatic fever and the reactive arthritides, in which infection at a site remote from the joint initiates arthritis, but the arthritis of these conditions has little in common clinically with rheumatoid arthritis.

One common thread connecting hereditary and environmental theories of causation is the apparent disturbance of immune modulation at the level of the synovium. Most of the lymphocytes in the infiltration are helper T-cells (Bankhurst et al., 1976) and are closely associated with HLA-DR-expressing cells in the synovial tissue (Klareskog et al., 1982). Many of the effective drugs seem to cause a down-regulation of these activated T-cells. Such observations have led many to conclude that there is excessive local antibody production as a result of a local deficiency in regulation.

A complete edifice of pathogenesis has been built upon the presence of the rheumatoid factors which parallel the progress of the disease and are believed to be the major component of the immune complexes which are formed within the joint, synovium and elsewhere, leading to the process of complement fixation and inflammation. This remains simply an hypothesis.

A great deal has been done to elucidate the mechanisms of joint damage. The destruction of cartilage and bone matrix appears to be

due to collagenase which is produced by synovial cells in response to interaction with mononuclear cells (Evanson et al., 1968; Dayer and Krane, 1978). The effect of the mononuclear cells may be mediated by prostaglandin E 2 production (Robinson et al., 1975; Dayer et al., 1977). The collagenase has been shown to be localized to the pannus/cartilage interface (Woolley et al., 1980). Less is understood about the mechanism of the bone demineralization which must precede bone matrix destruction.

A deficiency in the production of acute phase modulating reactants, particularly alpha-1 antitrypsin, has been postulated as a factor in the continuing destructive inflammation in this condition. However, plentiful deposits of alpha-1 antitrypsin and alpha-2 macroglobulin have been found at the pannus/cartilage junction in patients with rheumatoid arthritis (Flory and Muirden, 1983) and the genetic phenotype associated with alpha-1 antitrypsin deficiency is not found with an unusually high frequency in patients with rheumatoid arthritis (Geddes et al., 1977; Sjöblom and Wollheim, 1977). The situation may be different in juvenile chronic polyarthritis (Arnaud et al., 1977).

Radiographic Changes

The earliest change is soft tissue swelling around the joint. Then some juxta-articular osteoporosis appears. As the cartilage is destroyed there is gradual narrowing of the joint space. Erosions appear in the surface of the bone within the joint that is not covered by cartilage, that is, the bone between the joint surface and the reflection of the capsule. These erosions sometimes give the impression of cysts in the cortical bone. As the cartilage covering the joint surface is destroyed there is erosion also of the underlying bone. Reactive new bone formation is rare, but there may be sclerosis of the ends of weight-bearing joints. Subluxations may be seen, particularly in the joints of the hands and feet and the cervical spine.

Treatment

General

Apart from its symptomatic effects, treatment does influence the progression of the disease (Scott et al., 1983). A team approach involving the rheumatologist, physiotherapist and family doctor is ideal. Treatment is matched to the particular needs of the patient. What can be expected from therapy and its possible complications should always be kept in mind.

Drugs form only one aspect of treatment. Education and rehabilitation are important for the severely afflicted. In the acute stages enforced rest may be necessary. Immobilization of joints with splints, combined with other local measures such as steroid injection, may be very helpful for localized inflammation. Surgery has a reparative role in synovectomy, release of entrapped nerves, and fusion of the cervical spine. Arthrodesis, arthroplasty and prosthetic joint replacement may also be indicated to relieve pain and restore mobility. When the principal problems are mechanical ones, surgery may be a more appropriate line of management than ever increasing doses of potentially toxic drugs.

Drug Therapy

Introduction

The drug therapy of rheumatoid arthritis is the subject of constant change, particularly as the results of properly controlled trials become available. The following paragraphs are at best only a brief guide to current therapeutic attitudes.

Most patients are managed by non-steroidal antiinflammatory agents (NSAIDs) alone or in combination with analgesics. However, there are situations in which alternative therapeutic regimes are indicated from the outset and these are mentioned in appropriate sections.

(1) NSAIDs and salicylates
(2) Gold
(3) Antimalarials
(4) Sulphasalazine
(5) D-penicillamine
(6) Corticosteroids
(7) Cytotoxic drugs

1 NSAIDs and Salicylates

Patients vary greatly in their response to these drugs and a great deal of trial and error may be involved in finding the best one for an individual. They interfere with prostaglandin synthesis and produce a fall in synovial fluid prostaglandin levels (Higgs et al., 1974). They are not regarded as 'disease modifying' drugs and appear to have little effect on the progression of erosive lesions, despite the possibility that bone resorption may be related to prostaglandin production (Robinson et al., 1975). They have no effect on ESR or C-reactive protein (Amos et al., 1977; Walsh et al., 1979).

Indomethacin is the most widely used NSAID. It appears to have a

lower risk of producing bone marrow depression than the previously popular drugs phenylbutazone and oxyphenbutazone, which have now been withdrawn from general availability.

Epigastric discomfort is quite a common side effect. Gastric lesions occur in up to one-third of patients, although many are asymptomatic (Caruso and Bianchi Porro, 1980). Patients should also be warned of the possibility of light-headedness and giddiness.

Besides indomethacin many NSAIDs are available, including diclofenac, fenprofen, ibuprofen, ketoprofen, naproxen and tolmetin. The choice is very much an individual one (Huskisson et al., 1976).

Aspirin is much less commonly used in new cases than formerly, but it may be helpful when there are moderate constitutional symptoms as well as joint disease.

If disease does not respond rapidly to NSAIDs, resort may be had to a 'second line' drug regime. Patients requiring such therapy often have severe seropositive disease that makes rapid radiological progression. These 'disease modifying' drugs are now also used earlier in patients with severe extra-articular manifestations. Their effect may take several months to be fully manifest.

2 Gold

It is generally agreed that all criteria of disease activity are improved by gold therapy, including synovitis and the ESR, but a definite effect on radiological progression is far from proved (Empire Rheumatism Council, 1961; Co-operating Clinics Committee, 1973; Sigler et al., 1974). Remission is induced in up to one-third of cases. It is given intramuscularly in weekly doses of 50 mg until remission occurs, and then the dose is reduced to 25 or 12·5 mg/week until several years free of disease activity have passed. The mode of action is not understood but it induces changes in mononuclear phagocytes and is sequestered in organs rich in mononuclear cells (Ugai et al., 1979). Side effects include itching, rashes, hepatitis, proteinuria and bone marrow failure. About one-third of patients are prevented from completing a course of treatment because of toxicity.

3 Antimalarials

Chloroquine is effective in doses of 400 mg/day (Freedman and Steinberg, 1960) but there is a marked risk of retinopathy. It is probably safe for indefinitely prolonged therapy if the dose is kept below 250 mg/day, or 3·5 mg/kg/day (Mackenzie, 1983), although retinopathy has occurred at this dose (Marks, 1982). It has been suggested that with appropriate ophthalmic surveillance a daily dose of 400 mg

hydroxychloroquine is safe (Rynes et al., 1978). Patients taking these drugs should have ophthalmologic examination every 6 months while on treatment. It has to be recognized, however, that sophisticated tests are needed to detect early disorders of retinal function which may be missed on routine eye examination. In addition the visual damage may progress long after signs of toxicity have been detected and the drug stopped. Drug deposition in the cornea is regularly seen but is not usually of any clinicial importance. Many rheumatologists regard the antimalarials as less toxic overall than other second line drugs.

4 Sulphasalazine

Trials of sulphasalazine have been undertaken in recent years. It appears to be as effective as gold (Pullar et al., 1983). In the gut it is broken into sulphapyridine and 5-aminosalicylic acid and it shares the toxicity of these drugs. Nausea and headache are common but not usually serious side effects. Rashes sometimes occur. The dose is 40 mg/kg/day.

5 D-*penacillamine*

The clinical effect of D-penicillamine is similar to gold (Multicentre Trial Group, 1973). It is known to inhibit lymphocyte transformation (Roath and Wills, 1974) but may actually stimulate macrophages (Binderup et al., 1980). It has been given in doses of up to 1·5 gm/day, but 600 mg/day is probably all that is needed, and produces fewer side effects (Dixon et al., 1975). Toxic effects are common. Many people have to stop treatment because of rashes, nausea, marrow depression and proteinuria. It may also produce a myasthenia-like syndrome and pemphigus.

6 Corticosteroids

Steroids tend at present to be used mainly in selective situations. Whether or not they modify the disease is uncertain (Glass et al., 1971). Local injections may be effective if only one or two joints are involved. Systemic therapy may be indicated for severe systemic disease, particularly when there is evidence of major vasculitis, and in the elderly when the maintenance of mobility is of prime importance.

7 Cytotoxic Drugs

Azathioprine was initially used in an attempt to reduce steroid dosage in patients already under treatment (Mason et al., 1969). Cyclophosphamide was also used partly with the same objective (Cooperating

Clinics Committee, 1970). It is now more widely employed, particularly as the initial treatment for patients with severe 'vasculitic' disease. Methotrexate is undergoing reassessment. Weekly doses of methotrexate appear to be as effective as continuous azathioprine over a 6- to 12-month period, and no more toxic (Willkens, 1985). Patients must be monitored for the well-known side effects of cytotoxic drugs (Townes et al., 1976).

Two difficulties in interpreting the results of many of the clinical trials of the above drugs are that they have frequently been added to established regimes of treatment with other agents, and follow-up has been short.

Many of the drugs are known to interfere with macrophage function and lymphocyte proliferation, and an effect on the disease would support the hypothesis that rheumatoid arthritis is a chronic T-lymphocyte and macrophage-dependent response to antigens in the synovium (Wilder, 1984).

Prognosis

The fact that a large proportion of patients are not significantly disabled by disease has already been stressed. Most patients enjoy temporary or permanent remission, and there are criteria which define clinical remission (Pinals et al., 1981). A better prognosis is associated with disease of acute onset. A poorer prognosis is associated with seropositivity, onset at less than 30 years of age, a family history of seropositive disease, disease presenting without remission for more than a year, and the presence of extra-articular features (Gordon et al., 1973). Patients who are HLA DRw4 positive may also have a worse course.

High ESR and C-reactive protein levels correlate with erosive joint damage (Amos et al., 1977).

The presence of vascular lesions indicates the worst general prognosis. They are responsible for many of the deaths attributable to rheumatoid arthritis (Bywaters and Scott, 1963).

JUVENILE CHRONIC POLYARTHRITIS

(juvenile rheumatoid arthritis)

Diagnosis

The diagnosis is considered in patients under 16 years of age who have polyarthritis affecting more than 4 joints, present for at least 3 months,

or when synovial membrane biopsy in childhood arthritis shows pathological changes compatible with the diagnosis of rheumatoid arthritis, irrespective of how many joints are involved (Ansell and Bywaters, 1963). The widely observed American criteria for diagnosis (JRA Criteria Subcommittee, 1972) require only that one joint should be involved for 3 months or more, so long as rheumatic fever, collagen diseases such as SLE, dermatomyositis, scleroderma and polyarteritis nodosa, infective arthritis, inflammatory bowel disease, psoriasis and several dermatological and neoplastic disorders are carefully excluded. The most recent criteria revision proposal (JRA Criteria Subcommittee, 1977) requires only 6 weeks' duration for diagnosis. When joint disease has been present for less than 3 months, a concomitant rash, uveitis, pericarditis, involvement of the neck joints, tenosynovitis and a persistent intermittent fever suggest the diagnosis.

In the United Kingdom the term 'juvenile chronic polyarthritis' has replaced the term 'Still's disease'. In the United States the eponym is normally used to describe only one clinical subtype of disease, namely that associated with marked systemic disturbance (*see below*). Still's description of the condition (Still, 1897) includes most of the features recognized today. He discerned that this is a condition distinct from rheumatoid arthritis in the adult. Disease began in most of his 12 cases before the age of 6, and girls predominated. He did not observe eye disease, but corneal band degeneration was recognized as a complication some years later (Ohm, 1910).

Epidemiology

This disease is commoner in girls, except that the sex ratio is equal in disease of acute onset. There are peaks of incidence at 2–5 and 9–12 years of age. The prevalence in the United Kingdom is about 0·6/1000 (Bywaters, 1977).

The cause is entirely unknown and no environmental factors have been identified. A genetic predisposition is suggested by the finding of certain HLA associations which are different from those in rheumatoid arthritis.

HLA Dw4 is found less commonly than normal, in contrast to its raised incidence in rheumatoid arthritis (Stastny and Fink, 1979), but children who are IgM rheumatoid factor positive (*see* Laboratory Investigations) have an *increased* incidence (Clemens et al., 1983). Other D locus antigens have been found with increased incidence, especially Dw8 (Stastny and Fink, 1979; Glass et al., 1980). HLA-B27 is found in patients who progress to overt ankylosing spondylitis, but these patients would be reclassified retrospectively. It also occurs in males with pauciarticular disease, not all of whom progress to ankylosing spondylitis (Fink and Stastny, 1979).

Clinical Features

Many clinical subdivisions have been made but three are generally agreed (Brewer et al., 1972):

1. About 25% of cases, mostly boys, have high spiking fever at the onset, with profound systemic disturbance. Some have a rash which resembles measles, but the lesions do not evolve, but instead appear and disappear quite rapidly. Hepatosplenomegaly and generalized lymphadenopathy, pleuritis, pericarditis and occasionally myocarditis may occur. Definite signs of arthritis may be preceded in this group by polyarthralgia for several months. Tests for rheumatoid factor and ANA are negative, and eye disease is absent. Many develop very severe joint disease.
2. More than a third of patients, mostly girls, have polyarthritis without systemic symptoms and signs. Small joints are particularly involved, sometimes quite severely. A small number develop eye disease.
3. Persistent pauciarticular disease affecting 4 joints or fewer is seen in about one third of patients, also mostly girls. Severe systemic disease is absent. The large joints are mainly affected, but not severely. Most of the ocular pathology is seen in this type of disease. (*Fig.* 68.)

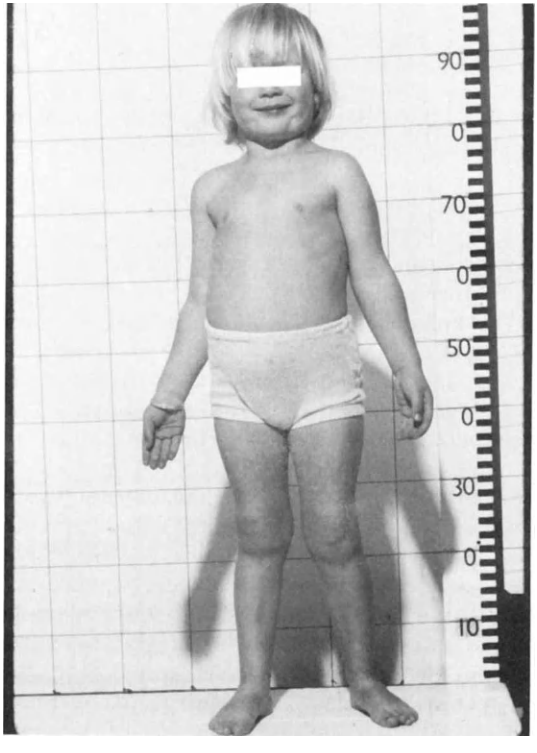


Figure 68 Juvenile chronic polyarthritis: child with both knees and one ankle involved.
(Dr Barbara Ansell.)

The arthritis is usually accompanied by systemic disturbances such as low-grade fever, lassitude, loss of appetite and weight, and increased irritability. There is guarding of affected joints, and since large joints such as knees and ankles are mainly involved the child tends to avoid walking. Elbows and wrists are also commonly affected, but much less frequently the small joints that form such an important part of adult disease. Arrest of growth may be noted.

Laboratory Investigations

A feature of juvenile chronic polyarthritis is that it is seronegative (*see* Rheumatoid Arthritis) but IgM rheumatoid factor is found in the serum of 10–20% of affected children. 'Seronegative' patients are frequently found to have IgG or IgA rheumatoid factors in the serum when these are sought. Antinuclear antibodies (ANA) are found in about 20% overall but the incidence is higher in patients with eye disease.

There is a peripheral blood neutrophil leucocytosis. C-reactive protein is raised to highest levels early in cases with a systemic onset, to less high levels in cases with a polyarticular onset, and is raised least in those with a pauciarticular onset. High levels persist in those rare patients who develop amyloidosis (Gwyther et al., 1982).

Pathological Changes

The findings in synovial fluid and membrane are essentially those of rheumatoid arthritis (q.v.), any differences probably being a result of the effects of the patient's age and stage of growth, and possibly greater regenerative capacity than the adult (Bywaters, 1977). Pannus formation and erosion of articular cartilage and underlying bone occur much later than in adult disease.

Lymph nodes show non-specific follicular hyperplasia.

Radiographic Changes

The findings are much as in rheumatoid arthritis, except that signs of premature epiphyseal closure and accelerated development may be seen. The former leads to stunting of growth, and the latter to abnormal lengthening of the affected bone.

Marginal erosions and joint space narrowing are late findings, as is subluxation of the atlantoaxial joint in the cervical spine.

Treatment

As with rheumatoid arthritis, a team approach is necessary for optimum management. The team should include an ophthalmologist, who should examine all patients twice a year for signs of eye disease until they are of an age at which they can be expected to complain promptly of ocular symptoms. Young children are frequently first seen when advanced eye disease is already present, and the uveitis may be so undramatic that the parents do not notice that the eye is slightly red.

Rest is combined with appropriate mobilizing exercises and splinting as necessary to prevent deformity.

The whole drug armamentarium as applied to rheumatoid arthritis is also used in juvenile chronic polyarthritis, starting with the non-steroidal antiinflammatory agents and aspirin. The possible association of aspirin therapy and Reye's syndrome is now well publicized. Aspirin is considered inadvisable for febrile illnesses in patients under 12 years of age unless specifically indicated for childhood rheumatic disease (Tarlow, 1986). Aspirin therapy in children need only be interrupted during local epidemics of chickenpox or influenza, but close monitoring is recommended at all times (Hall and Ansell, 1986). Second line drugs are used very selectively. Systemic corticosteroids are indicated if there is severe constitutional disease with fever, weight loss, anaemia and lymphadenopathy. Occasional local joint injections may be adequate when few joints are involved. Joint disease which continues to progress may respond to gold and D-penicillamine. Cytotoxic therapy may be life-saving in patients with amyloidosis.

Prognosis

About 70% of patients recover without gross disability but about 50% have evidence of general growth limitation. Severe disability most commonly results from hip joint disease. Persistent disease may lead to complete crippling, and amyloidosis may occur.

Ocular Disease

It has long been recognized that eye disease may precede arthritis by as much as several years. Indeed, there are a few patients who develop the eye signs typical of juvenile chronic polyarthritis who never appear to develop joint disease at all (Perkins, 1966). One presumes that in some of these patients the joint disease may have been effectively subclinical. However, the usual course is for eye disease to begin within five years of the onset of arthritis.

The reported incidence of ocular disease varies from 8% (Smiley,

1965) to 17% (Chylack, 1977). Girls preponderate in the group with eye disease more than they do in juvenile chronic polyarthritis as a whole. More than 75% of patients belong to the pauciarticular disease group, and 50% are ANA-negative. Most do not have IgM rheumatoid factor.

In the eye there is a triad of anterior uveitis, cataract and band keratopathy (*see Figs.* 7 and 8). The incidence of cataract and keratopathy increases the longer the patients are followed. Almost half are eventually affected (Kanski, 1977). The eye disease has no features specific to juvenile chronic polyarthritis. The uveitis is usually insidious in onset and tends to affect those whose joint disease began by the age of 4 (Chylack, 1977). About half the cases are asymptomatic and the eye not grossly inflamed. This obliges one to examine the eyes of children with established or suspected juvenile chronic polyarthritis at regular intervals. (*Fig.* 69.)

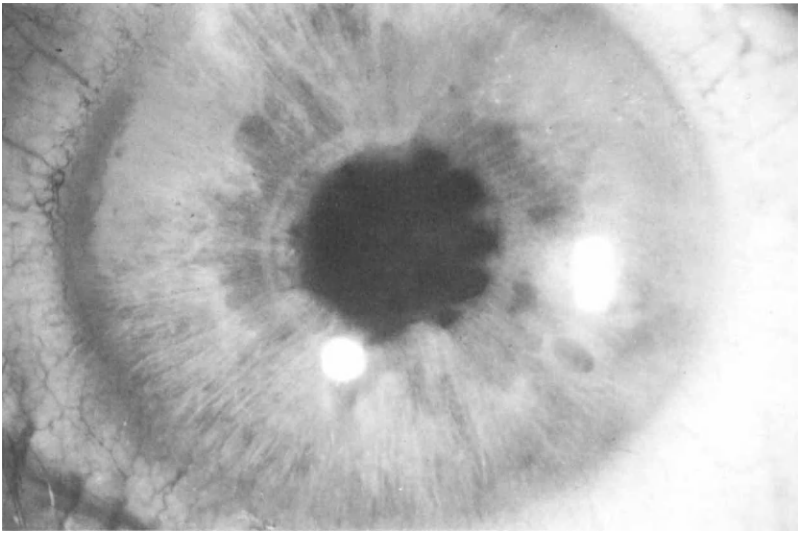


Figure 69 Juvenile chronic polyarthritis: band degeneration of the cornea and chronic anterior uveitis with formation of posterior synechiae.

There is no relationship between the intensity of ocular and joint inflammation. Ocular inflammation is chronic and potentially lifelong. Typically, there is a low-grade anterior uveitis with small keratic precipitates, and cells in the anterior vitreous. Multiple posterior synechiae form and if the condition does not respond to treatment the patient may be left with a small pupil bound completely to the lens, and a fibrous membrane across the lens surface. Posterior segment disease is uncommon, but macular oedema is by no means rare. The

visual impairment is essentially due to a combination of cataract, inflammatory deposition on the front of the lens and anterior vitreous opacity. Secondary glaucoma is a serious complication in up to 20% of these patients.

A small group of patients, mostly older boys, has an acute anterior uveitis indistinguishable from that occurring in adults. It responds well to local steroid and mydriatic therapy, is short-lived, but tends to recur. Many of these patients eventually develop the clinical picture of ankylosing spondylitis and sacroiliitis.

Ocular Histopathology

Interpretation of the few available histopathological studies of the eye is difficult because the disease is always far advanced. One study showed discrete epithelioid granulomas in the uvea and retina, particularly around blood vessels (Hinzpeter et al., 1971). Others have found many plasma cells in the inflammatory infiltrate (Sabates et al., 1979; Merriam et al., 1983).

Treatment of Eye Disease

Treatment with local steroids and mydriatics controls the disease in over half the cases (Kanski, 1977), but unfortunately when this type of treatment is ineffective systemic steroid treatment is often ineffective as well. Systemic steroids should be given in an alternate-day regime (MacGregor et al., 1969). Single dose therapy is just as effective as divided dose therapy (Harter et al., 1963; Ansell and Bywaters, 1974). Although it has not been strictly established by clinical trials, most experts in the use of corticosteroids in children believe that the harmful side effects are minimized by alternate-day treatment.

Steroids prevent serious visual loss in about 80% of patients (Chylack, 1977), but there is a residual group of patients in whom steady deterioration occurs. In view of the risks of cytotoxic therapy, most workers are reluctant to recommend this type of therapy even in those children faced with blindness. Martenet has achieved functional visual improvement in a number of patients in this desperate situation by the use of cyclophosphamide (Martenet, 1981). It remains to be seen if the improvement is sustained and the risk worth taking in the long term.

It must be emphasized that treatment controls but does not cure the eye disease, and the treatment may be needed for life. Not surprisingly, the incidence and severity of complications increases with the duration of the disease.

In the past the treatment of cataract in juvenile chronic polyarthritis has almost always failed (Smiley, 1965, 1974). It was rarely successful in clearing the optical pathway and the trauma to the eye from

repeated operations hastened the ultimate collapse of the globe (phthisis bulbi) which is often the end result of persistent chronic inflammation. The application to this problem of equipment developed for vitrectomy has allowed complete clearing of opacities in the lens and vitreous, and enlargement of a contracted pupil where necessary. Impressive results were reported from the Kelman phako-emulsification procedure with lensectomy alone via an anterior approach (Praeger et al., 1976), and from lensectomy combined with anterior vitrectomy (Kanski and Crick, 1977). Results from a pars plana approach are also satisfactory (Diamond and Kaplan, 1978; Treister and Machemer, 1978) and this is now the most popular technique. Despite reasonable apprehension that surgery would cause a flare-up of uveitis, this has not been a problem so long as inflammation is minimized before surgery. Postoperative inflammatory reaction responds well to local or systemic steroid treatment. Unfortunately, an excellent surgical result may be without much benefit because of macular oedema.

Another apprehension that has proved groundless is that surgery in eyes with low intra-ocular pressure would precipitate phthisis, as it had in the past. The new techniques which include anterior vitrectomy to remove retrolental and anterior vitreal membranes are often, in fact, followed by an improvement in intra-ocular pressure (Tutein and Deutman, 1983). It appears that retrolental membranes in some way impair the secretory function of the ciliary body.

Band keratopathy, due to superficial calcification of the cornea (in Bowman's layer), occasionally interferes physically with the clarity of the optical pathway. Even in blind eyes it can cause irritation and pain when areas of calcified material break away and cause recurrent ulceration. It may be necessary to remove the calcium with the assistance of disodium versenate.

The complication of secondary glaucoma is difficult to treat. It may precede phthisis. It is not always simply due to the mechanical obstruction to aqueous outflow resulting from pupil occlusion and iris bombé. Patients with chronic uveitis, whose pupils still permit the passage of aqueous from posterior to anterior chamber, may develop a gradual rise in intra-ocular pressure, presumably because of narrowing of the outflow channels at a microscopic level, by inflammation, scarring or deposition of debris.

Several points are worth emphasizing:

(1) The insidious onset of eye disease necessitates the regular ophthalmic examination of all children with juvenile chronic polyarthritis. Ocular disease usually begins within 5 years of the onset of arthritis.

(2) Although most cases respond well to steroids, those that do not often have very severe eye disease. Anterior uveitis and cataract have been stressed in

the literature but in the most severe cases there is often significant opacification of the vitreous, and macular oedema.

(3) Inflammation may persist for life. The incidence of complications increases with the duration of inflammation.

HLA-B27

The discovery that many diseases tend to affect those members of the population who bear particular histocompatibility antigens on the surface of their cells has served to intensify the quest of research and clinical investigation to understand disease as the product of an interaction between the individual and the initiating cause.

Associations so far discovered are for susceptibility to disease, rather than resistance. Most theories of how cell surface markers, as represented by the HLA (Human Leukocyte Antigen) system, may be connected with disease susceptibility centre on ideas that certain HLA antigens may impair immune competence against infective or toxic agents, lead to abnormal imbalances between immunologically potent cells once they are activated, or that the association is due not to the HLA antigen itself but to other genes in linkage disequilibrium with the genes controlling it, as might possibly be, for example, the genes responsible for immune functions.

The concept of molecular mimicry is important, particularly in regard to diseases associated with external pathogens, such as the reactive arthritides. The HLA antigens may confer on cell surfaces the qualities of receptor sites for viruses, bacteria or their toxins, for example.

Most associations at present recognized are with genes in the HLA-D region of the short arm of chromosome 6. Evidence is accumulating that this region codes for cell surface proteins as does the Ia region in the mouse, and that it is closely associated with immune response genes.

However, the first major association discovered, and still the most impressive one, was that of HLA-B27 and ankylosing spondylitis (Brewerton et al., 1973a). Brewerton and coworkers found that 96% of patients with ankylosing spondylitis had HLA-B27. They subsequently found that 75% of patients with Reiter's syndrome also had it, whereas in their population the prevalence of HLA-B27 was between 4% and 7% (Brewerton et al., 1973c).

It is noteworthy that in these, the strongest associations yet discovered, the association is by no means complete. Cases of classic ankylosing spondylitis and Reiter's syndrome occur in HLA-B27-negative persons, and despite intensive attempts to identify differences between the disease picture in B27-positive and B27-negative patients,

little has emerged except the impression that disease is more severe and perhaps more prone to extra-articular complications in B27-positive persons.

Besides the full picture of Reiter's syndrome, the association extends to other arthritides which follow intestinal infections. In Finland there has tended to be a particularly high incidence of arthritis following outbreaks of *Yersinia enterocolitis* infection. Figures as high as 33% are given (Ahvonen, 1972). HLA-B27 is found in 14% of Finns, but was found in 88% of patients with arthritis after Yersinia, 94% after Salmonella and 85% after Shigella dysentery (Aho et al., 1973, 1975). Among patients developing arthritis who are B27-negative there is a 3 : 1 female preponderance, which is not seen in the much larger group of patients who are B27-positive (Laitinen et al., 1977). Laitinen and coworkers have remarked upon the fact that although possession of HLA-B27 made no difference to the overall clinical picture of joint involvement, symptoms were more severe in B27-positive patients. In their group of 74 patients only the B27-positive ones suffered iritis, conjunctivitis, carditis, urological inflammation and the complete triad of Reiter's syndrome.

That possession of HLA-B27 is associated with susceptibility to sacroiliitis and spondylitis rather than distal arthropathy is emphasized by the fact that it is not found with unusual frequency in patients with rheumatoid arthritis or juvenile chronic polyarthritis, except in those patients who later evolve into the picture of ankylosing spondylitis. In addition, it is not associated with peripheral arthropathy in psoriasis except when there is radiographic evidence of sacroiliitis or ankylosing spondylitis (Brewerton et al., 1974; McClusky et al., 1974).

A similar but weaker relationship to HLA-B27 has been found in inflammatory bowel disease. When secondary arthritis takes a peripheral form the association is low, whereas when the picture of ankylosing spondylitis develops there is a high association (Masi, 1979).

It would be convenient if the same could be said for gonococcal arthritis. There is no clear relationship of the occurrence of arthritis after gonococcal infection and the possession of HLA-B27. Aho and coworkers found that all of 5 patients had the antigen (Aho et al., 1973) but others found that none of theirs did (Wagner and Fessel, 1975). 'Gonococcal arthritis' is not strictly comparable with other secondary arthritides, since the organism is frequently found in affected joints.

The specificity of HLA-B27 for disease susceptibility extends only to the genetic locus and not to any distinct haplotype, at least as far as ankylosing spondylitis is concerned (Lochead et al., 1983).

As is to be expected from the foregoing discussion, the syndromes involving sacroiliitis and ankylosing spondylitis are rare in races in which HLA-B27 is uncommon, such as the Negro.

This is an appropriate point at which to discuss the role of infection in producing acute anterior uveitis. This is the pattern of eye disease typically seen when the eye is involved in the conditions mentioned for their association with HLA-B27. The association of many cases of Reiter's syndrome including eye disease with antecedent bowel or genitourinary infection is beyond dispute, but it is not clear whether uveitis alone could be provoked in B27-positive patients by these triggers. The association of gonococcal or non-specific urethritis with arthritis has long been stressed (King et al., 1946). The more actively such infections are sought the more frequently they are found. For example, prostatitis was found in 79% of a group of patients with ankylosing spondylitis (Mason et al., 1958). Likewise, 75% of a group of patients with anterior uveitis had signs of chronic prostatitis (Catterall, 1961). Of this group 21% had Reiter's syndrome and 12% had ankylosing spondylitis.

Even if one allows for the remarkably high prevalence of 'chronic prostatitis' in the controls of this series (18·6%), one cannot avoid asking whether the cause of the prostatitis did not trigger the isolated anterior uveitis in the remainder of the group. The possible role of infection was further highlighted by the finding that many patients suffering from non-specific urethritis had genital chlamydial infection (Dunlop et al., 1965; Keat et al., 1978). Keat and coworkers found that isolation of Chlamydia was independent of HLA-B27. The B27 antigen does not seem to influence the acquisition of the infection but rather whether, having become infected, the patient will suffer from reactive arthritis or not. Despite a great deal of study the role of organisms which cause urethritis, such as Chlamydia, mycoplasmas and corynebacteria, in initiating these 'reactive' syndromes remains unsettled.

It has been suggested that the common feature of B27-positive individuals is that they have an unusual way of dealing with infection at environmental interfaces (gut, urogenital tract and skin) which permits the infection to have a more widespread systemic effect. In view of the increasing awareness that 'local' infections have disseminated but subclinical effects which can be revealed by sophisticated laboratory investigations, it might be more logical to postulate that the HLA antigen is in some way coupled with permitting these universal generalized changes to find clinical expression in forms such as arthritis, uveitis and carditis. Against this simplistic interpretation is the occurrence of all these syndromes in B27-negative persons, and the very real difficulty in identifying disease patterns which might be exclusive to B27-positive people. The latter goal is possibly in sight when strict clinical classification is applied to anterior uveitis (*see below*).

HLA-B27 and Acute Anterior Uveitis

Of the group of patients in whom the association of ankylosing spondylitis with HLA-B27 was first demonstrated (Brewerton et al., 1973a) 28% had had uveitis. When the association of B27 with acute anterior uveitis was examined, 55% of patients were found to possess the antigen (Brewerton et al., 1973b; Mapstone and Woodrow, 1975) and 40% of them had significant associated systemic disease (Brewerton et al., 1973b). The association with HLA-B27 and systemic disease has been amply confirmed by others (Linssen et al., 1983). It has been strongly argued that the acute anterior uveitis associated with HLA-B27 is a distinct clinical entity, being commoner in men than women, occurring at an earlier age, and tending to be more often unilateral, more violent and of shorter duration than that found in B27-negative patients (Rothova et al., 1983). Indeed, Mapstone and Woodrow suggested this themselves when they remarked upon the tendency of acute anterior uveitis in B27-positive patients to be more severe, with a tendency to fibrinous exudation in the aqueous (1975).

Detecting HLA-B27 in an individual patient might aid in giving a good prognosis for the uveitis. However, the experienced ophthalmologist has long been able to distinguish between typical acute anterior uveitis in young men and the often much more troublesome and indeed chronic uveitis in older people, which only masquerades as 'acute' uveitis for a matter of weeks. Testing for HLA-B27 might help to sharpen this separation, but it is not justified as a routine investigation.

It has been reported that faecal cultures are more often positive for *Klebsiella pneumoniae* in patients with ankylosing spondylitis during attacks of acute anterior uveitis than at other times (Ebringer et al., 1979). This organism is commonly found in the gut and is not regarded as a pathogen. It was suggested that Klebsiella antigens might cross-react with a gene product closely associated with HLA-B27 in patients with ankylosing spondylitis (Seager et al., 1979), but subsequent work has failed to find any cross-reactivity between Klebsiella antigens and HLA-B27-positive lymphocytes (Archer, 1981; Holland et al., 1982).

Faecal carriage of Klebsiella was not found to differ between patients with ankylosing spondylitis and those with rheumatoid arthritis, or to correlate with disease activity (Warren and Brewerton, 1980). In particular, an increased carriage rate of Klebsiella has not been confirmed in patients with acute anterior uveitis, whether in the first or recurrent attacks, whether the patient was B27-positive or not, and despite the fact that the search for the organism was performed within 2 weeks of the appearance of symptoms (Beckinsale et al., 1984). However, an association of increased faecal recovery in the first 2 weeks of acute anterior uveitis in B27-positive or B7 CREG-positive

patients (which cross-reacts with B27) has also been reported (White et al., 1984) and so the matter remains unsettled. The suggestion has been made that infection with enterobacteria, while perhaps not predisposing to ankylosing spondylitis *per se*, might trigger acute anterior uveitis in patients already suffering from ankylosing spondylitis.

ANKYLOSING SPONDYLITIS

Epidemiology

Ankylosing spondylitis affects at least 1/1000 Caucasian adults, men being three times as commonly affected as women (Masi, 1979). This is probably a gross underestimation of the prevalence in view of the failure to diagnose mild disease, particularly in women. It is well recognized that radiographic evidence of sacroiliitis is found much more commonly than clinical ankylosing spondylitis (Calin and Fries, 1975; Woodrow, 1977). Racial differences in the prevalence of the disease are almost entirely correlated with the prevalence of HLA-B27 in the population. The finding of spinal ankylosis, when taken in isolation, is almost confined to B27-positive individuals. It is estimated that ankylosing spondylitis eventually affects 1·3% of HLA-B27-positive persons (Van der Linden et al., 1984). HLA-B27 is found in more than 90% of patients (Brewerton et al., 1973). Twenty per cent of B27-positive first-degree relatives of patients may expect to suffer from the disease (Van der Linden et al., 1984). However, it clearly does occur in B27-negative relatives of probands (*Ibid.*). It is of interest that one survey found no increase in HLA B7-CREG alloantigens, which cross-react with sera recognizing HLA-B27, in B27-negative ankylosing spondylitis patients (Jajić et al., 1983).

Clinical Features

The primary disease begins in the late teens and early adult years, but secondary disease, for example enteropathic cases, may occur at any age. Back pain does not usually become troublesome for some years but it does tend to become progressively worse. It is improved by exercise. Pain is also common over tendon insertions, such as the tendo achillis and the plantar fascia. Peripheral joints, particularly those of the lower limbs, are affected in about 20% of patients by recurrent pain, swelling and sterile effusions (Wilkinson and Bywaters, 1958).

Restriction of back movement eventually becomes obvious and the lumbar lordosis is flattened. However, major disability from this is uncommon. Finally, ascent of the disease to the thoracic spine with involvement of the apophyseal and costovertebral joints interferes with

chest expansion. In advanced cases there may be marked kyphosis and reduction in body height. Flexion deformity may involve the neck and force the patient to adopt a characteristic turn of the body, neck and eyes to see where he is going.

Aetiology

The cause is unknown. The clear role of genetic predisposition has already been discussed. The more obscure role of genitourinary and enteric infection is discussed in the section 'Reactive Arthritides'.

Diagnosis

The formal 'New York' criteria for diagnosis and radiographic grading are often referred to (Bennet and Wood, 1968). These are as follows:

Criteria for Diagnosis

(1) Limitation of movement of the lumbar spine in all 3 planes
(2) History of pain at the dorsolumbar region or in the lumbar spine
(3) Limitation of chest expansion to 2·5 cm or less, measured at the level of the 4th intercostal space

Radiographic Grading of Sacroiliac Joint Changes

(0) Normal
(1) Suspicious changes
(2) Minimal alterations - small localized areas of erosion or sclerosis, without alteration in the joint width
(3) Unequivocal abnormality - moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing or partial ankylosis
(4) Severe abnormality - total ankylosis

In practice a diagnosis of *definite* ankylosing spondylitis is made when there are radiographic findings of grade 3 or 4 bilateral sacroiliitis and a history of back pain. The sacroiliac joints are graded separately, but in practice the changes tend to be symmetrical, in contrast with peripheral arthropathy when it occurs.

It is important to note that the diagnosis is made on sacroiliac changes, rather than on vertebral changes as one would conclude from its name. Similarly, most patients with Reiter's syndrome, in which the conceptual emphasis is on sacroiliac changes, do not actually develop sacroiliitis.

Radiographic Changes

The earliest changes are seen in the sacroiliac joints, perhaps only on one side. The joint margins are blurred, and focal erosions appear in the subchondral bone in association with sclerosis which increases progressively. Eventually the joint space is obliterated and the joints fused. Sclerosis then diminishes. (*Fig.* 70.)

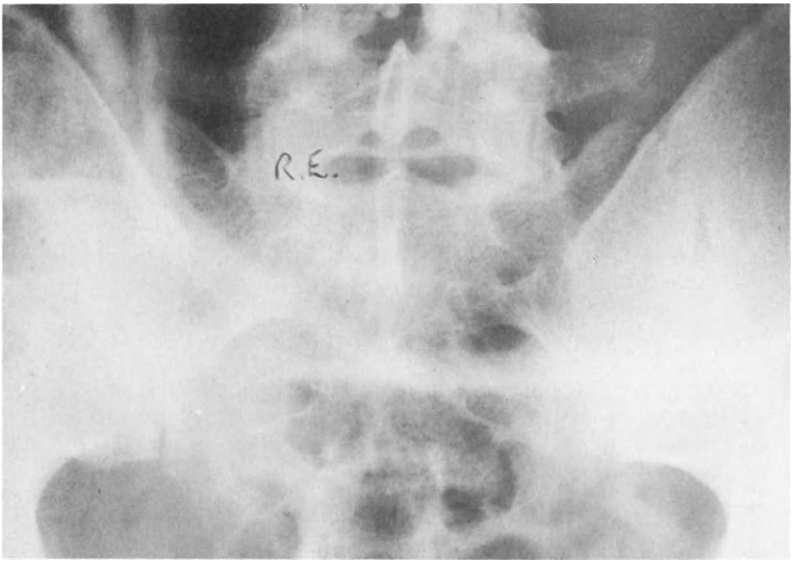


Figure 70 Ankylosing spondylitis: sacroiliitis. (Dr Carol Black.)

The edges of the vertebrae become eroded, giving the vertebral bodies a squared-off appearance. Linear calcification appears, bridging the gap between the front and sides of the vertebral bodies. The ultimate appearance of densely ossified syndesmophytes is described as 'bamboo spine' but progression to this stage is rare. Spinal involvement is symmetrical and advances from below upwards. Ossified spurs are seen particularly on the calcaneum, but plantar ossification is much less common than in Reiter's syndrome (Mason et al., 1959). (*Fig.* 71.)

Laboratory Findings

The ESR is raised and there may be a mild hypochromic anaemia. Tests for rheumatoid factor, ANA and LE cells are negative. Circulating immune complexes are not found (Duquesnoy et al., 1979).

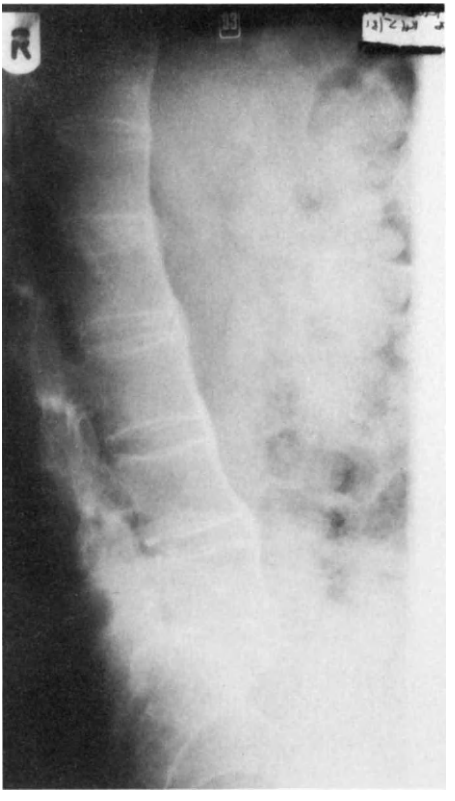


Figure 71 Ankylosing spondylitis.
(Dr Carol Black.)

Ocular Disease

Conjunctivitis and acute anterior uveitis occur in about 25% of patients (Wilkinson and Bywaters, 1958; Brewerton et al., 1973). The eye disease does not seem to be related to the activity of the skeletal disease, but like other complications it is more commonly found in patients with peripheral joint involvement. The conjunctivitis is rarely clinically troublesome, but the uveitis is recurrent, involves either eye at different times, and unless treated promptly may lead to visual damage.

The eye is painful, tender, photophobic and red. Vision is blurred. The iris is the primary site of inflammation and the posterior segment of the eye usually escapes significant involvement. An untreated attack

will usually settle in a few weeks, leaving permanent damage from organization of inflammatory exudate. The pupil may become completely bound to the lens and occluded by a fibrous membrane. Response to treatment is rapid but signs of inflammation do not usually disappear completely for a few weeks. Attacks occur at irregular intervals. Some patients have only one or a few episodes, but others have attacks over many years, with a tendency for the intervals between attacks to shorten initially and then gradually lengthen.

Other Manifestations

Aortitis occurs in up to 20% of patients and leads to aortic incompetence. It may appear before other signs of ankylosing spondylitis. Cardiomegaly and conduction defects are found with increasing frequency as the condition progresses.

Some patients have upper lobe pulmonary fibrosis.

In marked contrast to other seronegative arthropathies is the absence of skin lesions.

Pathology

In diarthrodeal joints the early changes are villous hypertrophy just as in rheumatoid arthritis (Cruickshank, 1971). There is a diffuse infiltration of lymphocytes and plasma cells, and the formation of lymphoid follicles. Most of the plasma cells contain IgG as in rheumatoid arthritis, many contain IgA and fewer contain IgM (Revell and Mayston, 1982).

In cartilaginous joints there is subacute osteitis, invasion of bone with inflammatory cells and vascular fibrous tissue near the joint, and osteoclastic resorption of surrounding bony trabeculae (Cruickshank, 1971). Fibrous tissue replaces the cartilage and adjacent bone and becomes ossified.

Beginning in the paravertebral connective tissue and at the bony attachments of the outer layers of the annulus fibrosus of the intervertebral discs there is fibrosis and eventual ossification. This process also involves the capsules and capsular ligaments of the vertebral apophyseal joints and the interspinous ligaments. Bony bridges (syndesmophytes) eventually unite the anterior and lateral margins of the vertebrae.

There is tendinitis and formation of bony spurs at the insertion of large tendons, particularly on the calcaneum.

In the aorta there is intimal fibrosis of the vasa vasorum and patchy destruction of the media. Changes are maximal at the very base of the aorta, immediately above the sinuses of Valsalva.

Treatment

Except for patients with severe pain and disability, who may need periods of hospitalization and temporary immobilization, exercise should be encouraged and the patient educated about the purpose of the exercise, emphasizing the objective of reducing deformity. Swimming is the pastime of choice.

The whole range of treatments as outlined for rheumatoid arthritis have sometimes been used, but if drug treatment is necessary at all the non-steroidal anti-inflammatory agents usually suffice (for example, indomethacin, 25–50 mg 3 times daily).

Prognosis

Women tend to have less severe and less rapidly progressive disease than men.

In the first few years the disease is unpredictable, but within ten years a pattern of behaviour is established (Wilkinson and Bywaters, 1958; Carette et al., 1983). Fluctuations in the severity of symptoms can be expected, as can progressive loss of spinal mobility, but most patients function well, even with severe spinal restriction. They should be encouraged to lead as normal a life as possible.

REITER'S SYNDROME

Introduction

Although the association had previously been recognized, Reiter's description served to focus attention on the triad of symptoms comprising urethritis, arthritis and conjunctivitis (Reiter, 1916). The complete condition is not easily mistaken for anything else, but there have been attempts at more formal definition of the syndrome. The American Rheumatism Association has proposed that the diagnosis could be made for an episode of peripheral arthritis lasting more than one month, and associated with urethritis or cervicitis. These criteria have been found to be very sensitive in excluding other seronegative arthropathy (Willkens et al., 1981). The omission of conjunctivitis from the criteria recognizes the fact that it only occurs in about one-third of patients.

Epidemiology

Precise prevalence figures cannot be given, but it is much less common

than ankylosing spondylitis and probably affects between 1/1000 and 1/10 000 of the population. It is rare in women. Only 10 women were affected in one series of 410 consecutive cases (Csonka, 1979a). Only 10% of cases reported in an epidemic of Flexner dysentery were women (Paronen, 1948).

About 75% of patients carry the HLA-B27 phenotype (Brewerton et al., 1973).

Aetiology

The cause is not known, although in specific instances the relationship to infection is indisputable. Paronen reported from Finland 344 cases occurring between 1943 and 1946, mostly related to a severe epidemic of Flexner dysentery (Paronen, 1948). Two-thirds of the patients developed the clinical syndrome 11 to 30 days after the onset of diarrhoea. A smaller epidemic of proven *Shigella* dysentery on an American warship resulted in 9 cases of Reiter's syndrome in 602 affected sailors (Noer, 1966). These patients have been followed and it is estimated that between one-sixth and one-third of HLA-B27-positive persons developed Reiter's syndrome after this single episode of shigellosis (Calin and Fries, 1976).

In these apparently infective situations there does appear to be a spectrum from diarrhoea alone, through diarrhoea with 'reactive arthritis', to diarrhoea followed by complete Reiter's syndrome (Leirisalo et al., 1982), with the possession of HLA-B27 tipping the balance towards the development of Reiter's syndrome, more severe acute disease, and a tendency towards chronicity (*Ibid.*).

The possible triggering role of chlamydial and other urogenital infections has already been outlined in the discussion of HLA-B27 in these interrelated conditions (*see* p. 152).

Despite the likelihood of an infective trigger in at least some cases of Reiter's syndrome, this does not appear to be true of many sporadic cases. The possibility that reinfection, for example with urethritis, might cause recurrences is even more controversial. It must be remembered that Reiter's syndrome is in fact a rare occurrence after dysenteric or urogenital infections. For example, in one series of 22 010 cases of urethritis it occurred in less than 1% (Csonka, 1958), and only 0·2% of the patients affected with dysentery in Paronen's large series developed Reiter's syndrome (Sairanen et al., 1969). In cases in which infection has been confirmed many workers have observed that treatment of the infection makes no difference to the arthritis.

Clinical Findings

There are no features to distinguish post-dysenteric from sporadic

disease. Most cases occur in young adults, but after large outbreaks of dysentery cases have occurred in all age groups.

Initial symptoms may be backache and pain and tenderness over one or both sacroiliac joints. The pain is frequently worse at night and on rising, and tends to become continuous. There is usually no limitation of movement. Associated fever at the onset may be a poor prognostic sign (Willkens et al., 1981). Sacroiliitis affects 75% of patients.

Most patients suffer from polyarthritis (Paronen, 1948; Csonka, 1979a) with pain and tenderness in the affected joints. Lower limb joints, especially the interphalangeal joints of the feet, the knees and the ankles, are affected much more commonly than upper limb joints.

Spondylitis also affects 40% of patients.

Plantar fasciitis occurs in almost 20% of patients, and achilles tendinitis is also common. These are associated with posterosuperior and inferior calcaneal erosions initially, and eventually with bony spur formation at these sites.

Long term follow-up of both post-dysenteric disease (Sairanen et al., 1969) and sporadic cases (Csonka, 1979b) has shown that over 50% of patients have either a remitting/relapsing course or recurrent attacks which may be years apart.

The joint disease is likely to be confused with ankylosing spondylitis, but in the latter the sacroiliitis is usually bilateral and symmetrical.

Radiological Changes

Cortical bone around the sacroiliac joints first becomes less dense, and then bone sclerosis occurs, followed by obliteration of the joint space by bony ankylosis. The changes are usually bilateral but may be quite asymmetric, unilateral or entirely focal, in contrast to ankylosing spondylitis, which is almost always bilateral and symmetrical (*see* Mason et al., 1959).

Peripheral joints, especially the metatarsophalangeal and interphalangeal joints of the feet, show destruction of the articular cartilage, osteoporosis of the bones, and periosteal new bone formation. The joints may subluxate.

The spondylitic changes resemble those of ankylosing spondylitis, but the bony bridges sometimes seen between adjacent vertebrae are asymmetric, large, and mainly confined to the lateral aspects of the vertebral bodies.

There appears to be a tendency to marked periosteal new bone formation in Reiter's syndrome, particularly in the calcaneum, as distinct from simple spur formation in the insertion of the plantar fascia.

Urethritis

The urethritis is non-specific in 75% of patients, and the gonococcus is isolated from many of the remainder (Csonka, 1979a). In recurrences of disease urethritis is commonly absent.

Eye Disease

In Paronen's large series 7% of patients had iritis (Sairanen et al., 1969). Attacks occurred independently of attacks of joint disease. The initial attack of eye disease may be many months after the onset of acute joint symptoms, just as has been observed with post-Yersinia arthritis and uveitis (Ahvonen, 1972). The recurrent iritis is a typical acute anterior uveitis which responds well to local treatment with mydriatics and steroids and settles completely within three months. Csonka found that only 2·4% of his 410 cases suffered from recurrent iritis, but conjunctivitis occurred in 34·4% (Csonka, 1979a). The appearance of eye lesions soon after the onset of disease suggests that they may feature in the pattern of recurrent disease (Csonka, 1960). Keratitis has also been described (Csonka, 1979a).

Mucocutaneous Disease

Skin disease resembles psoriasis, both clinically and histologically (Calin, 1979). The typical skin lesion, keratodermia blennorrhagica, affects 10–15% of cases. It is usually confined to the soles of the feet, the toes and the glans penis. Lesions begin as crops of vesicles which develop over a few days into hyperkeratotic nodules which may be a centimetre or more across. They persist from a few weeks to months and eventually peel off without scarring. They tend to recur, but are usually not painful.

Nail changes resembling those of psoriasis or fungal infection also occur, particularly subungual keratosis.

Balanitis affects 25–30% of patients. This also begins as small vesicles which rupture to form small ulcers. These tend to coalesce into a circinate pattern around the corona radiata and adjacent glans penis. They are painless but persistent.

Painless ulcers also occur in the mouth in about 10% of cases.

It is noteworthy that none of these mucocutaneous changes is found in ankylosing spondylitis.

Other Lesions

Severe cardiac lesions (but not aortic incompetence), central nervous

system lesions and deep vein thrombosis in the leg are also occasionally seen (Csonka, 1979b).

It has been estimated that 15% of men with Reiter's syndrome can be expected to develop ankylosing spondylitis independently (Woodrow, 1977). The distinct differences between the two conditions can be summarized:

(1) Frequent asymmetry of sacroiliac joint involvement in Reiter's syndrome
(2) Irregular, lateral vertebral syndesmophytes in Reiter's syndrome
(3) More florid calcaneal periosteal new bone formation in Reiter's syndrome (and also around other affected joints)
(4) Greater involvement of peripheral joints in Reiter's syndrome, both in terms of frequency and severity
(5) Absence of aortic disease in Reiter's syndrome
(6) Absence of skin disease in ankylosing spondylitis

Treatment

Treatment is given as described for rheumatoid arthritis. All measures previously outlined have been tried but many severe cases do not respond to systemic steroids. Methotrexate has been used successfully in such situations in the past (Mullins et al., 1966; Farber et al., 1967). It is currently being reassessed in the treatment of rheumatoid arthritis.

Associated infection is treated appropriately. It has already been mentioned that this has no influence on the disease.

Eye lesions are treated on their merits.

Mucocutaneous lesions usually do not require treatment, but keratodermia blennorrhagica may be improved by keratolytics or topical steroids.

Prognosis

Attacks usually last 2–3 months. Long-term follow-up amply demonstrates the severity of this disease. Up to 40% of patients eventually develop severe disability and only about 20% are entirely symptom-free after the initial attack (Sairanen et al., 1969). Recurrences of joint, skin or eye disease are not always accompanied by urethritis (Csonka 1979b). The role of recurrent chlamydial, mycoplasmic or corynebacterial genital infection in triggering recurrences is still quite obscure.

Adjuvant Disease in the Rat

Many of the features of Reiter's syndrome are produced in rats

immunized with Complete Freund's Adjuvant. This model may in time shed light on the role of the Major Histocompatibility Complex in human disease, because the susceptibility to adjuvant arthritis is strain-specific (Battisto et al., 1982) and the development of extra-articular disease also seems to be so, in that uveitis has been observed in particular strains (Pearson and Chang, 1979).

REACTIVE ARTHRITIS

Enteropathic Arthritis

At many points in the foregoing discussion of HLA-B27 and the seronegative arthritides the possible role of infection in the aetiopathogenesis has been raised. Before passing on to a brief review of inflammatory bowel disease it may be helpful to summarize these observations.

Arthritis following dysentery has been described after outbreaks of Yersinia, Salmonella, Neisseria, Brucella and Shigella infections. Reactive arthritis may develop in a small proportion of patients, usually those with the HLA-B27 phenotype. It varies widely in severity from a transient polyarthritis to a disease of remittent and relapsing course which evolves into complete Reiter's syndrome. Arthritis usually begins 10–30 days after the onset of diarrhoea and resembles rheumatic fever at this stage. Suspect organisms are isolated from the stool only in a minority of cases, possibly because they have been cleared from the gut by the time joint symptoms commence. Organisms are not found in the affected joints. The proportion of patients developing reactive syndromes differs in different epidemics. It seems likely that certain strains of organism may be more likely to induce extraintestinal disease than others.

Eye disease usually occurs in company with arthritis, but occasional patients are described in whom ocular inflammation is the only 'reaction' to the dysentery (Saari et al., 1980). In the series of 23 cases that Saari and coworkers have reviewed there were 17 cases of severe acute anterior uveitis associated often with vitritis and macular oedema. It was recurrent in half the cases. Nine patients also suffered from mild conjunctivitis which tended to resolve spontaneously in one week. There was no conjunctival chemosis or follicular reaction, and no keratitis. There was no marked sex predominance.

Brewerton has expressed the impression that the reactive symptoms appear synchronously with the intestinal disease in the rare cases affecting B27-negative patients, whereas there is no synchrony in B27-positive patients (Brewerton, 1979). HLA-B27-negative patients have milder disease.

Genitourinary Disease

Very similar associations exist for genitourinary infections. It has been estimated that non-specific urethritis occurring in B27-positive persons carries a 20% risk of developing joint disease. In recent years there has been a trend towards higher rates of isolation of organisms from the urethra of these cases, but adequate treatment of infection has no influence on the course of associated disease. This is also the case with enteropathic disease.

Reactive disease in association with *gonorrhoea* is not strictly analogous to the above disorders for several reasons. The gonococcus is cultured from at least 20% of affected joints. It is not clearly associated with HLA-B27 (Wagner and Fessel, 1975), although it was initially thought to be (Aho et al., 1973). All symptoms also respond fully to treatment with penicillin G, 1 million units IMI daily for a minimum of 3 days. There is no tendency to chronicity. Gonorrhoea has been traditionally associated with uveitis and conjunctivitis, but this is now rarely seen. Perhaps early treatment has altered the disease profile. However, gonococcal arthritis is less rare, but it is not possible to estimate what proportion of patients will suffer from it. Women are affected as commonly as men. It begins with migratory polyarthritis, fever and chills. The white cell count and ESR are raised. Joint involvement is less widespread than in Reiter's syndrome and sacroiliac and lumbar involvement is rare. Gonococcal skin lesions are common and are distinguishable from those of Reiter's syndrome by their distribution on the upper limbs, especially distally. They take the form of macules and papules which sometimes undergo central necrosis to form pustules.

Chapter 5 References

Introduction

Kimura S. A., Hogan M. J., O'Connor G. R. and Epstein W. V. (1967) Uveitis and joint disease. *Arch. Ophthalmol.* **77**, 309–316.

Perkins E. S. (1961) Uveitis associated with joint diseases and urogenital infection. *Uveitis and Toxoplasmosis*. London, Churchill, p. 25.

Sjögren's Syndrome

Alarcón-Segovia D., Díaz-Jouanen E. and Fishbein E. (1973) Features of Sjögren's syndrome in primary biliary cirrhosis. *Ann. Intern. Med.* **79**, 31–36.

Alarcón-Segovia D., Ibáñez G., Velázquez-Forero F., Hernández-Ortíz J. and González-Jiménez Y. (1974) Sjögren's syndrome in systemic lupus erythematosus *Ann. Intern. Med.* **81**, 577–583.

Bloch K. T., Buchanan W. W., Wohl M. J. and Bunim J. J. (1965) Sjögren's syndrome. A clinical pathological and serological study. *Medicine* **44**, 187–231.

Bunim J. J. (1961) A broader spectrum of Sjögren's syndrome and its pathogenetic implications. *Ann. Rheum. Dis.* **20**, 1–10.

Chisholm D. M. and Mason D. K. (1968) Labial salivary gland biopsy in Sjögren's disease. *J. Clin. Pathol.* **21**, 656–660.

Constantopoulos S. H., Papadimitriou C. S. and Moutsopoulos H. M. (1985) Respiratory manifestations in primary Sjögren's syndrome. A clinical, functional and histological study. *Chest* **88(2)**, 226–229.

Faguet G. B., Webb H. H., Agee J. F., Ricks W. B. and Sharbaugh A. H. (1978) Immunologically diagnosed malignancy in Sjögren's pseudolymphoma. *Am. J. Med.* **65**, 424–429.

Fox R. I., Carstens S. A., Fong S., Robinson C. A., Howell F. and Vaughan J. H. (1982) Use of monoclonal antibodies to analyse peripheral blood and salivary gland lymphocyte subsets in Sjögren's syndrome. *Arthritis Rheum.* **25**, 419–426.

Fox R. I., Howell F. V., Bone R. C. and Michelson P. (1984) Primary Sjögren syndrome: clinical and immunopathologic features. *Semin. Arthritis Rheum.* **14**, 77–105.

Kassan S. S., Thomas T., Moutsopoulos H. M., Hoover R., Kimberly R. P., Budman D. R., Costa J., Decker J. L. and Chused T. M. (1978) Increased risk of lymphoma in sicca syndrome. *Ann.. Intern. Med.* **89**, 888–892.

Kilpi A., Konttinen Y. T., Malmström M., Bergroth V., Reitamo S. and Helve T. (1983) Immunocompetent cells in labial salivary glands in secondary Sjögren's syndrome associated with SLE. *J. Oral Pathol.* **12**, 465–472.

Lawley T., Moutsopoulos H. M., Katz S. I., Theophilopoulos A. N., Chused T. M. and Frank M. M. (1979) Demonstration of circulating immune complexes in Sjögren's syndrome. *J. Immunol.* **123**, 1382–1387.

MacSween R. N. M., Goudie R. B., Anderson J. R., Armstrong E., Murray M. A., Mason D. K., Jasani M. K., Boyle J. A., Buchanan W. W. and Williamson J. (1967) Occurrence of antibody to salivary duct epithelium in Sjögren's disease, rheumatic arthritis and other arthritides. A clinical and laboratory study. *Ann. Rheum. Dis.* **26**, 402–411.

Manthorpe R., Morling N., Platz P., Ryder L. P., Svejgaard L. P. and Thomsen M. (1981) HLA-D antigen frequencies in Sjögren's syndrome. Differences between the primary and secondary form. *Scand. J. Rheumatol.* **10**, 124–128.

Moutsopoulos H. M., Mann D. L., Johnson A. H. and Chused T. M. (1979a) Genetic differences between primary and secondary sicca syndrome. *N. Engl J. Med.* **301**, 761 763.

Moutsopoulos H. M., Mann D. L., Johnson A. H. and Chused T. M. (1979a) Genetic differences between primary and secondary sicca syndrome. *N. Engl. J. Med.* **301**, 761–763.

Moutsopoulos H. M., Webber B. L., Vlagopoulos T. P., Chused T. M. and Decker J. L. (1979b) Difference in the clinical manifestations of sicca syndrome in the presence and absence of rheumatoid arthritis. *Am. J. Med.* **66**, 733–736.

Pavlidis N. A., Karsh J. and Moutsopoulos H. M. (1982) The clinical picture of primary Sjögren's syndrome; a retrospective study. *J. Rheumatol.* **9**, 685–690.

Sjögren, H. (1933) Zur Kenntnis der Keratoconjunctivitis sicca. *Acta Ophthalmol. (Copenh.)* **11** (Suppl. 11), 1–151.

Stephen K. W., Chisholm D. M., Harden R. McG., Robertson J. W. K., Whaley K. and Stuart A. (1971) Diagnostic value of quantitative scintiscanning of the salivary glands in Sjögren's syndrome and rheumatoid arthritis. *Clin. Sci.* **41**, 555–561.

Talal N., Zisman E. and Schur P. H. (1968) Renal tubular acidosis, glomerulonephritis and immunological factors in Sjögren's syndrome. *Arthritis Rheum.* **11**, 774–786.

Talal N., Asofsky R. and Lightbody P. (1970) Immunoglobulin synthesis by salivary gland lymphoid cells in Sjögren's syndrome. *J. Clin. Invest.* **49**, 49–54.

Talal N., Sylvester R. A., Daniels T. E., Greenspan J. S. and Williams R. C. (1974) T and B lymphocytes in the peripheral blood and tissue lesions in Sjögren's syndrome. *J. Clin. Invest.* **53**, 180–189.

Tarpley T. M., Anderson L. G. and White C. L. (1974) Minor salivary gland involvement in Sjögren's syndrome. *Oral Surg.* **37**, 64–74.
Whaley K., Williamson J., Wilson T., McGavin D. D. M., Hughes G. V. R., Hughes H., Schmulian L. R., MacSween R. N. M. and Buchanan W. W. (1972) Sjögren's syndrome and autoimmunity in a geriatric population. *Age, Ageing* **1**, 197–206.
Whaley K., Williamson J., Chisholm D. M., Webb J., Mason K. D. and Buchanan W. W. (1973) Sjögren's syndrome I. Sicca components. *Q. J. Med.* **42**, 279–304.
Zulman J., Jaffe R. and Talal N. (1978) Evidence that the malignant lymphoma of Sjögren's syndrome is a monoclonal B-cell neoplasm. *N. Engl. J. Med.* **299**, 1215–1220.

Rheumatoid Arthritis

Amos R. S., Constable T. J., Crockson R. A., Crockson A. P. and McConkey B. (1977) Rheumatoid arthritis: relation of serum C-reactive protein and erythrocyte sedimentation rates to radiographic changes. *Br. Med. J.* **1**, 195–197.
Arnaud P., Galbraith R. M., Faulk W. P. and Ansell B. M. (1977) Increased frequency of the MZ phenotype of alpha-1 protease inhibitor in juvenile chronic polyarthritis. *J. Clin. Invest.* **60**, 1442–1444.
Bankhurst A. D., Husby G. and Williams R. C. (1976) Predominance of T-cells in the lymphocytic infiltrates of synovial tissue in rheumatoid arthritis. *Arthritis Rheum.* **19**, 555–562.
Barnes C. G., Turnbull A. L. and Vernon-Roberts B. (1971) Felty's syndrome. A clinical and pathological survey of 21 patients and their response to treatment. *Ann. Rheum. Dis.* **30**, 359–374.
Bennett G. A., Zeller J. W. and Bauer W. (1940) Subcutaneous nodules of rheumatoid arthritis and rheumatic fever: a pathologic study. *Arch. Pathol.* **30**, 70–89.
Bennett P. H. and Burch T. A. (1967) New York symposium on population studies in the rheumatic diseases: new diagnostic criteria. *Bull. Rheum. Dis.* **17**, 453–458.
Binderup L., Bramm E. and Arrigoni-Martelli E. (1980) Effect of D-penicillamine in vitro and in vivo on macrophage phagocytosis. *Biochem. Pharmacol.* **29**, 2273–2278.
Bywaters E. G. L. (1971) Still's disease in the adult. *Ann. Rheum. Dis.* **30**, 121–133.
Bywaters E. G. L. and Scott J. T. (1963) The natural history of vascular lesions in rheumatoid arthritis. *J. Chronic Dis.* **16**, 904–914.
Caruso I. and Bianchi Porro G. (1980) Gastroscopic evaluation of anti-inflammatory agents. *Br. Med. J.* **1**, 75–78.
Cats A. and Hazevoet H. M. (1970) Significance of positive tests for rheumatoid factor in the prognosis of rheumatoid arthritis. *Ann. Rheum. Dis.* **29**, 254–259.
Cleary P. E., Watson P. G., McGill J. I. and Hamilton A. M. (1975) Visual loss due to posterior segment disease in scleritis. *Trans. Ophthalmol. Soc. U.K.* **95**, 297–300.
Cochrane W., Davies D. V., Dorling J. and Bywaters E. G. L. (1964) Ultramicroscopic structure of the rheumatoid nodule. *Ann. Rheum. Dis.* **23**, 345–363.
Cooperating Clinics Committee of the American Rheumatism Association (1970) A controlled trial of cyclophosphamide in rheumatoid arthritis. *N. Engl. J. Med.* **283**, 883–889.
Cooperating Clinics Committee of the American Rheumatism Association (1973) A controlled trial of gold salt therapy in rheumatoid arthritis. *Arthritis Rheum.* **16**, 353–358.
Dayer, J.-M. and Krane S. M. (1978) The interaction of immunocompetent cells and chronic inflammation as exemplified by rheumatoid arthritis. *Clin. Rheum. Dis.* **4**, 517–537.
Dayer J.-M., Robinson D. R. and Krane S. M. (1977) Prostaglandin production by rheumatoid synovial cells. *J. Exp. Med.* **145**, 1399–1404.

Dixon A. St. J., Davies J., Dormandy T. L., Hamilton E. B. D., Holt P. J. L., Mason R. M., Thompson M., Weber J. C. P. and Zutshi D. W. (1975) Synthetic D(-)penicillamine in rheumatoid arthritis. Double-blind controlled study of a high and low dose regimen. *Ann. Rheum. Dis.* **34**, 416–421.

Empire Rheumatism Council (1961) Gold therapy in rheumatoid arthritis. Final report of a multicentre controlled trial. *Ann. Rheum. Dis.* **20**, 315–334.

Engleman G. G., Sponzilli E. E., Batey M. E., Ramcharan S. and McDevitt H. O. (1978) Mixed lymphocyte reaction in healthy women with rheumatoid factor. *Arthritis Rheum.* **21**, 690–693.

Evanson J. M., Jeffrey J. J. and Krane S. M. (1968) Studies on collagenase from rheumatoid synovium in tissue culture *J. Clin. Invest.* **47**, 2639–2651.

Flory E. D. and Muirden K. D. (1983) Study of enzyme inhibitors in the rheumatoid pannus-cartilage area. *Rheumatol. Int.* **3**, 81–87.

Freedman A. and Steinberg V. L. (1960) Chloroquin in rheumatoid arthritis – a double blindfold trial of treatment for one year. *Ann. Rheum. Dis.* **19**, 243–250.

Geddes D. M., Webley M., Brewerton D. A., Turton C. W., Turner-Warwick M., Murphy A. H. and Milford Ward A. (1977) Alpha-1 antitrypsin phenotypes in fibrosing alveolitis and rheumatoid arthritis. *Lancet* **2**, 1049–1051.

Glass D., Snaith M. L., Russel A. S. and Daly J. R. (1971) Possible unnecessary prolongation of corticosteroid therapy in rheumatoid arthritis. *Lancet* **2**, 334–337.

Gordon D. A., Stein J. L. and Broder I. (1973) The extra-articular features of rheumatoid arthritis. A systematic analysis of 127 cases. *Am. J. Med.* **54**, 445–452.

Hart F. D. (1969) Rheumatoid arthritis: extra-articular manifestations. *Br. Med. J.* **3**, 131–136.

Hellgren L. (1970) The prevalence of rheumatoid arthritis in occupational groups. *Acta Rheumatol. Scand.* **16**, 106–113.

Hench P. S. and Rosenberg E. F. (1944) Palindromic rheumatism, a 'new', oft recurring disease of joints. *Arch. Intern. Med.* **73**, 293–321.

Higgs, G. A., Vane J. R., Hart F. D. and Wojtulewski J. A. (1974) Effects of anti-inflammatory drugs on prostaglandin in rheumatoid arthritis. In *Prostaglandin Synthetase Inhibitors*, eds. H. J. Robinson and J. R. Vane. New York, Raven, pp. 165–173.

Huskisson E. C., Woolf D. L., Balme H. W., Scott P. J. and Franklin S. (1976) Four new anti-inflammatory drugs: responses and variations. *Br. Med. J.* **1**, 1048–1049.

Jacoby R. K., Jayson M. I. V. and Cosh J. A. (1973) Onset, early stages and prognosis of rheumatoid arthritis. *Br. Med. J.* **2**, 96–100.

Kammer G. M., Soter N. A. and Schur P. H. (1980) Circulating immune complexes in patients with necrosing vasculitis. *Clin. Immunol. Immunopathol.* **15**, 658–672.

Klareskog L., Forsum U., Wigren A. and Wigzell H. (1982) Relationships between HLA-DR-expressing cells and T-lymphocytes of different subsets in rheumatoid synovial tissue. *Scand. J. Immunol.* **15**, 501–507.

Kobayashi I. and Ziff M. (1973) Electron microscopic studies of lymphoid cells in the rheumatoid synovial membrane. *Arthritis Rheum.* **16**, 471–486.

Kulka J. P., Bocking D., Ropes M. W. and Bauer W. (1955) Early joint lesions of rheumatoid arthritis. *Arch. Pathol.* **59**, 129–150.

Lawrence J. S. (1970) Rheumatoid arthritis – nature or nurture. *Ann. Rheum. Dis.* **29**, 357–379.

Loewi G., Lance E. M. and Reynolds J. (1975) Study of lymphoid cells from inflamed synovial membranes. *Ann. Rheum. Dis.* **34**, 524–528.

Luthra H. S., McDuffie F. C., Hunder G. C. and Samayoa E. A. (1975) Immune complexes in sera and synovial fluids of patients with rheumatoid arthritis. *J. Clin. Invest.* **56**, 458–466.

McGavin D. D. M., Williamson J., Forrester J. V., Foulds W. S., Buchanan W. W., Dick W. C., Lee P., MacSween R. N. M. and Whaley K. (1976) Episcleritis and scleritis. A study of their clinical manifestations and association with rheumatoid arthritis. *Br. J. Ophthalmol.* **60**, 192–226.

Mackenzie A. H. (1983) Antimalarial drugs for rheumatoid arthritis. *Am. J. Med. (Dec. Suppl.)*, 48–57.

McMichael A. J., Sasazuki T., McDevitt H. O. and Payne R. O. (1977) Increased frequency of HLA-Cw3 and HLA-Dw4 in rheumatoid arthritis. *Arthritis Rheum.* **20**, 1037–1042.

Marks J. S. (1982) Chloroquine retinopathy: is there a safe daily dose? *Ann. Rheum. Dis.* **41**, 52–58.

Mason M., Currey H. L. F., Barnes C. G., Dunne J. F., Hazleman B. L. and Strickland I. D. (1969) Azathioprine in rheumatoid arthritis. *Br. Med. J.* **1**, 420–422.

Mims C. A., Stokes A. and Grahame R. (1985) Synthesis of antibodies, including antiviral antibodies, in the knee joints of patients with arthritis. *Ann. Rheum. Dis.* **44**, 734–737.

Multicentre Trial Group (1973) Controlled trial of D(-)penicillamine in severe rheumatoid arthritis. *Lancet* **1**, 275–280.

Mundy W. L., Howard R. M., Stillman P. M. and Bevans M. (1951) Cortisone therapy in the care of rheumatoid nodules of the eye in rheumatoid arthritis. *Arch. Ophthalmol.* **45**, 531–538.

Munthe E. and Natvig J. B. (1972) Complement fixing intracellular complexes of IgG rheumatoid factor in rheumatoid plasma cells. *Scand. J. Immunol.* **1**, 217–229.

Nineham L. J., Hay F. C., Male D. K., Roitt I. M., Young A. and Perumal R. (1978) Immune complexes in rheumatoid arthritis: correlation with clinical features and effects of gold. In *Protides of Biological Fluids*, ed. H. Peeters. Oxford, Pergamon, pp. 179–182.

O'Sullivan J. B. and Cathcart E. S. (1972) The prevalence of rheumatoid arthritis. Follow-up evaluation of the effect of criteria on rates in Sudbury, Massachusetts. *Ann. Intern. Med.* **76**, 573–577.

Pinals R. S., Masi A. T. and Larsen R. A. (1981) Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum.* **24**, 1308–1315.

Pope R. M., Mannik M., Gilliland B. C. and Teller D. C. (1975) The hyperviscosity syndrome in rheumatoid arthritis due to intermediate complexes formed by self-association of IgG-rheumatoid factors. *Arthritis Rheum.* **18**, 97–106.

Pullar T., Hunter J. A. and Capell H. A. (1983) Sulphasalazine in rheumatoid arthritis: a double blind comparison of sulphasalazine with placebo and sodium aurothiomalate. *Br. Med. J.* **287**, 1102–1104.

Quinlan M. P. and Hitchings R. A. (1978) Angle closure glaucoma secondary to posterior scleritis. *Br. J. Ophthalmol.* **62**, 330–335.

Roath S. and Wills R. (1974) The effects of penicillamine on lymphocytes in culture. *Postgrad. Med. J.* **50** (Suppl. 2), 56–59.

Robinson D. R., Tashjian A. H. and Levine L. (1975) Prostaglandin E_2-induced bone resorption by rheumatoid synovia. A model for bone destruction in rheumatoid arthritis. *J. Clin. Invest.* **56**, 1181–1188.

Ropes M. W., Bennett G. A., Cobb S., Jacox R. F. and Jessor R. A. (1958) 1958 revision of diagnostic criteria for rheumatoid arthritis. *Bull. Rheum. Dis.* **9**, 175–176.

Rynes R. I., Krohel G., Falbo A., Reinecke R. D. and Bartholomew L. E. (1978) Ophthalmologic safety of long-term hydroxychloroquine treatment. *Arthritis Rheum.* **21**, 588.

Schumacher H. R. and Kitridou R. C. (1972) Synovitis of recent onset. A clinicopathologic study during the first month of disease. *Arthritis Rheum.* **15**, 465–485.

Scott D. L., Coulton B. L., Chapman J. H., Bacon P. A. and Popert A. J. (1983) The long term effect of treating rheumatoid arthritis. *J. R. Coll. Physicians Lond.* **17**, 79–85.

Sheldon P. J., Papamichail M. and Holborow E. J. (1974) Studies on synovial fluid lymphocytes in rheumatoid arthritis. *Ann. Rheum. Dis.* **33**, 509–514.

Siegel M., Lee S. L., Widelock D., Gwon N. V. and Kravitz H. (1965) A comparative family study of rheumatoid arthritis and systemic lupus erythematosus. *N. Engl. J. Med.* **273**, 893–897.

Sigler J. W., Bluhm G. B., Duncan H., Sharp J. T., Ensign D. C. and McCrum W. R. (1974) Gold salts in the treatment of rheumatoid arthritis. A double-blind study. *Ann. Intern. Med.* **80**, 21–26.

Sjöblom K. G. and Wollheim F. A. (1977) Alpha-1-antitrypsin phenotypes and rheumatic diseases. *Lancet* **2**, 41–42.

Smiley D. J., Sachs C. and Ziff M. (1968) In vitro synthesis of immunoglobulin by rheumatoid synovial membrane. *J. Clin. Invest.* **47**, 624–632.

Solkoloff L. and Bunim J. J. (1957) Vascular lesions in rheumatoid arthritis. *J. Chronic Dis.* **5**, 668–687.

Stastny P. (1978) Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. *N. Engl. J. Med.* **298**, 869–871.

Stastny P. (1983) Rheumatoid arthritis: relationship with HLA-D. *Am. J. Med. (Dec. Suppl.)*, 9–15.

Stastny P. and Fink C. W. (1979) Different HLA-D associations in adult and juvenile rheumatoid arthritis. *J. Clin. Invest.* **63**, 124–130.

Talal N., Asofsky R. and Lightbody P. (1970) Immunoglobulin synthesis by salivary gland lymphoid cells in Sjögren's syndrome. *J. Clin. Invest.* **49**, 49–54.

Theofilopoulos A., Burtonboy G., LoSpalluta J. J. and Ziff M. (1974) IgM rheumatoid factor and low molecular weight IgM. An association with vasculitis. *Arthritis Rheum.* **17**, 272–284.

Townes A. S., Sowa J. M. and Shulman L. E. (1976) Controlled trial of cyclophosphamide in rheumatoid arthritis. *Arthritis Rheum.* **19**, 563–573.

Ugai K., Ziff M. and Lipsky P. E. (1979) Gold-induced changes in the morphology and functional capabilities of human monocytes. *Arthritis Rheum.* **22**, 1352–1360.

Walsh L., Davies P. and McConkey B. (1979) Relationship between erythrocyte sedimentation rate and C-reactive protein in rheumatoid arthritis. *Ann. Rheum. Dis.* **38**, 362–363.

Watson, P. G. and Hayreh S. S. (1976) Scleritis and episcleritis. *Br. J. Ophthalmol.* **60**, 163–191.

Watson P. G., McKay D. A., Clemett R. S. and Wilkinson P. (1973) Treatment of episcleritis. A double-blind trial comparing betamethasone 0·1%, oxyphenbutasone 10% and placebo eye ointments. *Br. J. Ophthalmol.* **57**, 866–870.

Weisman M. and Zvaifler N. (1975) Cryoglobulinaemia in rheumatoid arthritis. Significance in serum of patients with rheumatoid vasculitis. *J. Clin. Invest.* **56**, 725–739.

Wilder R. L. (1984) Etiologic considerations, pp. 820–821. In: Decker J. L. (moderator) Rheumatoid arthritis: evolving concepts of pathogenesis and treatment. *Ann. Intern. Med.* **101**, 810–824.

Wilhelmus K. R., Watson P. G. and Vasavada A. R. (1981) Uveitis associated with scleritis. *Trans. Ophthalmol. Soc. U.K.* **101**, 351–356.

Williams M. H., Sheldon P. J. H. S., Torrigiani G., Eisen V. and Mattingly S. (1971) Palindromic rheumatism. Clinical and immunological studies. *Ann. Rheum. Dis.* **30**, 375–380.

Willkens R. F. (1985) Methotrexate treatment of rheumatoid arthritis. *Ann. Intern. Med.* **103**, 612–613.

Winchester R. J., Kunkel H. G. and Agnello V. (1971) Occurrence of gamma-globulin complexes in serum and joint fluid of rheumatoid arthritis patients: use of monoclonal rheumatoid factors as reagents for their demonstration. *J. Exp. Med.* **134**, 286–295s.

Woolley D. E., Tetlow L. C. and Evanson J. M. (1980) Collagenase immunolocalisation studies of rheumatoid and malignant tissues. In *Collagenase in Normal and Pathological Connective Tissues*, eds. D. E. Woolley and J. M. Evanson. New York, Wiley, pp. 105–125.

Young R. D. and Watson P. G. (1984) Microscopical studies of necrotising scleritis. *Br. J. Ophthalmol.* **68**, 770–789.

Ziff M. (1977) IgG rheumatoid factor in disease. In *Vascular Lesions of Collagen Diseases and Related Conditions*, ed Y. Shiokawa. Baltimore, University Park Press, pp. 120–123.

Juvenile Chronic Polyarthritis

Ansell B. M. and Bywaters E. G. L. (1963) Rheumatoid arthritis (Still's disease). *Pediatr. Clin. N. Am.* **10**, 921–939.

Ansell B. M. and Bywaters E. G. L. (1974) Alternate-day corticosteroid therapy in juvenile chronic polyarthritis. *J. Rheumatol.* **1**, 176–186.

Brewer E. J., Schaller J. and Wedgwood R. T. (1972) Juvenile rheumatoid arthritis: a review. *Pediatrics* **50**, 940–953.

Bywaters E. G. L. (1977) Discussion. In *Procedings of a Conference on the Rheumatic Diseases of Childhood*, eds. J. Schaller and V. Hanson. *Arthritis Rheum.* **20** (Suppl.), 235.

Bywaters E. G. L. (1977) Pathological aspects of juvenile chronic polyarthritis. In *Proceedings of a Conference on the Rheumatic Diseases of Childhood*, eds. J. Schaller and V. Hanson. *Arthritis Rheum.* **20** (Suppl.), 271–276.

Chylack L. T. (1977) The ocular manifestations of juvenile rheumatoid arthritis. In *Proceedings of a Conference on the Rheumatic Diseases of Childhood*, eds. J. Schaller and V. Hanson. *Arthritis Rheum.* **20** (Suppl.), 217–223.

Clemens L. E., Albert E. and Ansell B. M. (1983) HLA studies in IgM rheumatoid factor-positive arthritis in childhood. *Ann. Rheum. Dis.* **42**, 431–434.

Diamond J. G. and Kaplan H. J. (1978) Lensectomy and vitrectomy for complicated cataract secondary to uveitis. *Arch. Ophthalmol.* **96**, 1798–1804.

Fink C. W. and Stastny P. (1979) Pauciarticular juvenile rheumatoid arthritis: clinical and immunogenetic aspects. *Ann. Rheum. Dis.* **38** (Suppl.), 79–83.

Glass D., Litvin D., Wallace K., Chylack L., Garovoy M. and Carpenter C. B. (1980) Early onset pauciarticular juvenile rheumatoid arthritis associated with human leukocyte antigen-DRw5, iritis, and antinuclear antibody. *J. Clin. Invest.* **66**, 426–429.

Gwyther M., Schwarz H., Howard A. and Ansell B. (1982) C-reactive protein in juvenile chronic arthritis: an indicator of disease activity and possible amyloidosis. *Ann. Rheum. Dis.* **41**, 259–262.

Hall A. and Ansell B. M. (1986) Reye's syndrome, aspirin, and juvenile chronic arthritis. *Br. Med. J.* **293**, 270.

Harter J. G., Reddy W. J. and Thorn G. W. (1963) Studies on an intermittent corticosteroid dosage regimen. *N. Engl. Med. J.* **269**, 591–596.

Hinzpeter E. N., Naumann G. and Bartelheimer H. K. (1971) Ocular histopathology in Still's disease. *Ophthalmic Res.* **2**, 16–24.

JRA Criteria Subcommittee (Brewer E. J.) (1972) Criteria for the classification of juvenile rheumatoid arthritis. *Bull. Rheum. Dis.* **23**, 712–719.

JRA Criteria Subcommittee (1977) Current proposed revision of JRA criteria. *Arthritis Rheum.* **20** (Suppl.), 195–199.

Kanski J. J. (1977) Anterior uveitis in juvenile rheumatoid arthritis. *Arch. Ophthalmol.* **95**, 1794–1797.

Kanski J. J. and Crick M. P. D. (1977) Lensectomy. *Trans. Ophthalmol. Soc. U.K.* **97**, 52–57.

MacGregor R. R., Sheagren J. N., Lipsell M. B. and Wolff S. M. (1969) Alternate day prednisone therapy. Evaluation of delayed hypersensitivity response, control of disease and steroid side effects. *N. Engl. J. Med.* **280**, 1427–1431.

Martenet A.-C. (1981) Therapie der endogenen Uveitis: Immunosuppression. *Ber. Dtsch. Ophthalmol. Ges.* **78**, 223–228.

Merriam J. C., Chylack L. T. and Albert D. M. (1983) Early-onset pauciarticular juvenile rheumatoid arthritis. A histopathological study. *Arch. Ophthalmol.* **101**, 1085–1092.

Ohm J. (1910) Bandförmige Hornhauttrübung bei einem neunjährigen Mädchen und ihre Behandlung mit subkonjunktivalen Jodkaliumeinspritzungen. *Klin. Monatsbl. Augenheilkd.* **48**, 243.

Perkins E. S. (1966) Pattern of uveitis in children. *Br. J. Ophthalmol.* **50**, 169–185.

Praeger D. L., Schneider H. A., Sakowski A. D. and Jacobs J. C. (1976) Kelman procedure in the treatment of complicated cataract of the uveitis of Still's disease. *Trans. Ophthalmol. Soc. U.K.* **96**, 168–171.

Sabates R., Smith T. and Apple D. (1979) Ocular histopathology in juvenile rheumatoid arthritis. *Ann. Ophthalmol.* **11** 733–737.

Smiley W. K. (1965) Iridocyclitis in Still's disease. Prognosis and steroid treatment. *Trans. Ophthalmol. Soc. U.K.* **85**, 351–356.

Smiley W. K. (1974) The eye in juvenile rheumatoid arthritis. *Trans. Ophthalmol. Soc. U.K.* **94**, 817–829.

Stastny P. and Fink C. W. (1979) Different HLA-D associations in adult and juvenile rheumatoid arthritis. *J. Clin. Invest.* **63**, 124–130.

Still G. F. (1897) On a form of chronic joint disease in children. *Med. Chir. Trans.* **80**, 47.

Tarlow M. (1986) Reye's syndrome and aspirin. *Br. Med. J.* **292**, 1543.

Treister G. and Machemer R. (1978) Pars plana approach for pupillary membranes. *Arch. Ophthalmol.* **96**, 1014–1016.

Tutein P. A. and Deutman A. F. (1983) Surgical treatment of the complications of chronic uveitis. *Ophthalmologica* **186**, 11–16.

HLA-B27

Aho K., Ahvonen P., Lassus A., Sievers K. and Tiilikainen A. (1973) HL-A Antigen 27 and reactive arthritis. *Lancet* **2**, 175.

Aho K., Ahvonen P. and Alkio P. (1975) HL-A 27 in reactive arthritis following infection. *Ann. Rheum. Dis. (Suppl)* **34**, 29–30.

Ahvonen P. (1972) Human yersinosis in Finland. II. Clinical features. *Ann. Clin. Res.* **4**, 39–48.

Archer J. R. (1981) Search for cross-reactivity between HLA B27 and Klebsiella pneumoniae. *Ann. Rheum. Dis.* **40**, 400–403.

Beckinsale A. B., Williams D., Gibson J. M. and Rosenthal A. R. (1984) Klebsiella and acute anterior uveitis. *Br. J. Ophthalmol.* **68**, 866–868.

Brewerton D. A., Hart F. D., Nicholls A., Caffrey M., James D. C. O. and Sturrock R. D. (1973a) Ankylosing spondylitis and HL-A27. *Lancet* **1**, 904.

Brewerton D. A., Nicholls A., Caffrey M. and Walters D. (1973b) Acute anterior uveitis and HL-A27. *Lancet* **2**, 994.

Brewerton D. A., Nicholls A., Oates J. K., Caffrey M., Walters D. and James D. C. O. (1973c) Reiter's disease and HL-A27. *Lancet* **2**, 996.

Brewerton D. A., Caffrey M., Nicholls A., Walters D. and James D. C. O. (1974) HL-A27 and the arthropathies associated with ulcerative colitis and psoriasis. *Lancet* **1**, 956–958.

Catterall R. D. (1961) Significance of non-specific genital infection in uveitis and arthritis. *Lancet* **2**, 739–742.

Dunlop E. M. C., Al-Hussaini M. K., Garland J. A., Treharne J. D., Harper I. A. and Jones B. R. (1965) Infection of urethra by TRIC agent in men presenting because of 'non-specific' urethritis. *Lancet* **1**, 1225–1228.

Ebringer R., Cawdell D. and Ebringer A. (1979) Klebsiella pneumoniae and acute anterior uveitis in ankylosing spondylitis. *Br. Med. J.* **1**, 383.

Holland E. J., Loren A. B., O'Donnell M. J., Spence D. J., Tessler H. H. and Yokoyama M. M. (1982) HLA-B27, klebsiella pneumonia and the relation to acute anterior uveitis. *Invest. Ophthalmol. Vis. Sci.* **22**, 213–219.

Keat A. C., Maini R. N., Nkwazi G. L., Pegrum G. D., Ridgway G. L. and Scott J. T. (1978) Role of chlamydia trachomatis and HLA B27 in sexually acquired reactive arthritis. *Br. Med. J.* **1**, 605–607.

King A. J., Williams D. I., Nicol C. S. and Loudon J. (1946) The treatment of infective arthritis with special reference to hyperthermia. *Br. J. Vener. Dis.* **22**, 1.

Laitinen O., Leirisalo M. and Skylv G. (1977) Relation between HLA-B27 and clinical features in patients with yersinia arthritis. *Arthritis Rheum.* **20**, 1121–1124.

Linssen A., Dekker-Saeys A. J., Dandrieu M. R., Christiaans M. R., Baarsma G. S., Tjoa S. T., DeJong P. T. V. M., Kijlstra A. and Feltkamp T. E. W. (1983) Possible ankylosing spondylitis in acute anterior uveitis. *Br. J. Rheumatol.* **22**, 137–143.

Lochead J. A., Chalmers I. M., Marshall W. H., Larsen B., Skanes V. M., Payne R. H. and Barnard J. M. (1983) HLA-B27 haplotypes in family studies of ankylosing spondylitis. *Arthritis Rheum.* **26**, 1011–1016.

McClusky O. E., Lordon R. E. and Arnett F. C. (1974) HLA-27 in Reiter's syndrome and psoriatic arthritis: a genetic factor in disease susceptibility and expression. *J. Rheumatol.* **1**, 263 268.

Mapstone R. and Woodrow J. C. (1975) HL-A27 and acute anterior uveitis. *Br. J. Ophthalmol.* **59**, 270–275.

Masi A. T. (1979) Epidemiology of B27-associated disease. *Ann. Rheum. Dis.* **38** (Suppl.), 131–134.

Mason R. M., Murray R. S., Oates J. K. and Young A. C. (1958) Prostatitis and ankylosing spondylitis. *Br. Med. J.* **1**, 748–751.

Rothova A., Buitenhuis H. J., Christiaans B. J., Linssen A., Van der Gaag R., Kijlstra A. and Feltkamp T. E. W. (1983) Acute anterior uveitis and HLA-B27. *Br. J. Rheumatol.* **22** (Suppl. 2), 144–145.

Seager K., Bashir H. V., Geczy A. F., Edmonds J. and DeVere-Tyndall A. (1979) Evidence for a specific B27-associated cell surface marker on lymphocytes of patients with ankylosing spondylitis. *Nature* **277**, 68–70.

Wagner L. P. and Fessel W. J. (1975) HLA 27 (W27) absent in gonococcal arthritis. *Lancet* **1**, 1094–1095.

Warren R. E. and Brewerton D. A. (1980) Faecal carriage of klebsiella by patients with ankylosing spondylitis and rheumatoid arthritis. *Ann. Rheum. Dis.* **39**, 37–44.

White L., McCoy R., Tait B. and Ebringer R. (1984) A search for gram-negative enteric micro-organisms in acute anterior uveitis: association of Klebsiella with recent onset of disease, HLA-B27, and B7 CREG. *Br. J. Ophthalmol.* **68**, 750–755.

Ankylosing Spondylitis

Bennet P. H. and Wood P. H. N. (1968) Diagnostic criteria for ankylosing spondylitis. In *Population Studies of the Rheumatic Diseases*, eds. P. H. Bennet and P. H. N. Wood, Amsterdam/New York, Excerpta Medica, pp. 456–457.

Brewerton D. A., Hart F. D., Nicholls A., Caffrey M., James D. C. O. and Sturrock R. D. (1973) Ankylosing spondylitis and HL-A27. *Lancet* **1**, 904.

Calin A. and Fries J. F. (1975) The striking prevalence of ankylosing spondylitis in 'healthy' W27 positive males and females. A controlled study. *N. Engl. J. Med.* **295**, 835–839.

Carette S., Graham D., Little H., Rubenstein J. and Rosen P. (1983) The natural disease course of ankylosing spondylitis. *Arthritis Rheum.* **26**, 186–190.

Cruickshank B. (1971) Pathology of ankylosing spondylitis. *Clin. Orthop.* **74**, 43–58.

Duquesnoy B., Santoro F., Delcambre B. and Wattre P. (1979) Absence de complexes immunocirculants et d'anticorps anti-IgG sériques au cours de la spondylarthrite ankylosante. *Rev. Rhum. Mal. Osteoartic.* **46**, 397–401.

Jajić I., Kerhin V. and Kastelan A. (1983) Ankylosing spondylitis syndrome in patients without HLA-B27. *Br. J. Rheumatol.* **22** (Suppl. 2), 136.

Masi A. T. (1979) Epidemiology of B27-associated disease. *Ann. Rheum. Dis.* **38**, (Suppl.), 131–134.

Mason R. M., Murray R. S., Oates J. K. and Young A. C. (1959) A comparative radiological study of Reiter's disease, rheumatoid arthritis and ankylosing spondylitis. *J. Bone Joint Surg.* **41**, 137–148.

Revell P. A. and Mayston V. (1982) Histopathology of synovial membrane of peripheral joints in ankylosing spondylitis. *Ann. Rheum. Dis.* **41**, 579–586.

Van der Linden S. M., Valkenburg H. A., deJongh B. M. and Cats A. (1984) The risk of developing ankylosing spondylitis in HLA B27 positive individuals. *Arthritis Rheum.* **27**, 241–249.

Wilkinson M. and Bywaters E. G. L. (1958) Clinical features and course of ankylosing spondylitis as seen in a follow up of 222 hospital referred cases. *Ann. Rheum. Dis.* **17**, 209–228.

Woodrow J. C. (1977) Histocompatibility antigens and rheumatic diseases. *Semin. Arthritis Rheum.* **6**, 257–276.

Reiter's Syndrome

Ahvonen P. (1972) Human yersiniosis in Finland. II. Clinical Features. *Ann. Clin. Res.* **4**, 39–48.

Battisto J. R., Smith R. N., Beckman K., Sternlicht M. and Welles W. L. (1982) Susceptibility to adjuvant arthritis in DA and F344 rats. A dominant trait controlled by an autosomal gene locus linked to the MHC. *Arthritis Rheum.* **25**, 1194–1200.

Brewerton D. A., Nicholls A., Oates, J. K., Caffrey M., Walters D. and James D. C. O. (1973) Reiter's disease and HL-A27. *Lancet* **2**, 996.

Calin A. (1979) Keratodermia blennorrhagica and mucocutaneous manifestations of Reiter's syndrome. *Ann. Rheum. Dis.* **38**, (Suppl.), 68–72.

Calin A. and Fries J. F. (1976) An 'experimental' epidemic of Reiter's syndrome revisited. Follow-up evidence on genetic and environmental factors. *Ann. Intern. Med.* **84**, 564–566.

Csonka G. W. (1958) The course of Reiter's syndrome. *Br. Med. J.* **1**, 1088–1092.

Csonka G. W. (1960) Recurrent attacks in Reiter's disease. *Arthritis Rheum.* **3**, 164–169.

Csonka G. W. (1979a) Clinical aspects of Reiter's syndrome. *Ann. Rheum. Dis.* **38** (Suppl.), 4–7.

Csonka G. W. (1979b) Long-term follow-up and prognosis of Reiter's syndrome. *Ann. Rheum. Dis.* **38** (Suppl.), 24–28.

Farber G. A., Forschner J. G. and O'Quinn S. E. (1967) Reiter's syndrome: treatment with methotrexate. *JAMA* **200**, 171–173.

Leirisalo M., Skylv G., Kousa M., Voipio-Pulkki L.-M., Suoranta H., Nissilä M., Hvidman L., Nielsen E. D., Svejgaard A., Tiilikainen A. and Laitinen O. (1982) Follow up study on patients with Reiter's disease and reactive arthritis, with special reference to HLA-B27. *Arthritis Rheum.* **25**, 249–259.

Mason R. M., Murray R. S. and Oates J. K. (1959) A comparative radiological study of Reiter's disease, rheumatoid arthritis and ankylosing spondylitis. *J. Bone Joint Surg.* **41B**, 137–148.

Mullins J. F., Maberry J. D. and Stone O. J. (1966) Reiter's syndrome treated with folic acid antagonists. *Arch. Dermatol.* **94**, 335–339.

Noer H. R. (1966) An 'experimental' epidemic of Reiter's syndrome. *JAMA* **198**, 693–698.

Paronen I. (1948) Reiter's disease, a study of 344 cases observed in Finland. *Acta Med. Scand.* (Suppl. 213) **131**, 1–114.

Pearson C. M. and Chang Y. H. (1979) Adjuvant disease: pathology and immune reactivity. *Ann. Rheum. Dis.* **38**, (Suppl.), 102–110.

Reiter H. (1916) Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica). *Dtsch. Med. Wochenschr.* **42**, 1535–1536.
Sairanen E., Paronen I. and Mähönen H. (1969) Reiter's syndrome: a follow-up study. *Acta Med. Scand.* **185**, 57–63.
Willkens R. F., Arnett F. C. and Bitter T. (1981) Reiter's syndrome. Evaluation of preliminary criteria for definite disease. *Arthritis Rheum.* **24**, 844–849.
Woodrow J. C. (1977) Histocompatibility antigens and rheumatic diseases. *Semin. Arthritis Rheum.* **6**, 257–276.

Reactive Arthritides

Aho K., Ahvonen P., Lassus A., Sievers K. and Tiilikainen A. (1973) HLA antigen 27 and reactive arthritis. *Lancet* **2**, 157.
Brewerton D. A. (1979) Discussion. *Ann. Rheum. Dis.* **38** (Suppl), 94.
Hurd E. R., Johns J. and Chubick A. (1979) Comparative study of gonococcal arthritis and Reiter's syndrome. *Ann. Rheum. Dis.* **38**, (Suppl.), 55–58.
Saari K. M., Laitinen O., Leirisalo M. and Saari R. (1980) Ocular inflammation associated with yersinia infection. *Am. J. Ophthalmol.* **89**, 84–95.
Wagner L. P. and Fessel W. J. (1975) HLA 27 (W27) absent in gonococcal arthritis. *Lancet* **1**, 1094–1095.

Chapter six

Psoriasis, Relapsing Polychondritis and Inflammatory Bowel Disease

PSORIASIS

Clinical Features

This common skin condition affects at least 1% of the population. Many mild cases of psoriasis of the scalp are probably misdiagnosed as dandruff. It affects persons at any age and there is no sex preponderance. It runs a chronic course of irregular exacerbations and remissions.

The rash appears initially on the skin of the extensor surfaces, especially of the elbows and knees, the scalp and the lower back. Other sites are much less commonly affected. The lesions are elevated, sharply demarcated, bright red or even violaceous in colour. The surface is covered with silvery white scales. There may be a limited number of large lesions several centimetres across (*nummular psoriasis*), a scattering of smaller lesions (*guttate psoriasis*), or a combination of lesions of various sizes. (*Fig.* 72.)

Although it is not specific for psoriasis, pitting of the nails is highly suggestive of the diagnosis, especially when there are many pits on each nail. The edges of the nails also tend to disintegrate (onycholysis) and subungual hyperkeratosis may elevate the nail from its bed. Nail changes occur in at least 30% of patients.

Pustular psoriasis is a rare but severe form of disease in which neutrophils accumulate in the skin in locules, and eventually discharge.

There may be a marked systemic disturbance.

There is no mucosal involvement apart from the glans penis.

Aetiology

The cause is unknown, but certain metabolic and immunological abnormalities are well established. There is increased proliferation of

the cells of the epidermis. The increased levels of cyclic GMP and products of arachidonic acid metabolism found in psoriatic skin are probably related to this. Antibodies to the stratum corneum of the skin may be found in the serum. The production of these may be related to the reduced number of suppressor T-cells sometimes found in the circulation.

Figure 72 Psoriasis of the knee.
(Dr Jeffrey Cream.)

Rheumatoid factor, ANA and LE cells are absent, but circulating immune complexes have been reported. Their relevance to the pathology is doubtful, and vasculitis is not a feature of the disease.

HLA-B13, B17 and Cw6 are found more frequently than normal (Green et al., 1981; Armstrong et al., 1983). HLA-B27 and DR7 are increased in patients who develop arthritis (Armstrong et al., 1983) but not to the levels found in ankylosing spondylitis or Reiter's syndrome.

Staphylococcus aureus can be more readily isolated from the skin of psoriatics than from unaffected persons, but this may well be a

secondary phenomenon. An abnormal response to infection has been postulated as the cause, in the same way as it has been put forward in inflammatory bowel disease.

Pathology

There is hyperkeratosis and parakeratosis. The dermal papillae are elongated and the capillary loops dilated. There is perivascular infiltration of lymphocytes, monocytes and neutrophils in the dermis. The neutrophils are seen to invade the epidermis, which becomes oedematous. There are increased mitoses in the basal layer of the epidermis and thinning of the granular layer, both changes being signs of increased proliferation of the epidermis. Tiny microabscesses occur in the stratum corneum.

Complications

Arthritis

Up to 40% of patients develop arthritis (Lambert and Wright, 1977; Green et al., 1981) but much of this is asymptomatic sacroiliitis revealed only on radiological surveys. Symptomatic disease is mainly an arthritis of the distal interphalangeal joints in association with nail changes. It is just like rheumatoid arthritis except for its distribution and restriction to fewer joints. Many patients develop the typical picture of ankylosing spondylitis or Reiter's syndrome. There is also an uncommon severe deforming type of arthritis. Joint disease is associated with HLA-B27 and DR7. It tends to begin some time after the skin disease and is more severe in patients with severe skin disease.

Radiographic changes in affected peripheral joints are typical of rheumatoid arthritis. In axial joints they resemble ankylosing spondylitis. The distal phalanges show osteolysis and cup-shaped expansion of their articular surfaces, and there are erosions on both sides of the terminal interphalangeal joints.

The pathology of the joints is likewise similar to rheumatoid arthritis.

Eye Disease

Acute anterior uveitis may occur in psoriasis without arthritis being present, but eye complications are mainly found in patients with psoriatic arthritis. In one series of such patients about one-third had some sort of eye inflammation, principally conjunctivitis (19·6%) and

iritis (7·1%) (Lambert and Wright, 1976). A few had episcleritis and keratoconjunctivitis sicca. Patients with sacroiliitis are particularly prone to develop iritis, and these also tend to have HLA-B27.

Other Complications

Some patients also suffer from inflammatory bowel disease some time after the psoriasis begins.

Treatment

Farber and colleagues have produced an excellent review of current management options (Farber et al., 1983).

There is an ill-defined but accepted relationship of exacerbations of psoriasis with stress. Patients are well advised to avoid stressful occupations wherever possible.

Bland lotions and ointments containing 1,8,9-trihydroxyanthracine (dithranol) or coal tars are adequate for limited disease. Salicylic acid ointments may be used to remove scales or crusts. Topical steroids may be effective and can be combined with occlusive dressings to enhance the effect. Intralesional injections of steroids may be appropriate, but systemic steroids are to be avoided, even for the complications.

Ultraviolet light has a beneficial effect in moderate doses. The combination of 8-methoxypsoralen with high intensity UVA light (PUVA) is believed to exert its impressive therapeutic action by reducing DNA synthesis in the epithelium (Leading Article, 1978). Retinoids are also under investigation as therapeutic agents. These newer modalities may replace cytotoxic agents such as azathioprine (DuVivier et al., 1974) in severe cases. Psoralens enter the lens of the eye and remain there for 12 hours after ingestion. Reaction with UVA light in that time may contribute to the development of cataract. The risk of this seems negligible if patients wear dark glasses for 12 hours after psoralen ingestion (Stern et al., 1985).

Treatment of the skin has little apparent effect on the course of complications, which must be managed on their own merits. Arthritis may not require specific therapy but non-steroidal anti-inflammatory agents are usually sufficient. Antimalarials should be avoided because of the risk of precipitating a very severe exfoliative dermatitis.

RELAPSING POLYCHONDRITIS

This rare condition occurs at any age and has no sex predominance. Many patients have evidence of autoimmune disease elsewhere.

It consists of inflammation and destruction of non-articular and articular cartilage, and inflammatory eye disease. Dolan and colleagues were able to review 49 cases (Dolan et al., 1966). Most had fever and arthropathy with inflammation of ear, nasal and laryngeal cartilage. Episcleritis and conjunctivitis occurred in 60% and iritis in 27%. Hearing loss was common, as was costochondral disease. Isolated cases have been described of exudative retinopathy (Anderson, 1967), and abducens nerve paresis and exophthalmos (Rucker and Ferguson, 1965).

Inflammation occurs in recurrent attacks leading to obvious distortion of the ears and collapse of the nose, as well as destruction of cartilage at other sites. Joint symptoms resemble rheumatoid arthritis in its early stages, but it is not erosive. Death may occur from cardiovascular or respiratory disease, but tracheal collapse is probably the commonest cause of death.

The ESR is raised and anaemia is usual. Rheumatoid factor and antinuclear antibodies are absent. During exacerbations acid mucopolysaccharides may be found in the urine. Many patients have circulating antibodies to type II collagen (Froidart et al., 1978).

Biopsy of cartilage shows fragmentation, and loss of normal basophilic staining, indicating the loss of chondroitin sulphate from the matrix. Cartilage is infiltrated by round cells and replaced by fibrous connective tissue.

Treatment is with high doses of corticosteroids, which may need to be maintained for life. Dapsone has also been found helpful in doses between 25 and 200 mg/day.

INFLAMMATORY BOWEL DISEASE

Crohn's Disease and Ulcerative Colitis

There is a considerable overlap between these two diseases, but each has a reasonably individual clinical pattern. With the exception of histological findings they are not distinguishable from each other on laboratory findings alone. They tend to occur in families, and cases of either disease may be found in the same family. No genetic markers have been found so far.

The cause is unknown. It has been suggested that they may represent variations in host response to a common exogenous antigen, but there is no solid evidence for infection.

The pathogenesis is also obscure. It is possible that absorbed endotoxins may be responsible for some of the systemic disease (Aoki, 1978). Raised levels of circulating immune complexes have been found in patients with active bowel disease and extraintestinal disease (Hodg-

son et al., 1977; Nielsen and Svehag, 1978). No evidence for an abnormality of immunoregulation by T-lymphocytes has been found, either locally or in the peripheral blood (James et al., 1985).

The role of emotional factors and psychological disturbances as triggers has been explored, but it is difficult to discriminate cause from effect in such chronic and debilitating diseases. These would seem to be more important in ulcerative colitis than in Crohn's disease.

The incidence of inflammatory bowel disease in Indian immigrants to Britain is similar to that of the native British population, rather than the incidence in India. This and similar findings in other racial groups suggests that diet may be an important aetiological factor (Hodgson, 1985).

Crohn's Disease

This is an uncommon condition, the annual incidence being of the order of 2–3/100 000.

Clinical Findings

It usually presents with episodic colicky abdominal pain, fever, diarrhoea and weight loss. Rectal bleeding sometimes occurs. Severe acute disease mimics acute appendicitis. Chronic peritonitis, adhesions of adjacent loops of bowel to each other and to the abdominal wall, and fistula formation is common, but frank bowel perforation much less so. Perirectal and ischiorectal fistulae are often found in chronic disease. Other manifestations depend upon the degree and sites of involvement, for example anaemia, malabsorption and obstruction. A seronegative polyarthritis, usually affecting the larger joints, occurs in about 5% of cases. Signs of sacroiliitis or ankylosing spondylitis are sometimes seen (Mueller et al., 1974). The joint complications show no sex preponderance or HLA B27 association (Hyla et al., 1976).

Investigation

There is anaemia, leucocytosis, and a raised ESR.

Contrast radiographic studies show loss of mucosal detail in affected bowel, straightening of bowel segments and separation of adjacent loops (because of mesenteric and glandular swelling). In chronic scarring disease there are segments of narrowing with proximal dilatation. Many fistulae are undetected by these studies. (*Fig.* 73.)

Course

Most patients have many years of exacerbation and remission but usually the same segments of bowel are involved. About one-third

have an unremitting course. Disease appears to be more severe when it begins at an early age.

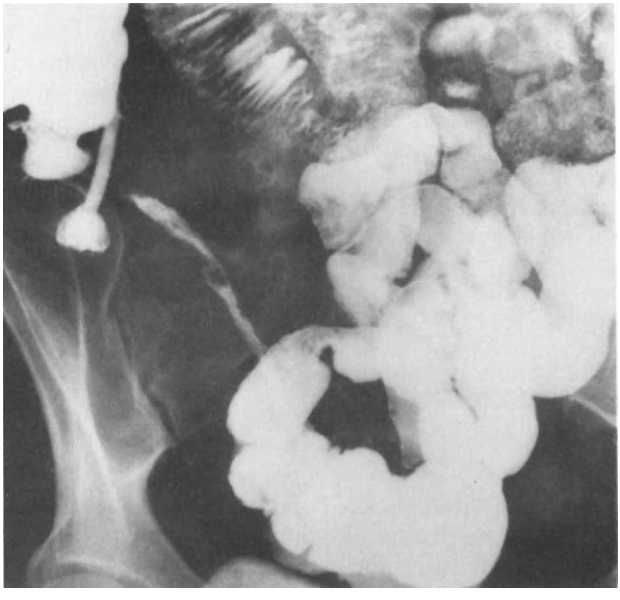


Figure 73 Crohn's disease: barium follow-through of terminal ileum showing a long stricture.
(Dr Roy Pounder.)

Pathology

There is a chronic granulomatous inflammation of the submucosal tissue of the small intestine, particularly the lower ileum (Van Patter et al., 1954; Crohn and Yarnis, 1958; Daffner and Brown, 1958). Disease has been described as high as the gastric antrum and is not uncommon in the colon (*granulomatous colitis*). Inflammation spreads through all layers of the gut wall leading to segmental scarring and narrowing of the lumen. The overlying mucosa commonly ulcerates. Between affected segments the gut wall is normal.

Treatment

General measures include the correction of complications such as anaemia and malnutrition. Rest is indicated in acute phases.

Systemic corticosteroid therapy is the most effective for active disease. Treatment may be started with prednisolone at 60 mg/day, which is reduced as the disease remits. It is probably wise to maintain

prolonged low-dose therapy to maintain the remission, but drug therapy does not appear to be prophylactic if given first in quiescent cases (Malchow et al., 1984).

Sulphasalazine (3 g/day) is effective in colonic disease, but not in classical disease of the small intestine (Summers et al., 1979; Malchow et al., 1984).

Metronidazole (20 mg/kg/day) may be helpful in colonic and perianal disease.

Surgery is reserved for the management of complications such as obstruction, blind loops and fistulae.

Ulcerative Colitis

This is commoner than Crohn's disease, with an annual incidence of about 10/100 000.

Clinical Findings

Most patients have an insidious onset of recurrent bloody diarrhoea and abdominal pain, with fever and weight loss. Others have a quite acute onset, and a few present with fulminant colitis from involvement of the whole colon. The latter are in immediate peril of death from the loss of blood, fluid and electrolyte.

As many as 20% of patients have sacroiliitis but it is often asymptomatic (Wright and Watkinson, 1965). In these patients other complications such as uveitis (*see below*) tend also to occur.

Significant liver disease, including fatty infiltration, pericholangitis and active chronic hepatitis, occurs in a small percentage of patients.

Erythema nodosum is not uncommon. The other skin manifestation, pyoderma gangrenosum, is only seen with very active colonic disease.

Investigation

Anaemia, leucocytosis and raised ESR occur, with varying degrees of hypoalbuminaemia and fluid and electrolyte disturbance.

Sigmoidoscopy or colonoscopy shows a classic friable mucosa which bleeds on contact. However, such examinations are not performed in acute disease because there is a very great risk of perforating the bowel. The same applies to contrast radiographic studies in the acute phase.

Barium studies show the colon generally shortened by contraction. The rectosigmoid is straightened. Involvement is in a continuous manner, in contrast to the 'skip areas' of normal bowel in Crohn's disease. The haustral pattern is lost, and polyps are outlined by barium. (*Fig.* 74.)

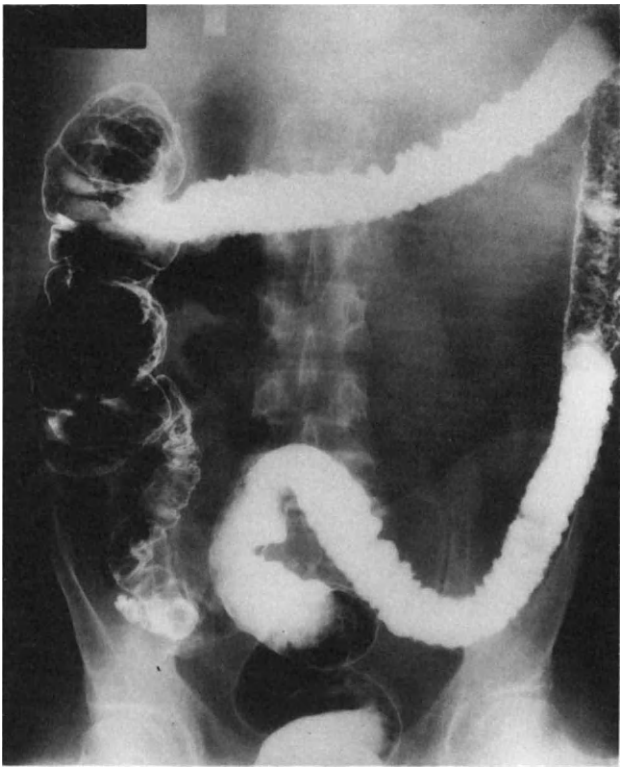


Figure 74 Ulcerative colitis: barium enema showing relative sparing of the rectum due to the use of prednisolone enemas, but extending to the hepatic flexure.
(Dr Roy Pounder.)

Course

The disease tends to be more severe when it begins in childhood or in the over-50s. Exacerbations and remissions occur over many years. There is overall 10 times the normal risk of developing carcinoma in the affected bowel, and this rises with the duration of disease. Current medical therapy is effective in controlling disease in at least 75% of cases. Disease confined to the rectum (proctitis) has a good prognosis and does not carry such a high risk of carcinoma.

Pathology

In contrast to the transmural inflammation of Crohn's disease, the inflammation in ulcerative colitis is superficial, in the mucosa and

submucosa. The epithelium is damaged and ulcerates, and multiple abscesses develop in the intestinal crypts. The surface becomes covered by a bloody and purulent exudate. Along with the mucosal damage and thinning there is an overgrowth of regenerating mucosa in a polypoid fashion.

Massive loss of the mucosa may be associated with dilatation of the colon as a result of damage to the myenteric plexus of nerves in the exposed muscularis.

Disease tends to begin low in the colon and spreads upwards. More than half the colon becomes involved in one-third of patients, but in a few cases disease remains confined to the rectum.

Treatment

The principles are similar to those for Crohn's disease except that hospitalization is more often needed to correct severe metabolic derangements and replace blood.

Attention to emotional factors is also more important. Substantial changes in life style may be indicated in order to reduce stress.

Steroids can be given by enema directly to disease of the lower colon, thus avoiding the dangers of prolonged systemic therapy.

Colectomy may be required for fulminant disease and toxic megacolon, severe haemorrhage, or perforation, and sometimes when medical management fails to control chronic disease. It is also performed when disease has lasted more than 10–15 years, as prophylaxis against carcinoma.

The Eye in Inflammatory Bowel Disease

Ocular disease is a rarity in classical Crohn's disease. In their series of 542 cases Crohn and Yarnis give no figures for prevalence (1958). Daffner and Brown describe 2 cases of uveitis, 1 of episcleritis and 1 of choroiditis in a series of 100 cases (1958). However, with granulomatous colitis (Crohn's disease of the colon) a significant number of patients do get eye disease (Greenstein et al., 1976). This is also true of ulcerative colitis, and the main reported manifestation is a non-granulomatous anterior uveitis (Wright et al., 1965; Korelitz and Coles, 1967). Occasional cases of episcleritis, conjunctivitis, retrobulbar neuritis and orbital cellulitis are also reported (*Ibid.*; Wright, 1980).

Uveitis, joint and skin manifestations all tend to be associated with *colonic* disease, no matter whether it is ulcerative or granulomatous (Korelitz and Coles, 1967; Haslock and Wright, 1973). The occurrence of uveitis is not related to activity of the colonic disease.

Chapter 6 References

Psoriasis

Armstrong R. D., Panayi G. S. and Welsh K. I. (1983) Histocompatibility antigens in psoriasis, psoriatic arthropathy, and ankylosing spondylits. *Ann. Rheum. Dis.* **42**, 142–146.

DuVivier A., Munro D. D. and Verbov J. (1974) Treatment of psoriasis with azathioprine. *Br. Med. J.* **1**, 49–51.

Farber E. M., Abel E. A. and Charuworn A. (1983) Recent advances in the treatment of psoriasis. *J. Am. Acad. Dermatol.* **8**, 311–321.

Green L., Meyers O. L., Gordon W. and Briggs B. (1981) Arthritis in psoriasis. *Ann. Rheum. Dis.* **40**, 366–369.

Lambert J. R. and Wright V. (1976) Eye inflammation in psoriatic arthritis. *Ann. Rheum. Dis.* **35**, 354–356.

Lambert J. R. and Wright V. (1977) Psoriatic spondylitis: a clinical and radiological description of the spine in psoriatic arthritis. *Q. J. Med.* **46**, 411–425.

Leading Article (1978) PUVA. *Br. Med. J.* **2**, 2–3.

Stern R. S., Parrish J. A. and Fitzpatrick T. B. (1985) Ocular findings in patients treated with PUVA. *J. Invest. Dermatol.* **85**, 269–273.

Relapsing Polychondritis

Anderson W. B. (1967) Ocular lesions in relapsing polychondritis and other rheumatoid syndromes. *Am. J. Ophthalmol.* **64**, 35–50.

Dolan D. L., Lemmon G. B. and Teitelbaum S. L. (1966) Relapsing polychondritis. Analytic literature review and studies on pathogenesis. *Am. J. Med.* **41**, 285–299.

Froidart J.-M., Abe S., Martin G. R., Zizic T. M., Barnet E. V., Lawley T. J. and Katz S. I. (1978) Antibodies to type II collagen in relapsing polychondritis. *N. Engl. J. Med.* **299**, 1203–1207.

Rucker C. W. and Ferguson R. H. (1965) Ocular manifestations of relapsing polychondritis. *Arch. Ophthalmol.* **73**, 46–48.

Inflammatory Bowel Disease

Aoki, K. (1978) A study of endotoxaemia in ulcerative colitis and Crohn's disease: I. Clinical Study. *Acta Med. Okayama* **32**, 147–158.

Crohn B. B. and Yarnis H. (1958) *Regional Ileitis.* New York, Grune and Stratton.

Daffner J. E. and Brown C. H. (1958) Regional enteritis: I. Clinical aspects and diagnosis in 100 patients. *Ann. Intern. Med.* **49**, 580–594.

Greenstein A. J., Janowitz H. D. and Sachar D. B. (1976) The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine* **55**, 401–412.

Haslock I. and Wright V. (1973) The musculoskeletal complications of Crohn's disease. *Medicine* **52**, 219–225.

Hodgson H. J. F. (1985) Inflammatory bowel disease and food intolerance. *J. R. Coll. Physicians Lond.* **20**, 45–48.

Hodgson H. J. F., Potter B. J. and Jewell D. P. (1977) Immune complexes in ulcerative colitis and Crohn's disease. *Clin. Exp. Immunol.* **29**, 187–196.

Hyla J. F., Franck W. A. and Davis J. S. (1976) Lack of association of HLA B27 with radiographic sacroiliitis in inflammatory bowel disease. *J. Rheumatol.* **3**, 196–200.

James S. P., Fiocchi C., Graeff A. S. and Strober W. (1985) Immunoregulatory function of lamina propria T cells in Crohn's disease. *Gastroenterology* **88**, 1143–1150.

Korelitz, B. I. and Coles, R. S. (1967) Uveitis (iritis) with ulcerative and granulomatous colitis. *Gastroenterology* **52**, 78–82.

Malchow H., Ewe K., Brandes J. W., Goebell H., Ehms H., Sommer H. and Jesdinsky H. (1984) European cooperative Crohn's disease study (ECCDS): results of drug treatment. *Gastroenterology* **86**, 249–266.

Mueller C. E., Seeger J. F. and Martel W. (1974) Ankylosing spondylitis and regional enteritis. *Radiology* **112**, 579–581.

Nielsen H. and Svehag S.-E. (1978) Circulating immune complexes in ulcerative colitis. I. Correlation to disease activity. *Clin. Exp. Immunol.* **31**, 72–80.

Summers R. W., Switz D. M., Sessions J. T., Becktel J. M., Best W. R., Kern F. and Singleton J. W. (1979) National cooperative Crohn's disease study: results of drug treatment. *Gastroenterology* **77**, 847–869.

Van Patter W. N., Bargen J. A., Dockerty M. B., Feldman W. H., Mayo C. W. and Waugh J. M. (1954) Regional enteritis. *Gastroenterology* **26**, 347–450.

Wright P. (1980) Conjunctival changes associated with inflammatory disease of the bowel. *Trans. Ophthalmol. Soc. U.K.* **100**, 96–97.

Wright R., Lumsden K., Luntz M. H., Sevel D. and Truelove S. C. (1965) Abnormalities of the sacroiliac joints and uveitis in ulcerative colitis. *Q. J. Med.* **34**, 229–236.

Wright V. and Watkinson G. (1965) Sacroiliitis and ulcerative colitis. *Br. Med. J.* **2**, 675–680.

Chapter seven

Infectious Diseases and the Eye

INTRODUCTION

Intraocular inflammation has long been known to occur in specific infections, such as the retinitis of syphilis, the retinochoroiditis of toxoplasmosis, and the choroiditis of tuberculosis. In these conditions the organism has been isolated from the eye.

Other conditions appear to be in some way caused by infection in that they occur as part of a reaction to certain specific infections. Organisms are never found in the eye. Examples of this are the uveitides accompanying infection by Salmonella, Shigella, Yersinia and Chlamydia. In these conditions it is clear that certain properties of the host permit the manifestation of disease remote from the actual site of infection. In such organs as the eyes and joints it has until recently been impossible to do more than guess at the mechanisms of this type of disease.

Even more remote is the concept that ocular inflammation can be caused by foci of infection elsewhere, such as sinusitis and dental caries. Tuberculosis was once in this way commonly held responsible for attacks of anterior uveitis.

This concept cannot be jettisoned altogether. It can be brought into a new perspective with the help of new immunological insights. It is strange that it ever held such a prominent place in uveitis theory when one considers that uveitis has never been common in tuberculosis (except when the organism is in the eye), nor in septicaemias. It is not commoner in persons with known focal infection than it is in others, and focal infections are not commoner in those with uveitis. There is no solid evidence that the eradication of foci of infection discovered in the investigation of patients with uveitis will alter the course of the disease.

While this nebulous concept does not provide a convincing hypothesis about the origin of uveitis, it may help to understand how all

manner of stimuli (including infective ones) can apparently trigger a *recurrence*. In experimental models it has been found that when the eye is rechallenged with the antigen used to produce the initial inflammation, only a small proportion of the antibody produced in the eye is specific to that antigen (Hall and Pribnow, 1974; Shimada and Silverstein, 1975). The eye appears to have become seeded at the time of the initial inflammation with lymphocytes bearing memories for many other antigens, and in effect behaves subsequently like a lymph node.

If this is true in human uveitis, then once the initial attack has occurred the eye may contain lymphocytes able to respond to a vast number of the antigens to which the patient has previously been exposed. They could conceivably become reactivated by subsequent exposure, turning on a process which would appear non-specific. The clinical import of this reasoning is that apart from the effect on the patient's general well-being, treatment of foci of infection in patients already suffering from uveitis might shorten attacks or reduce the rate of recurrence. On the other hand it is naive in the extreme to imagine that one could eliminate even a fraction of the number of potential stimuli, knowing as we now do that the healthy immune system is not quiescent but in a complex state of controlled response.

Advances in immunology and cell biology now permit us to envisage entirely new roles for external agents in the production of disease. It seems likely that infection will be found to be responsible for many of the conditions whose cause is at present unknown. For example, it is conceivable that virus-infected bacteria may cause a type of disease that neither the virus nor the bacterium can cause alone. An infective agent may so alter the expression of cell surface markers as to render certain cells immunogenic, thus causing autoimmune disease. Disease expression may also be modified by the portal of entry of the agent, or how it is first presented to the host's immune system.

The clinical course of some eye diseases, such as geographic choroiditis, also suggests a viral infection. Indirect methods for detecting virus have renewed the search for virus in Behçet's syndrome, and viral particles have been found in the retina in the acute retinal necrosis syndrome.

Immunosuppression is causing an increasing incidence of opportunistic infection, particularly with cytomegalovirus.

The advent of safer and more effective antiviral agents has made the search for infective causes in inflammatory eye disease of much more than theoretical interest.

Discussion in this chapter will be confined to the eye changes in well-defined systemic infections. Despite the above speculations that a larger role for infection in ocular inflammation will be recognized in the future, it has to be admitted that in most of the diseases to be outlined in the following pages eye manifestations are uncommon. The

subject is too broad to permit more than a brief discussion of some of the more interesting non-ophthalmological aspects of these infections.

Systemic Infections with Organisms in the Eye

Bacterial

- Tuberculosis
- Leprosy
- Syphilis

Protozoan

- Toxoplasmosis

Helminthic

- Onchocerciasis
- Toxocariasis

Viral

- Herpesvirus: Herpes simplex, types 1 and 2
  - Varicella-zoster
  - Cytomegalovirus
  - Epstein–Barr virus
- Rubella (German measles)
- Rubeola (measles)
- Miscellaneous viral infections in which eye disease is probably caused directly by the virus, but in which the virus has not yet been isolated from the eye, for example:
  - Influenza
  - Rift Valley fever
  - Poliomyelitis
  - Vaccinia
  - Variola
  - Mumps

  (In many of these conditions it is possible that the rare ocular inflammation may be due to a hypersensitivity reaction rather than to a direct toxic effect of the virus on the cells.)
- HTLV III Reference to infection by human T-cell leukaemia virus III (HTLV III), now renamed HIV, (Human Immunodeficiency Virus) will be found under Cytomegalovirus.

Systemic Infections without Spread of Organisms to the Eye

- Gonorrhoea
- Chlamydia
- Shigella
- Yersinia
- Salmonella

(In these conditions eye disease is typically in the form of acute anterior uveitis and accompanies sterile arthritis. They have been discussed in Chapter 5 under the heading of Reiter's syndrome.)

BACTERIAL DISEASES

Tuberculosis

Epidemiology

Tuberculosis is generally regarded as an uncommon disease in developed countries, but 7406 new cases were notified in England and Wales in 1982 (Communicable Disease Statistics, 1973–1983). The vast majority of cases occur in immigrants from the Indian subcontinent (National Survey of Tuberculosis Notifications in England and Wales, 1978–9). Immigrants also contribute significantly to the incidence of new cases in parts of the United States, such as southern Florida, but native-born Blacks bear the brunt of the disease in the United States. It comes as a surprise to many to learn that the overall prevalence in the United States is comparable to that in Great Britain. It is sobering to realize that sanatoria are still widely employed in eastern Europe, where disease prevalence is higher, and living standards lower than our own. Patients living in overcrowded conditions, alcoholics, the elderly, and immunocompromised people are at greatest risk of infection with *Mycobacterium tuberculosis* and are also more prone to infection with so-called 'atypical' mycobacteria.

Pathology

Most of the signs and symptoms of tuberculosis are due to the presence, at least at some time, of *M. tuberculosis* or 'atypical' mycobacteria in the lesions. Some manifestations appear to be caused by hypersensitivity to mycobacterial antigens, to which the patient has previously been exposed.

The typical lesion is a granulomatous tissue response to intracellular multiplication of the organism. An identical reaction involves the lymph nodes draining the sites of primary infection. It is still predominantly a disease of the chest but other systems such as the kidney, skin and gastrointestinal tract may be the primary site of infection. Giant cells are found centrally, surrounded by epithelioid cells and lymphocytes. A characteristic cheese-like central necrosis tends to occur (caseation), and there may be extensive surrounding fibrosis.

Some years before Robert Koch demonstrated the existence of the tubercle bacillus, Julius Cohnheim showed that choroidal tubercles were histologically identical with tubercles elsewhere.

Intraocular disease is always secondary to disease elsewhere in the body. The eye is infected as part of blood-borne dissemination. Large numbers of organisms may be released into the circulation when caseation involves the wall of a blood vessel. Although one tends to associate ocular disease with miliary tuberculosis, cases occur in the

absence of widespread disease, and are presumably the result of otherwise trivial bacteraemia from old foci. When tuberculosis was common, most cases of ocular disease did in fact occur in otherwise healthy people who had some sign of healed disease elsewhere in the body.

Ocular Tuberculosis

Ocular disease probably occurs in no more than 1–2% of patients with tuberculosis (Donahue, 1967). Reports of appreciable numbers of cases still come from eastern Europe (Bakholdina et al., 1983) but most reports now come from India (Sen, 1977; Agrawal et al., 1977; Sen, 1980).

1 Disease of the Eyelids, Conjunctiva, Cornea, Sclera and Orbit

(a) EYELIDS Lupus vulgaris may involve the lids. This is a chronic type of cutaneous tuberculosis which is now rarely seen. It consists of plaques and nodules with marked scarring. Sometimes there is deep ulceration and destruction of facial features.

Orbital lesions may discharge through the lids and give rise to scarring around the discharging sinuses.

(b) CONJUNCTIVA The classical conjunctival lesion is the phlycten, usually a single lesion appearing near the cornea as a small vesicle in a zone of erythema. It rapidly develops into a small yellow ulcer and heals within a few weeks. It is believed to be a local allergic response to the tubercle bacillus in sensitized individuals, but most phlyctens seen nowadays are probably due to other allergic stimuli (Koppert and Van Rij, 1982).

Primary conjunctival disease has been described (Archer and Bird, 1967) and may also occur as a result of spread from endogenous foci (Liesegang and Cameron, 1980; Lamba and Srinivasan, 1983).

(c) CORNEA AND SCLERA Tuberculous keratitis and scleritis are usually due to spread of infection and granulomatous reaction from within the eye. Primary keratitis due to *Mycobacterium fortuitum* has been reported (Waldman, 1982).

(d) ORBIT Spread from orbital periostitis is the principal cause of orbital disease (Agrawal et al., 1977; Sen, 1980). Spread may also occur from within the eye itself, and orbital structures may be involved by direct haematogenous spread (Segal et al., 1980; Sheridan et al., 1981; Oakhill et al., 1982).

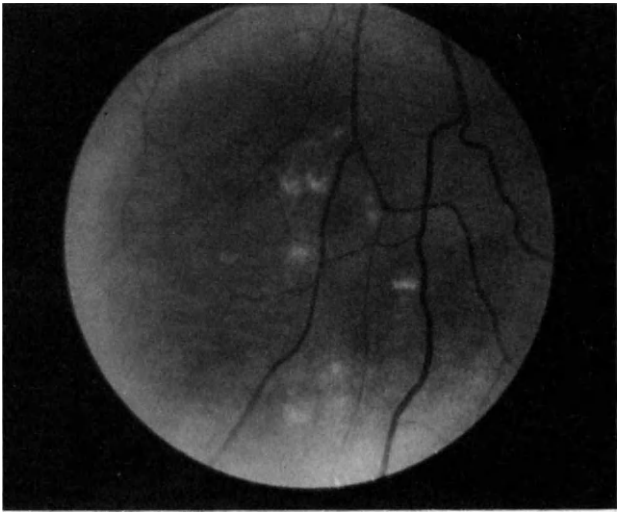


Figure 75 Miliary tuberculosis: patchy retinal oedema.

2 Granulomatous Intraocular Disease

All parts of the uveal tract may be involved, the more posterior uvea more commonly than the more anterior.

The earliest signs of disease are small white patches of retinal oedema overlying tiny foci of choroiditis (*Fig.* 75). These lesions vanish rapidly with specific antituberculous chemotherapy before elevation occurs from any sizeable granulomatous reaction in the choroid. Larger, more established lesions have a more solid appearance, though still white or yellow, and they heal with retinal and choroidal scarring (*Fig.* 76). Lesions may be very large and spread as plaques or nodules (tuberculomas), invading adjacent structures and producing extensive retinal detachment (*Fig.* 77). Lesions in the ciliary body have been known to perforate the sclera.

Lesions in all stages of evolution may be seen simultaneously.

Severe uveal disease gives rise to extensive synechia formation and secondary glaucoma.

Choroidal tuberculosis is the result of blood-borne spread of infection and is seen in most cases of unrestricted miliary disease.

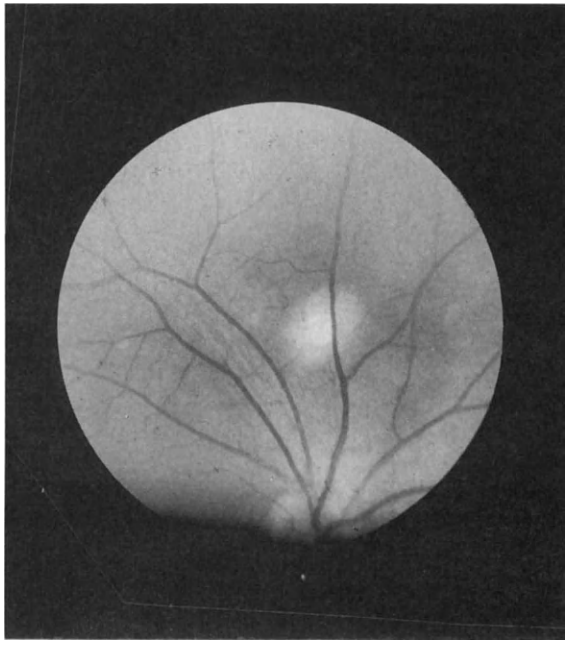


Figure 76 Miliary tuberculosis: healed choroidal lesion.

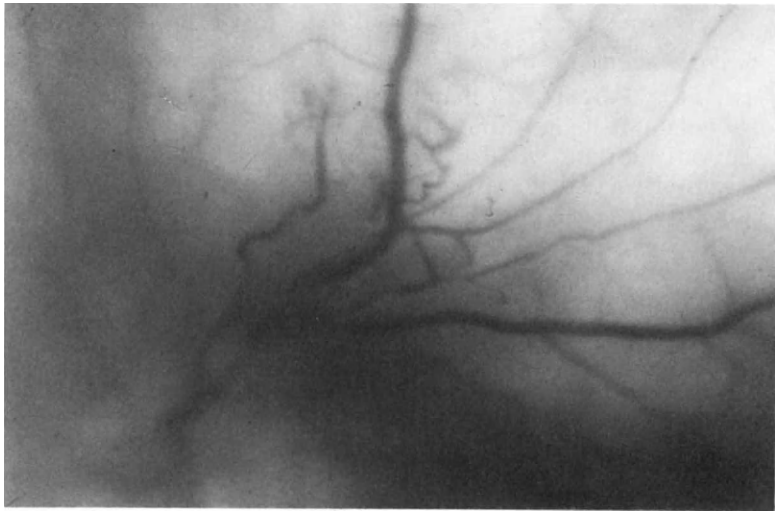


Figure 77 Large choroidal granuloma above optic disc in other eye of same patient as *Fig.* 76.

3 Panuveitis

Particularly when tuberculosis was a common disease, there was a tendency to ascribe cases of non-specific panuveitis to this cause when it occurred in patients known to have had past tubercular disease. Although there may be some clinical features akin to those of granulomatous intraocular disease, such as iris nodules, keratic precipitates and extensive synechia formation, no histological evidence of granulomatous disease is ever found in these cases. It is now largely a diagnosis made following resolution of disease in response to a trial of antituberculous chemotherapy in patients with strong tuberculin positivity and no sign of other potential cause for the uveitis (Schlaegel and O'Connor, 1981).

4 Allergic Reactions to Tuberculin

Ocular reactions are occasionally reported following tuberculin testing. Heydenreich (1978) reported 2 cases in which uveitis worsened, and one of central serous retinopathy. Heydenreich's suggestion that reactions reported many years ago may have been due to impurities in Old Tuberculin preparations then in use seems a reasonable one, considering their current rarity.

5 Eales' Disease

The notion that this nebulous entity of recurrent vitreous haemorrhage and retinal vascular abnormalities is due to tuberculosis has no good foundation, but on the other hand it has not been disproved that it may represent a delayed local hypersensitivity in the walls of peripheral retinal veins in individuals sensitized to tuberculoprotein (Elliott, 1975).

Diagnosis

There are no specific tests apart from isolation of the organism on histology or culture, and this goal can rarely be approached with eye disease. The diagnosis is made on the basis of the clinical findings, as outlined *above*, when they occur in the presence of tuberculous disease elsewhere in the body, and is confirmed by resolution of the lesions when appropriate chemotherapy is given.

An increasing frequency of infection with 'atypical' mycobacteria has been observed in recent years. These organisms are less virulent than *Mycobacterium tuberculosis* itself and tend to infect people with altered host defences (Waldman, 1982).

Treatment

A wide variety of specific antituberculous drugs is available. Specific therapy brings about rapid resolution of eye lesions. It should be managed by a tuberculosis specialist. In practice most cases are already under the care of such an internist, who has referred them to the ophthalmologist. Local mydriatics and steroids are given to the eye as indicated. It is particularly important not to neglect local aspects of treatment when there is much generalized uveitic reaction. Severe eye disease may be an indication for systemic steroid therapy, but the patient must be taking effective specific chemotherapy as well.

Resistant cases are seen, and choroidal tubercles have arisen in patients during chemotherapy, and even after completion of an apparently successful course of treatment for pulmonary disease.

Leprosy

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae* (Hansen's bacillus). This obligate intracellular organism multiplies slowly and has a tendency to affect neural tissues, especially in the cooler parts of the body. Thus the skin, upper respiratory passages, superficial nerves and the eyes are principally affected. It is estimated that 20 million people in the world suffer from this disease. Close and prolonged contact is necessary for spread, which tends to be in families. The organism is probably disseminated from ulcers in the nasal mucosa to the skin and nasal mucosa of others.

Clinical Features

Initially, one or several hypo- or hyperpigmented macules appear on the skin. These areas are frequently anaesthetic. The subsequent course tends to follow one of two clinical patterns, *tuberculoid* or *lepromatous*, depending upon whether there is a strong cell-mediated immunological response in the host, or not. However, these two types have many features in common and it is often impossible to make a classification in early disease. In some patients the disease may run its course with a mixture of the features of both types.

Although this polarity is not obvious in infections with the related organism *Mycobacterium tuberculosis*, some evidence does suggest that a similar spectrum of clinical and immunological response exists in tuberculosis also (Lenzini et al., 1977).

It is generally estimated that 25% of patients with leprosy have some form of eye involvement but in some series much higher figures are given (47%, Weerekoon, 1969; 95%, Harrell, 1977).

Tuberculoid Leprosy

The host mounts a strong cell-mediated immune response to the infecting bacillus, the lesions tend to be more localized, and only small numbers of organisms are found in the tissues. Severe peripheral nerve lesions occur early in the disease and the superficial nerves may be palpably enlarged. Patients may suffer considerable pain but there is eventually motor and sensory loss with muscle atrophy and loss of phalanges.

The commonest ocular disease is due to corneal anaesthesia and incomplete closure of the eyelids (lagophthalmos). The latter is a result of facial nerve palsy. Ultimately, corneal ulceration, scarring and blindness may occur.

Uveitis and scleritis are also common, but less so than in lepromatous disease.

Lepromatous Leprosy

In the host there is little or no evidence of a cell-mediated immunological reaction to the bacillus and myriads of bacilli are found in the cells and peripheral blood. There is extensive diffuse granulomatous disease of superficial tissues. In contrast to the isolated and well-defined skin lesions of tuberculoid leprosy, the skin lesions are more numerous and less well defined. There is diffuse cellular infiltration between the lesions. Progression is relentless. Nasal ulceration occurs early and may lead to nasal collapse. Neurological involvement tends to be less prominent but takes the same form as in tuberculoid disease.

Corneal and eyelid lesions are equally common in both types of disease, but the incidence of uveitis is much higher in lepromatous disease (Ticho and Ben Sira, 1970).

Stromal keratitis and beading of the corneal nerves are also common (ffytche, 1981b).

Scleritis is also described (Michelson et al., 1979).

Acute Anterior Uveitis

This is uncommon and varies greatly in severity, but can lead to phthisis of the eye. It may occur as part of the reaction to therapy.

Chronic Anterior Uveitis

This develops insidiously and progresses over many years to a stage of marked iris atrophy, particularly of the dilator muscle. The unmyelinated autonomic nerves in the iris are affected early (ffytche, 1981b). The result is meiosis, distortion and displacement of the pupil. Com-

plete holes may appear in the iris. Multiple posterior synechiae and secondary cataract occur. In the early stages so-called 'iris pearls' develop on the anterior surface of the iris, especially towards the pupil margin. They are small white granulomas (lepromas) consisting of mononuclear cells laden with bacilli, and are characteristic of lepromatous iritis.

The resemblance of this condition to a slow, degenerative process has been noted, and a neuroparalytic basis has been proposed (ffytche, 1981a).

Posterior Uveitis

This is much less common than anterior uveitis, although in one series of 106 cases an incidence of choroiditis of 3·4% was found, against 8·2% for iritis (Van Poole, 1934). In this series an unusually high incidence of optic neuritis was also reported.

The choroiditis is multifocal or disseminated, eventually producing atrophic scars with variable pigmentary disturbance, mostly in the periphery of the fundus.

Leprosy in Other Species

Research in leprosy has been hampered by the fact that the usual laboratory animals do not normally support the growth of the bacillus. The nine-banded armadillo has emerged from obscurity because it can be infected with relative ease. Irradiated and thymectomized mice are also used. In both these animal models bacilli are found in the choroid, but this is not so in human disease (Hobbs et al., 1978). Recently the disease has been produced in three monkey species (Wolf et al., 1985).

Treatment

Systemic treatment with dapsone by mouth is continued for several years after the bacilli are no longer found in skin specimens. Chemotherapy is gradually increased in dose over the first few weeks to a maintenance level. Progress is arrested and skin lesions regress to some extent. Neurological recovery is limited. Treatment may be complicated by reactional states, particularly erythema nodosum leprosum. In this condition perivascular deposits of immunoglobulin and complement are found in the dermis (Wemambu et al., 1969). The acute iritis that sometimes accompanies this condition may be caused by the deposition of immune complexes in the iris (Hobbs et al., 1978).

Rifampicin may also be used, but only under the strict control of experts in the management of leprosy, since the development of resistance could present serious problems to patients and contacts alike.

The uveitis and other inflammatory manifestations in the eye are treated with corticosteroids in the normal way. Cataract surgery may be required. If patients are treated aggressively and relatively early in the disease they appear to suffer little from severe visual problems, although a high proportion still have signs of ocular abnormalities (Spaide et al., 1985).

Syphilis

Introduction

Very few ophthalmologists currently in practice have managed cases of active ocular syphilis. It is now very rare, although tests for syphilis are still routinely performed in the investigation of cases of uveitis and retinitis.

The incidence of severe morbidity from syphilis fell dramatically on the introduction of penicillin treatment. Despite this and the pursuit of educational and public health measures the population incidence of the disease has steadily increased in the last twenty years. It is caused by a spiral-shaped organism, the *Treponema pallidum*. Except for the clinical differences in the diseases they cause there are no major differences between this organism, *Treponema pertenue* of yaws, and *Treponema careteum* of pinta.

Clinical Features: Acquired Disease

Primary Infection

Infection is usually transmitted venereally. The organism can penetrate intact mucous membranes, and rapid spread occurs by lymphatics and blood to all parts of the body. About three weeks after infection the primary lesion appears (the chancre). This begins as a hard nodule at the site of infection, which breaks down to form an ulcer. There is associated regional lymphadenopathy but little or no pain. Spirochaetes are seen on dark-field microscopy of exudate from the lesion. At this stage serological tests are negative. Antibodies do not appear in the blood until 4 to 6 weeks after infection. The chancre heals spontaneously after a few weeks.

Secondary Syphilis

Two to three months after the initial infection systemic evidence of generalized disease appears in about 25% of untreated patients. There is a symmetrical skin rash which may be macular, papular or occasionally pustular, and is most evident on the trunk. Shallow grey ulcers

appear on mucous membranes in about one-third of patients with secondary syphilis. In moist areas of skin the papules may enlarge and ulcerate to form broad, shallow grey ulcers, known as condylomata lata. All these lesions are highly infectious. There is usually a low-grade fever, lymphadenopathy and other constitutional symptoms.

This is the stage at which eye lesions appear.

Tertiary Syphilis

Symptoms and signs of tertiary syphilis can be expected to develop in about 25% of untreated patients. They begin to appear 2 to 3 years after the primary infection. They are generally the result of local destruction by chronic inflammatory reaction which may involve any part of the body. Sometimes large granulomas form (gummas) and undergo central necrosis. They heal with scarring, and great deformity may result from involvement of bone.

Cardiovascular System Disease

This becomes symptomatic in about 10% of untreated patients and is the result of disease of large vessels whose walls are supplied by vasa vasorum. The latter become progressively occluded by periarteritis and endarteritis. The ascending aorta is most severely affected, with medial necrosis and destruction of elastic tissue, resulting in aneurysmal dilatation, aortic valve incompetence and coronary artery ischaemia because of narrowing of the coronary ostia. Aortic calcification may be visible on X-ray.

Cardiovascular complications are the usual cause of death from syphilis.

Central Nervous System Disease

Three clinical pictures are recognized but there is much overlap:

MENINGOVASCULAR SYPHILIS is the first of the clinical syndromes to appear, five to ten years after infection. It is due to meningeal inflammation and obliterative endarteritis. Cranial nerve palsies are common and there is usually evidence of widespread cerebral vascular disease.

GENERAL PARALYSIS OF THE INSANE may occur 20 years after infection and presents a combination of symptoms which reflect the global deterioration of cerebral function resulting from parenchymal disease.

TABES DORSALIS may appear even later. It is the result of demyelination

of the posterior columns of the spinal cord, and the dorsal nerve roots and ganglia. Patients have general ataxia and walk with a characteristic broad-based gait, the feet slapping against the ground. There is also sensory and proprioceptor loss and areflexia. The Charcot joint of tabes dorsalis is a joint deprived of pain sensation and the associated protective reflexes which becomes damaged and distorted by repeated trauma.

Abnormalities in the cerebrospinal fluid are found in about 20% of untreated patients but only a relatively small proportion of these develop overt cerebral syphilis. The likelihood of CSF changes increases with time from the initial infection.

Clinical Features: Congenital Syphilis

If maternal syphilis is not effectively treated before the 16th week of gestation more than 75% of fetuses are infected. There is a high rate of abortion, death *in utero* and neonatal death.

There is widespread inflammation of most organs, in particular a pericellular hepatic cirrhosis, which together with pulmonary haemorrhage and secondary bacterial infection is a major cause of neonatal death.

Less severely affected infants develop rashes, mucous membrane lesions, rhinitis and infection of bone epiphyses. If the condition is untreated, other manifestations may develop later. Cardiovascular disease is rare and central nervous system syphilis is much less common than in adults with tertiary syphilis. However, corneal disease is common, as are dental abnormalities including poorly developed, notched upper central incisors (Hutchinson's teeth), and facial deformities from thickening of the frontal bones and destruction of the nasal bones.

Ocular Disease

Acquired Syphilis

In acquired disease the ocular involvement appears in the secondary stage. In about 5% of cases an acute anterior uveitis accompanies the rash and generalized systemic inflammation. Acute anterior uveitis may also occur as part of the Herxheimer reaction (*see under* Treatment) but despite this it responds well to penicillin and conventional local corticosteroid therapy. The anterior uveitis has no particular features except that it is usually quite severe, but occasionally small red foci of hyperaemia appear in the iris. These are known as roseolae, and last only a few days. They sometimes develop into small grey-yellow papules with tufts of neovascularization on their surface. These gradually absorb and leave patches of atrophy in the iris.

Later in the secondary stage a diffuse retinochoroiditis sometimes occurs. The retinal elements of this disease have not been duly emphasized in the literature, possibly because cases were not observed early enough in the process. The whole retina may be involved but the more peripheral parts may be spared. The retina and optic disc are oedematous, giving the fundus a greyish appearance over which are spread multiple yellow foci indicating more severe retinal and choroidal inflammation. These foci may become confluent. Retinal arteries and veins are sheathed and fine retinal haemorrhages may be seen. There is usually a dense vitreous haze. Healing leaves the retina and choroid diffusely scarred and pigmented. Marked optic atrophy is sometimes seen (Kranias et al., 1981). Cases are described in which optic neuropathy is the main finding and signs of inflammation in other parts of the eye are minimal.

Some patients in the tertiary stage develop a panuveitis which is heralded by severe ocular pain and inflammation of the iris, with fibrinous exudate in the pupil and the formation of multiple posterior synechiae. Inflammatory cells aggregate in the iris and may be visible as nodules on slit lamp microscopy. There is usually diffuse inflammation of choroid, retina and optic nerve. This type of disease, in contrast to that accompanying secondary syphilis, does not always respond well to treatment and has a tendency to recur.

Interstitial keratitis occasionally develops in patients with tertiary syphilis.

The classic ocular sign of cerebral syphilis is the Argyll Robertson pupil. This is a small, irregular pupil in which the near reflex is preserved but the direct light reflex is lost. Interested readers might consult the extensive review of this subject by Loewenfeld (1970).

Congenital Syphilis

Interstitial keratitis and retinochoroiditis are the common ocular findings in congenital syphilis. Sometimes an acute, bilateral anterior uveitis occurs, either alone or in company with keratitis.

Ocular manifestations may be present at birth and may first be diagnosed at a late stage when much scarring has occurred.

Interstitial Keratitis

This may not occur until many years after birth. Cases have been reported as late as the fifth decade. The affected eye first becomes injected and then the cornea becomes cloudy. Corneal vascularization appears, and the cornea begins to clear from the periphery inwards. Finally, fibrous repair leaves the cornea somewhat thinned, with patchy opacification. The ghosts of stromal blood vessels persist.

Endothelial damage is common and splits may appear in Descemet's membrane. Superficial corneal calcification may also occur in time. The phase of active keratitis lasts a few months. Antisyphilitic therapy may improve it or make it worse. It is believed to be a delayed hypersensitivity reaction in tissue previously sensitized by infection, and this may account for the favourable response to treatment with steroids.

The keratitis that sometimes occurs in acquired syphilis is pathologically similar but is usually uniocular and may be sectorial.

Anterior uveitis usually accompanies active keratitis.

Retinochoroiditis

Because the onset of this is intrauterine it is usually only seen when it has already reached an advanced stage. Classically, both fundi show fine scattered pigmentation with intervening areas of pallor, producing the so-called 'pepper and salt fundus'. Pigmentation may, however, be in large patches as in any other multifocal choroiditis. It tends to be more marked peripherally. The fundus appearance varies greatly; although attempts have been made to classify this into different groups, the underlying pathology is the same. Indeed, it does not seem to differ fundamentally from acquired disease, except that in the latter the pigment disturbance is generally less marked.

In one reported series of 223 patients with congenital syphilis and interstitial keratitis, 13·4% had choroidoretinal changes and 8% had signs of vasculitis (Klauder and Meyer, 1953). Choroidoretinitis has also been frequently reported in the absence of corneal disease, as one would expect from the characteristically late onset of the keratitis.

Optic atrophy is common. Evidence of active retinal vasculitis may be found and sometimes patches of subretinal fibrosis are seen.

Pathology

The destruction initiated by the presence of organisms in the uveal tissues is thought to be mediated by immune complex deposition in small blood vessels. The unifying pathological process is an obliterative endarteritis. This accompanies the infiltration by lymphocytes, plasma cells and macrophages in the skin lesions of acquired disease. Periarteritis and endarteritis of the vasa vasorum are responsible for cardiovascular disease.

In acquired tertiary disease the chronic inflammatory reaction sometimes produces large granulomas, or gummas, which may undergo central necrosis. They are thought to be due to extreme cell-mediated sensitivity to the organism, since very few organisms are found in these lesions.

Interstitial keratitis begins with a lymphocytic infiltration in the paralimbal conjunctiva. This infiltrate invades the cornea. The epithelium and stroma become oedematous and necrosis and neovascularization follow. Changes are less severe towards the endothelial surface of the cornea. Macrophages then appear and finally a process of stromal atrophy and fibrosis occurs (Wescamp, 1949).

The uveal tract tends to show similar changes whether the disease is congenital or acquired, except that the iris is more susceptible in the acquired condition, whereas the choroid is more commonly involved in congenital disease. There is a non-specific infiltration of lymphocytes and plasma cells which tend to aggregate into microscopic nodules, especially in the deeper layers of the iris and in the choriocapillaris. Retinal vasculitis of both the arteries and the veins occurs in the acute phase and lymphocytic and plasma cell infiltration is also found in and around the vessel walls, which eventually become thickened and then obliterated by fibrosis. The retinal pigment epithelium undergoes a variable pattern of destruction and proliferation.

In eyes obtained at autopsy from infants dying from congenital syphilis only small numbers of spirochaetes are found, and these are mostly in sheaths of blood vessels penetrating the sclera over the ciliary body (Friedenwald, 1929). Spirochaetes are not found in the cornea in the late keratitis of congenital syphilis (Wescamp, 1949). This supports the likelihood that this reaction is essentially the result of hypersensitivity rather than fresh invasion by large numbers of organisms. Late uveal inflammation such as sometimes occurs in tertiary acquired syphilis may also be due to a hypersensitivity reaction.

Investigation

Dark field and phase contrast microscopy of the surface moisture of the primary chancre or condylomata lata of secondary disease reveals the organism in large numbers. It can also be found in aspirates from lymph nodes during the secondary stage. A negative examination does not exclude syphilis.

Serological Tests

There are two groups of serological tests for syphilis.

The first are tests designed to detect IgG and IgM antibodies which the host produces to an antigen which is generated in the host–organism interaction. The *Wassermann reaction* belongs to this group, but the one currently in wide use is the *VDRL Flocculation Test*. These tests indicate active syphilis. Unfortunately, the VDRL test is negative in many patients with active disease, particularly those with very early or late disease. About one-third of positive reactions are false. False

positive reactions are found in a variety of infections, and in collagen diseases, especially systemic lupus erythematosus.

The second group of tests detect specific antitreponemal antibody. The fluorescent treponemal antibody absorption test (*FTA–Abs*) is in standard use. The *Treponema pallidum* immobilization test (*TPI*) and the *T. pallidum* haemagglutination assay (*TPHA*) also belong to this group. The specific antibodies detected by these tests generally persist for a lifetime, even after effective treatment. A negative FTA–Abs test excludes syphilis.

In testing for the disease both VDRL and FTA–Abs tests should be done.

A modification of the FTA–Abs test to detect IgM antibody is available for testing infants suspected of congenital syphilis. IgG antibody may simply reflect transplacental passage of maternal antibody but IgM indicates active syphilis in the infant.

Examination of the cerebrospinal fluid is necessary to exclude central nervous system infection, which may be entirely asymptomatic.

Treatment

Treatment should be in the hands of an expert in the management of venereal diseases, with an ophthalmologist supervising local ocular therapy. A very broad multidisciplinary approach is necessary for optimum treatment of patients with advanced systemic disease.

Penicillin is the drug of choice. Tetracycline or erythromycin may be substituted for patients allergic to penicillin. Within a few hours of beginning therapy about half the patients experience an acute febrile reaction with headache and myalgia. This, the Herxheimer reaction, settles within 24 hours and is believed to be due to a reaction to toxins released from killed treponemes.

All patients with active eye disease should have a full course of systemic penicillin treatment, as well as local antiinflammatory ocular therapy. Systemic corticosteroids may be indicated to try to minimize inflammatory damage to the retina and choroid.

Anterior uveitis is managed on its merits with local mydriatics and steroids. Secondary glaucoma sometimes develops and must not be neglected.

It has already been noted that the response of interstitial keratitis to the course of specific antisyphilitic therapy is totally unpredictable. It does, however, respond well to local steroid therapy, which may need to be continued for up to two years before all signs of activity disappear.

Prognosis

Treatment with penicillin in the acute phase limits tissue destruction

and prevents progression. Adequate treatment of primary syphilis will thus prevent the appearance of eye disease. However, if ocular disease has already occurred, complete restoration of function cannot be expected because there will be at least some irreversible tissue damage.

In the era before curative treatment was available the general impression was that more than two-thirds of those with primary syphilis progressed no further. Of those who went on to manifest signs of secondary disease more than half recovered and suffered no further sequelae. Probably fewer than 25% of originally infected persons eventually suffered symptoms of cardiovascular or nervous system degeneration, or recurrent inflammatory reactions such as late uveal disease.

PROTOZOAN DISEASES

Toxoplasmosis

Epidemiology

Infection with *Toxoplasma gondii* is worldwide and common, but there is great geographic variation in prevalence. When different populations are examined for the presence of antibodies to the organism, figures as low as 2% positive are found in areas of low disease prevalence, and as high as 70% in areas of high prevalence.

In the United Kingdom about 1200 new cases are reported each year. About two-thirds of these are noted because of ocular lesions, and the remaining one-third because of fever of unknown origin or lymphadenopathy. Thus the annual incidence figure is likely to be a gross underestimate of the true incidence of acute acquired disease.

Immigrants from West Africa and the West Indies have been found to make up almost one-half of the cases presenting with ocular disease in the United Kingdom (Chesterton and Perkins, 1967).

The Organism and Mode of Infection

T. gondii is an obligate intracellular protozoön. All birds and mammals so far investigated can be infected, and in nature infection is widespread. However, the sexual cycle of the organism appears to be confined to the feline species, which excrete oöcysts in their faeces as a result of multiplication of the organism in the gut epithelium.

Modes of infection are not understood with absolute certainty but most transmission is probably from ingestion of meat infected with cysts, or infected faeces.

The excreted oöcysts appear to become infective on exposure to

warmth and moisture. On ingestion, each oöcyst releases many organisms which resemble the merozoites of malaria (sporozoites). These invade and migrate through the tissues beyond the intestine, undergoing asexual multiplication and infecting all tissues, especially muscle and brain. Infected cells are destroyed by the multiplication of organisms within them until they rupture. In non-immune hosts the organisms destroy the macrophages which engulf them. For some reason the macrophage lysosomes fail to fuse with phagosomes, and the contents of the phagosomes do not undergo lysis. In all tissues, especially muscle and central nervous system, there is a tendency towards cyst formation. Cysts may contain thousands of organisms which remain viable for years. In time stimulated T-lymphocytes bring the multiplication of organisms to a halt. Finally, antibody-secreting plasma cells are believed to contribute to cyst formation (Shimada et al., 1974).

Production of Inflammatory Lesions

There is firstly the direct destruction of cells by bursting from the proliferation of organisms within them. Engulfing macrophages are killed by a similar process, and lytic enzymes are released into the surrounding tissues (Yoshizumi, 1977).

It is believed that in recurrence of inflammation (*see below*, Recurrent Inflammation) the cysts rupture and release organisms into the adjacent tissues. Whether the resultant inflammation is caused by direct cellular invasion by the organism (O'Connor, 1970), or by hypersensitivity reaction on the part of the immune host (Wyler et al., 1980), or both is not clear. It has also been suggested that autoimmunity to retinal antigens may play a role in the inflammation (Nussenblatt et al., 1980).

A full discussion of what is known of the immunology of infection with this fascinating organism is given by Krahenbuhl and Remington (1982).

Clinical Features

Acute Acquired Disease

Primary acute infection commonly passes unnoticed, but when symptomatic it produces a febrile illness with headache, myalgia, lymphadenopathy and splenomegaly. Sometimes there is a transient rash. Myocarditis and pneumonia are also described. Serological examination reveals a rising titre of antitoxoplasma antibodies (*see below*, Diagnosis). Acute retinochoroiditis has been seen with acute infection but most eye disease is the result of reactivation of lesions acquired in the fetus by transplacental passage of organisms from the mother suffering from acute infection.

Congenital Disease

The fetus so infected suffers an altogether more severe disease. Abortion may occur, or premature birth. Children born at full term may have recovered or may still suffer from active systemic disease. This takes the form of fever, jaundice with hepatosplenomegaly, skin rashes and sometimes convulsions. Ocular disease may be evident at birth but more commonly the evidence of congenital infection comes to light years later on routine ocular examination in asymptomatic persons. Subsequent radiographs may reveal foci of cerebral calcification. These may produce epilepsy, which can present years after birth. Severely affected patients may be mentally retarded and have micro- or hydrocephaly.

Ocular Disease

Ocular disease is rare in acquired toxoplasmosis but there is no doubt that lesions are seen which are indistinguishable from those of the congenital disease (Saari et al., 1976). In an extensive review Perkins (1973) determined that retinochoroiditis occurred in 1·2% of cases.

The typical ocular lesion of congenital toxoplasmosis is a focal or multifocal retinochoroiditis with necrosis of tissue, and often marked opacification of the overlying vitreous. The active lesion is yellowish white, with ill-defined edges. Surrounding blood vessels show perivascular sheathing. Lesions heal slowly over weeks or months, leaving focal scars with varying degrees of pigmentation. Multiple lesions are often seen and may be found anywhere in the retina. When close to the optic disc the active picture suggests optic papillitis. Sometimes more diffuse retinal involvement occurs.

If lesions do not involve the macula or optic disc, no visual symptoms are produced after healing. Lesions are only discovered later if the child has a careful eye examination, or if recurrence of inflammation occurs and causes symptoms.

RECURRENT INFLAMMATION It is impossible to estimate what proportion of those who have retinal scars from congenital infection suffer recurrence in later life. Nor is it known why recurrence should affect one person and not another. Many who get recurrences continue to do so all their lives.

Most recurrences occur at the edge of preexisting lesions. A fresh fluffy yellowish area of retinochoroiditis is seen beside an old pigmented scar (*Fig.* 78). However, lesions can develop apart from old scars, in retina which was previously macroscopically normal.

There is commonly a mild anterior uveitis early in the course of a recurrence. This is probably a hypersensitivity reaction, since there is no evidence that the organism spreads to the anterior uvea.

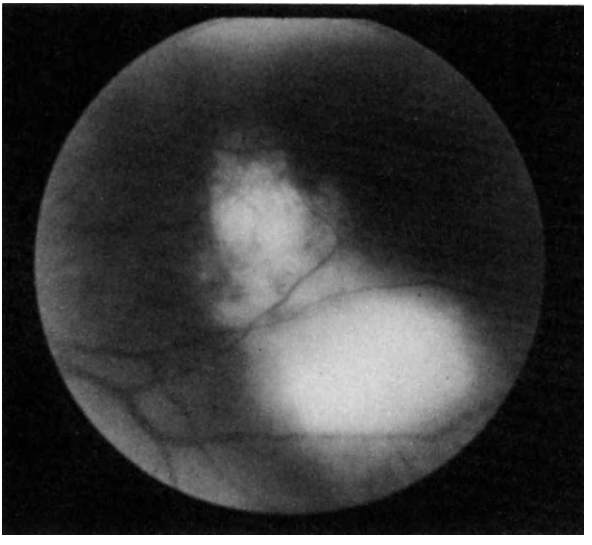


Figure 78 Toxoplasmosis: fresh retinal lesion below an old healed lesion.

If the lesion is near the macula profound visual loss occurs, but when peripheral regions of the retina are involved the patient initially complains of seeing floating spots because of the vitreous reaction. Lesions settle in weeks to months, leaving a typically pigmented extension to the original scar. Patients often complain of floaters for a year or more. Occasionally the inflammation is very severe and results in retinal detachment and permanent vitreous clouding.

DIAGNOSIS The physical characteristics of the ocular disease usually permit a presumptive diagnosis and the initiation of treatment. There are several laboratory tests which can be performed.

Antibodies to toxoplasma arise within a few days of infection and persist for years. The traditional test for these is the *dye test* (Sabin and Feldman, 1948), which uses living toxoplasma organisms. The healthy organism stains with methylene blue, but the combination of specific antibody with complement changes the cell wall. The resulting cellular disruption interferes with uptake of the dye.

In congenital ocular toxoplasmosis serum antibody levels are usually low and positivity of the dye test is significant in any dilution, although usually levels of 1 : 16 or more are regarded as positive.

In acute acquired infection much higher dye test titres are found and a rising titre in the course of the illness strongly supports the diagnosis. A rise in titre is not seen in recurrent congenital eye disease.

It has been mentioned previously that a large proportion of the population has anti-toxoplasma antibodies. The clinical ocular picture is therefore the most important factor in diagnosis, but a completely negative dye test would make one question the diagnosis, even in the presence of typical retinal findings.

The enzyme-linked immunosorbent assay (*ELISA*) is now also widely used. It can detect serum IgM or IgG antibodies. IgM antibodies are only found early in acute acquired infection. They are not found in recurrence of retinal disease. IgG antibody levels rise more slowly in acquired disease. They persist in gradually falling levels for many years.

Treatment

Treatment of acute acquired disease is essentially symptomatic. No regime is available which will eradicate encysted forms.

Each case of ocular disease should be assessed on its own merits. No treatment may be needed for small peripheral lesions which do not threaten the macula and are not producing much vitreous infiltration. When there does appear to be a significant threat to sight a course of an appropriate antibiotic should be given.

Suitable regimes are:

(1) Pyrimethamine 75 to 100 mg loading dose on the first day, followed by 25 to 50 mg thereafter for 4 weeks.

Many ophthalmologists also recommend simultaneous treatment with sulphadiazine 1 g 4 times daily, although the evidence for synergism with pyrimethamine is equivocal.

(2) Clindamycin 300 mg 4 times daily for 2 weeks.

Clinical impressions of the response to clindamycin are favourable and it may be an advance in therapy. Unfortunately the results of comparative trials are not available.

The above doses are for adults, and must be reduced appropriately for children.

Both regimes require careful supervision. Pyrimethamine is a folic acid antagonist and may produce leucopenia and thrombocytopenia. Risks are minimized by giving yeast tablets with the pyrimethamine, and weekly blood counts should be performed. Clindamycin may produce diarrhoea from a colitis due to overgrowth of *Clostridium difficile* in the bowel. Fortunately this responds rapidly to oral therapy with vancomycin, but patients must be warned to stop taking clindamycin if they begin to get any bowel disturbance.

The role of steroids in management is unclear, but some guidelines can be given:

(1) Orbital injection of steroid, or oral therapy are logical adjuncts to antibiotic therapy when the inflammatory reaction threatens the macula, or when there is profound vitreous reaction.

(2) There are good theoretical reasons for *not* using steroids alone.

(3) In practice the continuing use of steroids in a reducing dose for some weeks after the completion of an appropriate course of antibiotics as outlined above has not led to any difficulties.

(4) Steroid therapy should only be continued until the fundus lesion appears quiescent. Vitreous changes will take many months to clear, and it is doubtful that the beneficial effects of steroids in hastening clearing outweigh the risks of prolonged therapy.

(5) In practice it is usually sufficient to begin with a dose of 30 to 40 mg prednisolone daily. Reduction in dose can begin after 2 weeks.

It is important to reassure mothers of affected children that subsequent pregnancies will not be affected. Maternal antibodies from the original infection prevent reinfection. It has been suggesed that persistent maternal uterine infection could account for the occasional case of sibling disease (Stern and Romano, 1978). It is also conceivable that a specific immunological defect in the mother could permit persistent parasitaemia and infection of a subsequent fetus.

HELMINTHIC DISEASES

Onchocerciasis

General

Onchocerciasis is due to infection with a filarial nematode *Onchocerca volvulus*. It is transmitted from person to person by a biting fly, which is its natural host.

It is estimated that at least 40 million people in central America and Africa suffer from the disease. After infection there is an initial period of pruritus. This is followed by the development of a wide variety of skin lesions. The adult form of the worm persists for many years in skin and other superficial structures, including subcutaneous fibrous nodules. The microfilarial form is also found in skin, lymphatics, the eye, and sometimes in blood and urine. The main morbidity is from blindness. Onchocerciasis rivals trachoma as the leading cause of blindness in the world.

Eye Disease

Eye disease is due to the infection itself, and also to treatment. Much if not all of the eye damage follows the death of organisms. In endemic regions it is known as 'river blindness'.

Conjunctivitis and *keratitis* are common. Fluffy white opacities are found around parasites in all depths of the cornea. The cornea may become densely opaque from sclerosing keratitis due to invasion of a fibrovascular pannus between the corneal epithelium and Bowman's membrane (Garner, 1976).

Anterior uveitis is also common and may be associated with distortion of the pupil and spongy atrophy of the iris. Secondary glaucoma is a frequent complication (Anderson and Fuglsang, 1978). Uveitis may be granulomatous or non-granulomatous. The former is believed to result from reaction to parasites resident in the iris, and the latter to be a response to free microfilarial antigen (Garner, 1976).

The posterior segment of the eye shows large scattered areas of *retinal pigment epithelial atrophy* with or without *atrophy of the choriocapillaris*. These are the consequences of chronic choroiditis characterized by an infiltration with lymphocytes, plasma cells and eosinophils. This is also true of inflammatory infiltrates elsewhere in this disease and suggests an allergic reaction. There is great heterogeneity of these lesions (Bird et al., 1976), and on fluorescein angiography there tends to be retinal vascular leakage. However, despite this, Bird and coworkers found that the most common cause of blindness in their series of patients was *optic atrophy* (87·6%) from optic neuritis.

During treatment, changes similar to those described above have all been observed (Bird et al., 1979; Taylor and Greene, 1981), especially optic nerve disease.

Treatment

Treatment usually produces some degree of hypersensitivity reaction. This may be life-threatening when there is a heavy infection and is presumed to be due to release to the body's primed immune system of large amounts of antigens from killed organisms. There is an occlusive microvasculitis, which is also found locally when diethylcarbamazine (DEC) is used topically in the eye (Jones et al., 1978). This hypersensitivity reaction bears the name of Mazzotti, who suggested that it could be used as a diagnostic tool if evoked in a mild form by a small dose of DEC (Mazzotti, 1948).

Drugs in use are diethylcarbamazine (DEC) which kills the microfilariae but not the adult worms, and suramin which kills the adult worms only. Ideally these drugs could be used together but suramin therapy has itself an appreciable mortality, and requires expert supervision, ideally in hospital. Heavily infected patients can, however, be cleared of microfilariae by combined therapy without unacceptable side effects (Anderson and Fuglsang, 1978). Ivermectin, which only kills microfilariae, may prove a safer treatment (Aziz et al., 1982), but since much of the pathology seems to be dependent upon the death of

the organism it is difficult to envisage a form of treatment free of all risk of producing adverse reactions.

Once an ocular lesion has appeared it is likely to advance, despite a course of treatment with suramin. However, suramin does seem to inhibit the appearance of new lesions and the progression of existing ones (Budden, 1976).

The results of surgery for cataract are reasonable, but glaucoma is difficult to manage (Maertens, 1981).

The problems of treatment and eradication are enormous. Much effort is currently being expended on the search for safer therapy. Even when therapy is combined with vector control in small areas the results may be disappointing (Rolland et al., 1980).

Toxocariasis

Visceral Larva Migrans

Ingestion by young children of soil contaminated with ova of the ascarids *Toxocara canis* and *Toxocara cati* may result in the syndrome of visceral larva migrans. The adult worms live in the gut of infected puppies and cats and ova are shed in the faeces. They incubate in the soil for several weeks before becoming infective. They remain infective for years. Larvae migrate from the bowel and cause eosinophilic granulomas in all parts of the body, especially the lungs, liver and brain. In man the parasite cannot mature fully and does not replicate and shed ova.

The child has a cough, fever, lymphadenopathy and often central nervous system symptoms as well. There is marked eosinophilic leucocytosis and hypergammaglobulinaemia. A specific ELISA test is now available for the detection of antibodies to *Toxocara* in the body fluids (Cypess et al., 1977). Skin testing has been performed for many years using *T. canis* as the antigen (Wiseman and Woodruff, 1968). Biopsy is rarely indicated. Symptoms usually persist for months, but much infection is probably asymptomatic. It has been estimated that up to 2% of people in southern England are infected (*Ibid*).

Treatment is usually given with thiabendazole or levamisole, but is not specific. Sometimes corticosteroids are needed if respiratory symptoms are severe. They may also be given at the same time as the antihelminthic agent, to protect against severe hypersensitivity reactions which might occur as a result of the death of many parasites.

Ocular Disease

Granulomas may occur in the eye in the syndrome of visceral larva

migrans but in older children and young adults granulomas may occur in the retina in the absence of eosinophilia or signs of more widespread disease. The reason for this is unknown, but it may be that older persons are likely to be exposed to a much lower dose of parasite because of their more hygienic habits (Glickman and Schantz, 1981). The ocular disease takes one of 3 forms (O'Connor, 1976):

(1) A solitary retinal granuloma occurs, usually at the posterior pole of the eye, causing severe and permanent loss of central vision. The lesion is elevated, several millimetres across, and often haemorrhagic (*Fig.* 79.)

(2) Migration of larvae through the vitreous causes severe intraocular inflammation and the formation of glial strands in the vitreous.

(3) Sometimes there is a chronic inflammatory reaction localized to a segment of the peripheral retina and ciliary body, giving rise to a dense white lesion and glial bands radiating from it into the vitreous.

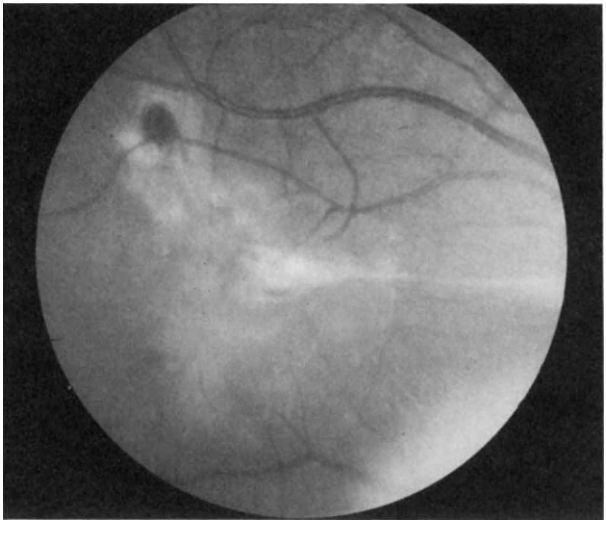


Figure 79 Toxocariasis: healed lesion at posterior pole.

All forms may result in detachment of the retina.

Molk (1983) has summarized the quite wide variety of clinical appearance that has been reported.

It is not surprising that such disease is easily mistaken in young children for retinoblastoma. The parasite has been found in eyes

enucleated for this reason (Duguid, 1961). In doubtful cases it is now possible to perform ELISA for Toxocara antibodies in vitreous aspirate. High levels favour the diagnosis.

The appropriate treatment for eye disease is debatable. Topical steroids and orbital injections of depot steroids may suppress the inflammatory reaction in the eye and minimize tissue damage. The role of antihelminthic therapy is questionable. It is widely believed that the worst inflammatory damage occurs when the parasite dies. If this is true, it is unreasonable to expect systemic therapy to do more than kill living parasites. It is conceivable, therefore, that the killing of a parasite while it migrated through the retina could do more harm than good to the eye. Whatever treatment is given, vision remains poor in cases with macular lesions, but vitrectomy may improve the sight in peripheral cases.

VIRAL DISEASES

Herpesvirus

A Herpes simplex virus, types 1 and 2 (HSV)
B Varicella/Zoster virus (VZV)
C Cytomegalovirus (CMV)
D Epstein–Barr virus (EBV)

A Herpes Simplex

Herpes simplex characteristically produces recurrent, localized disease of the skin and mucosal surfaces. The acute lesion is a painful vesicular rash which ulcerates, crusts over and heals during a period of 7–14 days. The face and lips are most commonly affected, although primary infection is also common in the mouth. Vesicles rarely cover more than a few cm^2 of surface. These lesions are usually due to HSV type 1 infection, and most people have antibodies to HSV1 by the end of childhood. Infection of the genitals, usually with HSV type 2, is becoming increasingly prevalent.

Latent infection is set up in sensory ganglia related to the area of initial infection, by spread along the sensory nerves (Bastian et al., 1972). In a high proportion of people reactivation occurs and lesions reappear in a similar site to the original infection. The virus has spread back to the surface from the ganglion, and can be isolated from the lesions, which are highly infectious. Many stimuli to reactivation are recognized, especially sunlight and intercurrent infection – hence the popular name 'cold sores'.

Much of what is known about herpes simplex infection has been

learned from animal experimentation. Virus cannot be detected in the ganglia during latency, but it can be revealed by *in vitro* culture techniques (Stevens and Cook, 1971). The biology of latency and reactivation is still largely unknown (Openshaw et al., 1982).

Acute infection of the skin or mucosal surfaces may affect the eye in several ways (*see below*). Spread from superficial lesions can result in severe disseminated disease, even in otherwise healthy people. It causes a very serious form of encephalitis in adults. Antecedent skin or mucosal lesions may not have been evident in all proven cases. At greater risk than adults are neonates who acquire infection during delivery, and immunocompromised patients. It is in disseminated infection that severe uveal and retinal disease may occur.

Ocular Disease

SUPERFICIAL LESIONS The vesicular eruption may occur on the eyelids. Conjunctivitis, episcleritis and scleritis may be seen. The most common superficial manifestation is the typical branching epithelial ulceration of the cornea (dendritic keratitis). This may heal, but in a proportion of cases a stromal keratitis develops, representing a delayed immunological response. As with skin lesions the keratitis may recur. A degree of anterior uveitis is common, especially with stromal keratitis.

INTRAOCULAR LESIONS Intraocular inflammation may occur in the following circumstances:

Local infection

(1) Uveitis secondary to keratitis
(2) Anterior uveitis in the absence of keratitis

Generalized infection

(3) Choroidoretinitis in newborn infants
(4) Choroidoretinitis in immunocompromised patients
(5) Choroidoretinitis in healthy adults, with or without clinical encephalitis.
(6) (possible) Acute retinal necrosis (*see* Herpes zoster).

(1) and *(2) Anterior uveitis* Anterior uveitis is common in herpetic keratitis, but it probably can occur in the absence of corneal disease. Virus has been isolated from the aqueous in such cases (Cavara, 1952). The uveitis accompanying acute herpetic epithelial lesions of the cornea is usually mild, which is fortunate because steroids cannot be used until the epithelial defect has healed. When uveitis of more than a transient nature occurs it tends to be prolonged in its course.

(3) Choroidoretinitis in the newborn In the newborn most infections are due to HSV type 2 (Nahmias et al., 1976) and some sort of eye involvement occurs in almost 20% of cases (*Ibid.*).

Neonatal infection need not become generalized, and much of the ocular involvement forms part of the localized superficial infection of the face. Ulcerative lesions occur on the lids, and conjunctivitis, dendritic epithelial keratitis and stromal keratitis may occur (Nahmias and Hagler, 1972). Ophthalmic manifestations are in fact less common in systemic than in localized infection (*Ibid.*) but it is in disseminated disease that one expects to meet the choroidoretinitis. In the latter there are large patches of yellow-white exudate in the retina, a marked vitritis and retinal perivasculitis in the acute phase (*Ibid.*).

In the rabbit model a high proportion of newborn animals artificially infected in the skin by HSV2 develop disseminated disease and 40% have eye lesions, mostly in the retina and choroid (Brick et al., 1981).

(4) Choroidoretinitis in immunosuppressed patients Choroidoretinitis, with sheathing of retinal vessels and sometimes areas of retinal necrosis, has been described in immunosuppressed patients suffering from disseminated herpetic infection.

(5) Choroidoretinitis in healthy adults A patient who died of encephalitis has been described, from whose brain tissue HSV1 was cultured. Typical viral inclusions were found in the brain, optic nerves, retina and choroid. He had bilateral optic papillitis, central retinal vein obstruction and exudative retinal detachment (Minckler et al., 1976). Two other cases are described of retinal vasculitis, oedema and haemorrhage (one with areas of arteriolar occlusion) occurring several weeks after the onset of encephalomyelitis (Savir et al., 1980). In these cases the diagnosis was made from rising titres of HSV antibodies in the blood and cerebrospinal fluid. The delay in the development of the eye disease has led to the suggestion that it might be immunologically mediated, rather than a direct effect of the virus.

Ocular changes more akin to those described in neonates have been reported from cases not associated with encephalitis. One case of bilateral panuveitis had choroidal haemorrhages, diffuse choroidal and retinal exudates and narrowed arterioles. HSV was isolated from the aqueous (Pavan-Langston and Brockhurst, 1969). More recently a patient was reported in whom the diagnosis was made by culture from a choroidoretinal biopsy specimen, and who then responded to antiviral therapy (Grutzmacher et al., 1983). In both these cases there was a long delay between attacks of disease in each eye, leading to speculation as to whether the virus might travel from one eye to the other, and how it could do this.

(6) Acute retinal necrosis (*see* Herpes zoster) Evidence is accumulating that this condition is due to a herpes virus, possibly H. zoster.

B Varicella/Zoster

The varicella/zoster virus (VZV) produces two, and possibly three types of eye disease:

(1) Varicella (chickenpox)
(2) Herpes zoster (shingles)
(3) (possible) Acute retinal necrosis

1 Varicella

Varicella is a common febrile illness in young children. It is characterized by the appearance of a fine maculopapular rash which evolves through a stage of vesiculation. The vesicles collapse and small scabs are formed. The lesions occur mainly on the trunk, appear two to three weeks after exposure to the virus, and evolve over several days. Fresh crops of lesions appear for about four days. There are no scars or other sequelae. Pneumonia of varying severity may occur, especially when the infection is acquired by an adult. X-rays show nodular infiltration of the lungs. A rare encephalomyelitis similar to that of measles may occur in children.

Despite the frequency of the disease, ocular findings are rare. Retinal pigmentation and uveitis have been reported (Strachman, 1955).

2 Herpes Zoster

In a proportion of patients who recover from varicella the virus appears to persist in a latent form in the sensory ganglia of cranial and spinal nerves. Motor nerve involvement is rare but may cause paralysis. There is evidence that the manifestations of *Herpes zoster* are due to reactivation of the virus and reinvasion of the skin, but in contrast to *Herpes simplex* infection virological confirmation of this latency is still lacking.

Why this should only occur in some people is not understood, but they are frequently elderly or suffering from debilitating disease at the time. It is particularly common in patients with lymphomas, and in these it may recur.

The disease begins with a few days of pain or discomfort in the skin corresponding to the distribution of one sensory nerve trunk. It is almost always unilateral. The affected skin then becomes red and papules appear. These evolve through stages of vesiculation and pustulation. Finally, thick scabs form, the whole process taking about two weeks. When the scabs eventually clear the skin is atrophic. The vesicle fluid contains the virus and susceptible children can contract varicella from it.

There is usually a degree of systemic disturbance. Pain can be very severe and may persist for months after the skin has healed. Fever is common. Signs of meningeal irritation are often seen when cranial nerves are affected.

OCULAR DISEASE When herpes zoster affects the ophthalmic division of the trigeminal nerve the eye is involved indirectly by lid swelling and later by corneal exposure if the upper eyelid becomes retracted by tough crusting lesions. When the geniculate ganglion of the facial nerve is involved Bell's palsy may occur and the cornea may then be in danger from inadequate lid closure.

Direct corneal disease occurs in the form of epithelial or stromal keratitis. Sometimes dendritic ulcers occur in the epithelium and resemble those of herpes simplex. Corneal sensation is reduced.

Episcleritis and scleritis are very common.

Anterior uveitis is also a common occurrence. The onset may be sudden and painful and associated with secondary glaucoma, but it usually takes a chronic and less dramatic form. The underlying pathology is a vasculitis. In the iris a segmental atrophy of the pigment epithelium is produced by occlusion of sections of the radially-arranged iris vasculature (Marsh et al., 1974). Atrophy may be more diffuse and may involve the ciliary body (Naumann et al., 1968). Retinal vasculitis has also been described (*Ibid.*), giving rise in some cases to thrombosis of retinal veins (Hesse, 1977) and also arteries (Brown and Mendis, 1973).

3 Acute Retinal Necrosis

The syndrome of acute retinal necrosis was first described in Japan (Urayama et al., 1971). In the Occident the condition began to appear in the early 1970s (Young and Bird, 1978). In the past few years evidence has been obtained from electron microscopic studies of enucleated eyes or choroidoretinal biopsy specimens that a herpes virus is responsible. The condition appears fairly suddenly in one eye and progresses to dramatic visual loss within a few days. Large patches of necrosis appear in the mid and far periphery of the retina, extend and become confluent. There is clear demarcation between affected and unaffected retina. The yellow, thickened retina is then shed to varying degrees into the vitreous, which becomes very cloudy. Necrosis progresses posteriorly but may be arrested before much of the posterior pole of the eye is involved. The retinal vessels are very narrow, and vanish in necrotic areas. When the vitreous clears the posterior retina may still be in place, but the peripheral retina has usually disintegrated completely. Eventual detachment of the remaining intact retina is almost inevitable. At this stage it may be possible to avoid this by

photocoagulation around the edges of the attached retina.

About one-third of cases are bilateral, the second eye becoming involved within a few weeks.

Inclusions typical of herpes virus have been found in the retina (Culbertson et al., 1982). Characterization is incomplete because the virus has yet to be cultured from these specimens, and so the aetiology still remains in doubt. There are some similarities to the acute stages of choroidoretinitis associated with HSV infection (Watanabe et al., 1983). When haemorrhages occur in the necrotic areas these may resemble cytomegalovirus retinitis (*see below*). Of special significance may be the case of unilateral necrotizing retinopathy reported in a patient who died of herpes zoster ophthalmicus and pneumonia. Intranuclear inclusions were found in the sensory retina (Schwartz et al., 1976). In so far as it is relatively easy to grow, the failure to isolate HSV from any of these lesions weighs against it as the aetiological agent.

C Cytomegalovirus

Cytomegalovirus (CMV) can be cultured from the saliva of up to 25% of normal people. In one group of adults complement-fixing antibodies were found in 80% (Rowe et al., 1956). Infection was almost always subclinical until renal transplantation became common. Occasional cases of pneumonia have been reported in infants. Protracted fever and liver disease accompanied by blood changes as in infectious mononucleosis may occur (Klemola et al., 1969), except that the Paul–Bunnell test is negative. Intrauterine infection of the fetus has a serious outcome with a high incidence of mental retardation.

Ocular disease was extremely rare except in immunocompromised patients, such as those with leukaemia and those taking steroid or cytotoxic therapy. In the early 1970s reports began to appear of cytomegalovirus retinitis in renal transplant patients (DeVenecia et al., 1971; Aaberg et al., 1972). Eye disease is often the first manifestation of the viral infection (Murray et al., 1977). There are white, granular areas of retinal necrosis, with irregular arteriolar sheathing and phlebitis. Small patches become confluent over a period of several weeks. Retinal haemorrhages occurring in the necrotic retina give the appearance described as tomato ketchup stirred into scrambled eggs. The posterior pole is often spared and central vision preserved until death. The centre of lesions tend to clear and leave grey-brown areas of avascularity and atrophy of the retina and retinal pigment epithelium. The edge of the lesion gradually advances. A fluffy peripheral zone indicates necrosis and vessel occlusion. The virus spreads from cell to cell, and intranuclear and intracytoplasmic inclusions are found in cells of the retina, retinal pigment epithelium and endothelium of the retinal vessels. There is little vitreous or anterior segment reaction.

At present most cases occur in patients with the acquired immune deficiency syndrome (AIDS) (Holland et al., 1982; Palestine et al., 1984).

Acquired Immune Deficiency Syndrome (AIDS)

This condition is a result of infection with the retrovirus HTLV III (human T-cell leukaemia virus III) (Barré-Sinoussi et al., 1983; Gallo et al., 1984). The virus (now renamed HIV, Human Immunodeficiency Virus) gains access to the body through breaches in the epithelial barriers. Intercourse and intravenous drug abuse are the main modes of transmission. Most cases at present occur in homosexual men. Several years may elapse between the time of infection and the manifestation of disease. The virus can be found in most body fluids but it is not known if it is infectious in any but semen and blood.

Presentation is usually with pneumonia or with fever, lymphadenopathy, anorexia and weight loss. Patients are found to be suffering from opportunistic infections such as cytomegalovirus, herpesvirus, *Pneumocystis carinii* and Candida. The disease is essentially untreatable but these infections can frequently be controlled for a time. They eventually recur and are the usual cause of death.

The marked immunosuppression appears to be the result of a severe defect in the number and function of T-lymphocytes, mainly helper T-cells.

Kaposi's sarcoma is common in AIDS sufferers and may affect the conjunctiva. (*Fig.* 80.)

Patients frequently have cottonwool spots in the retina which tend to be evanescent (*see Fig.* 38). Their cause is unknown. They do not appear to be necessarily a precursor of cytomegalovirus retinitis. With this possible exception all the ocular inflammatory disease seen in AIDS is due to opportunistic infection, usually with cytomegalovirus, but sometimes with cryptococcus (Newman et al., 1983) or toxoplasma (Schuman and Friedman, 1983). (*Fig.* 81.)

D Epstein–Barr Virus

The condition caused by the Epstein–Barr virus (EBV) in which eye symptoms sometimes occur is *infectious mononucleosis* (glandular fever).

This is a benign and common infection of adolescents and young adults. It comprises fever, lymphadenopathy and splenomegaly, pharyngitis, and the finding of a lymphocytosis in the blood, with a high proportion of atypical cells. Heterophile antibodies are found in the serum almost from the onset of the illness, rising to a peak level at four to six weeks and disappearing after several months. They are the

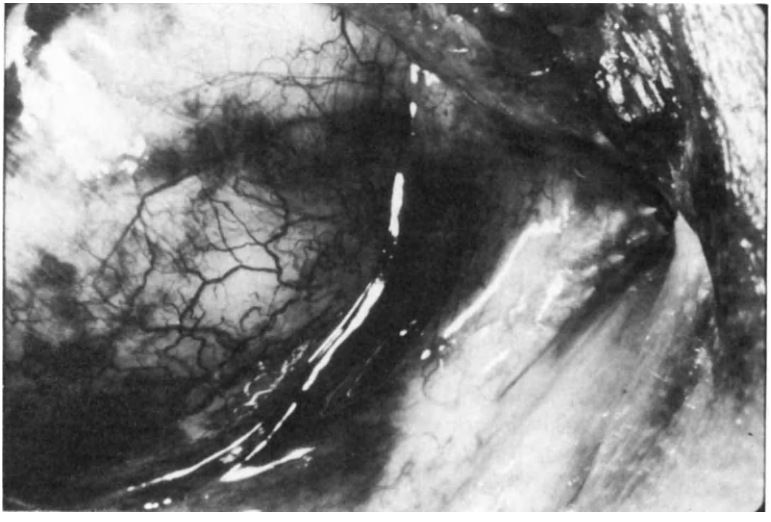


Figure 80 Kaposi's sarcoma of conjuctiva.
(Dr Alan Palestine.)

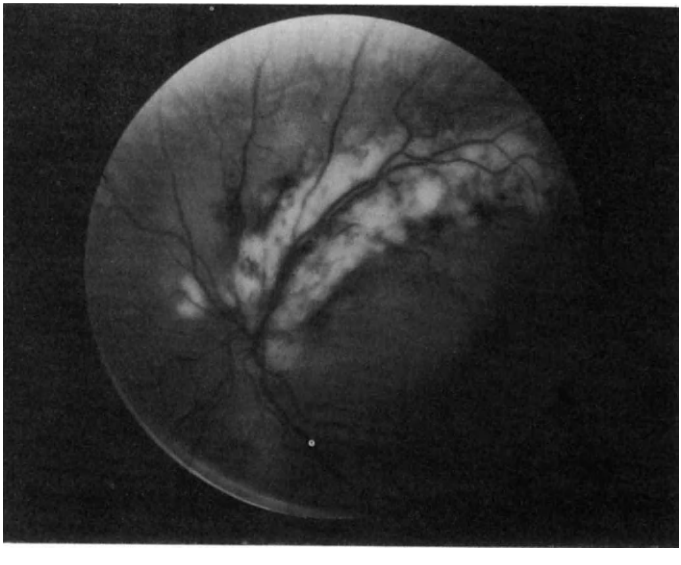


Figure 81 Cytomegalovirus retinitis.
(Dr Alan Palestine.)

basis for the Paul–Bunnell test. Antibodies to EBV rise in a similar way. They are found in 95% of adults and persist for many years because the virus produces a persistent infection of B-lymphocytes.

The characteristic atypical lymphocytes are large cells with oval, indented or frankly horseshoe-shaped nuclei. They are $T8^+$ (suppressor/cytotoxic) T-lymphocytes. Transient granulocytopenia, anaemia or thrombocytopenia are common but not usually serious. There may be a transient rash which is made worse if the patient is treated with ampicillin in the mistaken belief that he is suffering from a bacterial infection. Asymptomatic hepatitis is very common in this infection. Although the acute manifestations are resolved within about three weeks, fluctuating lassitude and a general feeling of ill-health often persist for many months. The virus produces the effect of mild immunosuppression and patients are unduly susceptible to viral and bacterial infections for some time after apparent recovery. Transmission is believed to be by close oropharyngeal contact.

Many neurological disturbances have been reported and one group of ocular manifestations is due to these. This group includes nystagmus, disturbances of conjugate deviation of the eyes, visual field defects, extraocular muscle palsies with diplopia, papilloedema and optic neuritis (Tanner, 1954). The other group encompasses the local effects of swelling of the lacrimal glands, eyelids and orbital tissues (which are common) and episcleritis, uveitis, retinal oedema and retinal haemorrhages (which are rare) (Thygeson et al., 1957).

Rubella

The ocular changes in rubella are seen in the congenital form of the disease due to intrauterine infection. The full-blown syndrome consists of congenital heart disease, eye lesions and deafness, microcephaly and mental retardation. It occurs when infection is in the first trimester of pregnancy.

Eye lesions include microphthalmia, cataracts and a retinopathy in which the changes are confined to the retinal pigment epithelium. There are focal areas of increased and decreased pigmentation together with atrophy, giving the fundus a mottled appearance, especially at the macula (Krill, 1972). In a review of 50 patients born after an epidemic in 1940–41 in Sydney it was reported that 19 had retinopathy which did not in itself seriously affect vision and appeared not to be progressive. Two cases had unilateral choroiditis (Hertzberg, 1968). Glaucoma may develop in eyes with cataracts and microphthalmos.

The virus has been isolated from cataractous lenses removed years after birth (Menser et al., 1967).

Acute retinal pigment epitheliitis with bullous neuroepithelial detachments has been described in acquired adult rubella (Hayashi et al., 1982).

A picture similar to rubella retinopathy has occasionally been described in typhoid, diphtheria, scarlet fever and typhus.

Rubeola

The virus of rubeola is a paramyxovirus. It produces the clinical picture of measles, and rarely, after a period of latency, that of subacute sclerosing panencephalitis.

Measles

Measles is a common and benign febrile illness of childhood. When the disease occurs in adults it tends to be more serious. The virus is spread in nasopharyngeal secretions to the conjunctiva and respiratory tract. In susceptible individuals it produces a high fever, conjunctivitis and upper respiratory tract symptoms about 10 days after exposure. Small red lesions with pale centres (Koplik's spots) then appear on the oral mucosa, and then a fine maculopapular rash appears on the face and spreads down the trunk to the limbs. This usually clears within a further week, and the illness is over in 2 weeks. Patients are infectious from about 4 days before the rash appears to about 5 days after. Immunity after an attack is lifelong. Complications, although rare, may be serious. Sometimes an interstitial pneumonia occurs, characterized by giant cell infiltration of the lungs. These multinucleated giant cells are found in the respiratory epithelium and secretions and in the lymphoid tissues. However, a more common type of pneumonia than this is that due to secondary bacterial infection. Encephalomyelitis occurs in 0·1% of cases, but many more patients will show electroencephalographic abnormalities without signs of neurological disease.

The conjuntivitis is occasionally severe and may be associated with keratitis which heals with some opacification of the cornea. Neuroretinitis is described in the absence of other signs of encephalitis (Bedrossian, 1955). In one patient the course of the retinopathy was observed over 17 years (Scheie and Morse, 1972). The early phase was marked by retinal oedema and narrowing of retinal vessels. After apparent recovery the picture of a secondary retinal pigmentary degeneration developed, with optic atrophy and 'bone corpuscle' pigmentation in the retinal midperiphery. As with the encephalitis, it has been suggested that the retinitis is not directly due to the virus but to an allergic vasculitis. A similar type of retinitis has been reported in variola, varicella, mumps, vaccinia, poliomyelitis and herpes simplex infection.

There is no specific treatment for measles. Antibiotics are given for

associated bacterial infection. Live vaccine provides effective protection.

Subacute Sclerosing Panencephalitis (SSPE)

This is a late and rare complication which occurs years after apparent complete recovery from measles. It affects children and adolescents and begins with intellectual and personality deterioration, followed by ataxia and myoclonic jerking. The latter may be seen to be in time with characteristic slow wave complexes on the electroencephalogram. Finally a decerebrate state occurs and the patient dies from infection. The whole illness lasts about one year. The first description of the disease was made by Dawson in 1933, and he suspected that it was caused by a virus (Dawson, 1933). It was not until 1967 that particles like a myxovirus were demonstrated in the brain of one patient who also had a high titre of antimeasles antibody in his serum (Dayan et al., 1967). Measles virus was first grown from a brain biopsy in 1969 (Chen et al, 1969).

The cerebral vessels show perivascular round cell infiltration and there are intranuclear and intracytoplasmic inclusions of myxovirus nucleocapsids in neurones and glial cells. They have been demonstrated in affected retina (Landers and Klintworth, 1971; Font et al., 1973). Identical inclusions are found in brain, optic nerve and retina.

Unilateral choroidoretinitis has been reported (Dubois et al., 1949). Choroiditis affecting the macular area was reported in two children. In one of these it appeared before the onset of neurological symptoms (Otradovec, 1963). Most reports refer to macular scarring from retinal necrosis (Hiatt et al., 1971) but a more widespread disturbance of the retinal pigment epithelium may occur (Robb and Watters, 1970; Morgan et al., 1976).

Treatment is of no avail.

Miscellaneous Virus Infections

Subacute iridocyclitis has been reported in the convalescent phase of influenza (Thygeson et al., 1957).

Rift Valley fever is due to an arthropod-borne virus and is probably transmitted by mosquito bites. Sporadic cases of retinitis have been reported (Deutman and Klomp, 1981) and a number of cases were observed in the 1977 epidemic in Egypt (Siam et al., 1980). These patients had retinal vasculitis with patchy retinal haemorrhages and oedema in the macular or paramacular areas. Vascular occlusions were also seen in the retina. Half the patients had severe permanent visual loss.

Rare cases of retinopathy have been reported in poliomyelitis, smallpox, vaccinia and mumps.

Treatment of Virus Diseases

Local Treatment

Herpetic Keratitis

Until the advent of idoxuridine (IDU) it was customary to remove the affected corneal epithelium by débridement or careful chemical coagulation with alcohol or carbolic acid. The spread of the lesion was arrested and healthy epithelium rapidly proliferated from the edge of the ulcer to cover the defect. Because of the inconvenience the tendency has been away from débridement but it is probable that optimum therapy is a combination of débridement and topical antiviral agents (Wilhelmus et al., 1981).

Idoxuridine (IDU) is a halogenated pyrimidine nucleoside analogue (5 iodo-2′ deoxyuridine). When instilled frequently into the eye it hastens epithelial healing (Burns, 1963; Patterson and Jones, 1967). It must be used hourly as 0·1% drops, or 4-hourly as 0·5% ointment. Unfortunately it tends to cause a punctate epitheliopathy after a week of use, and alternative therapy may be needed for protracted cases. Sometimes reaction to the drug leads to frank ulceration of the cornea and conjunctival epithelial hypertrophy. This leads to a very confusing clinical picture when the drug is continued in the mistaken belief that HSV is causing these changes.

Trifluorothymidine (F3T) also leads to accelerated epithelial healing when applied as 1% drops every 2 hours for 7–10 days (Wellings et al., 1972; Laibson et al., 1977). Punctate epithelial keratopathy can also occur with this drug.

Vidarabine (ARA-A) (9-beta-D-arabinofuranosyladenine) as 3% ointment is effective when used 4-hourly. It seems less toxic than IDU (Pavan-Langston and Dohlman, 1972).

Acyclovir [9-(2-hydroxyethoxymethyl)guanine] as 5% ointment may be the treatment of choice at the moment (McCulley et al., 1982). Although it is not more effective in promoting healing than IDU, it is less toxic to the eye.

In the absence of adverse reactions drug therapy should be continued for up to seven days after epithelial healing.

When stromal keratitis occurs local steroids are used in conjunction with antiviral drugs once the epithelial defect has healed. Virus cannot normally be cultured from the corneal stroma and the stromal reaction appears to be essentially an immunological one. Unlike the often disastrous effect on epithelial lesions due to enhancement of viral replication, steroids are usually beneficial for stromal and endothelial

lesions. After the epithelium has healed steroid drops can be introduced in weak concentration (e.g. prednisolone drops 0·1%) once or twice a day, and the frequency or concentration increased so long as adverse reactions are not encountered. It is essential to continue treatment with an effective antiviral agent during the period following introduction of steroids. This has been an important stimulus to the search for antiviral agents which could be used topically for several weeks without producing severe toxic reactions.

Herpes Zoster Ophthalmicus

Ocular lesions are treated with local steroids and mydriatics. Unlike HSV, epithelial lesions are not aggravated by steroids. The uveitis may take weeks to resolve and inflammation may rebound when steroids are withdrawn. Topical acyclovir may be a useful alternative to steroids (McGill et al., 1981).

The skin lesions resolve more quickly if treated with idoxuridine in dimethylsulphoxide (Juel-Jensen et al., 1970), especially if applied before the vesicular stage of the rash. The pain of the active disease may be very severe and resistant to treatment. Long-term pain relief may be needed even after healing.

Systemic Treatment (*see* Dolin, 1985)

Idoxuridine (IDU) is too toxic for systemic use.

Vidarabine (ARA-A) (9-beta-D-arabinofuranosyladenine) has been shown to have beneficial effects in immunosuppressed patients with herpes zoster and varicella and also in herpes simplex encephalitis. It reduces mortality in the newborn but many survivors still have major central nervous system damage. Early therapy is critical. Vidarabine is poorly water-soluble. It is given by intravenous infusion over 12 hours in a dose of 10–15 mg/kg/day for 5 days. It has not been effective in CMV retinitis (Pollard et al., 1980). Severe gastrointestinal, bone marrow and neurological toxicity may occur.

Acyclovir [9-(2-hydroxyethoxymethyl)guanine] is active against HSV and VZV. It is much more water-soluble than vidarabine and is usually given by intravenous infusion. It has been given orally in a dose of 200 mg/day for 5 to 10 days in the treatment of genital herpes, with results comparable to the intravenous route. Only 20% is absorbed from the gut. Topical therapy also accelerates healing of genital lesions. CMV and EBV are resistant to acyclovir.

DHPG [9-(1,3-dihydroxy-2-propoxymethyl)guanine] is an analogue of acyclovir which is currently under trial in CMV retinitis. Promising reports are now appearing of results in patients with AIDS (Bach et al., 1985). It is effective in experimental HSV keratitis (Trousdale et al.,

1984; Smith et al., 1984) and appears to be more active than any other antiviral agent against CMV and EBV.

Resolution of cytomegalovirus retinitis has also been achieved with a similar drug, 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine (Felsenstein et al., 1985).

None of these drugs has been shown to have any effect on the establishment of latency.

Chapter 7 References

Introduction

Hall J. M. and Pribnow J. F. (1974) Specificity of antibody formation after intravitreal immunization with bovine gamma globulin and ovalbumin. II. Non-specific enhancement of the secondary response. *Cell. Immunol.* **11**, 64–73.

Shimada K. and Silverstein A. M. (1975) Induction of booster antibody formation without specific antigenic drive. *Cell. Immunol.* **18**, 484–488.

Bacterial: Tuberculosis

Agrawal P. K., Nath J. and Jain B. S. (1977) Orbital involvement in tuberculosis. *Indian J. Ophthalmol.* **25**, 12–16.

Archer D. and Bird A. (1967) Primary tuberculosis of the conjunctiva. *Br. J. Ophthalmol.* **51**, 679–684.

Bakholdina L. P., Tuganova V. E. and Laurenova V. N. (1983) The role of intrathoracic lymphatic tuberculosis in the pathogenesis of eye tuberculosis. *Vestn. Oftalmol.*, 53–55 (1983 (3)).

Community Tuberculosis Control Services (1985) Annual Report for 1983. Department of Health and Rehabilitative Services, State of Florida, USA.

Donahue H. C. (1967) Ophthalmologic experience in a tuberculosis sanatorium. *Am. J. Ophthalmol.* **64**, 742–748.

Elliot A. J. (1975) 30-year observation of patients with Eales's disease. *Am. J. Ophthalmol.* **80**, 404–408.

Heydenreich A. (1978) Die Augentuberkulose. *Z. Gesamte Inn. Med.* **33**, 735–738.

Koppert H. C. and Van Rij G. (1982) The phlycten, a come-back? *Doc. Ophthalmol.* **52**, 339–345.

Lamba P. A. and Srinivasan R. (1983) Conjunctival tuberculosis of endogenous origin associated with miliary tuberculosis. *Indian J. Ophthalmol.* **31**, 89–92.

Liesegang T. J. and Cameron J. D. (1980) Mycobacterium bovis infection of the conjunctiva. *Arch. Ophthalmol.* **98**: 1764–1766.

National Survey of Tuberculosis Notifications in England and Wales, 1978–9 (1980) *Br. Med. J.* **281**, 895–898.

Oakhill A., Shah K. T., Thompson A. G., Stokes M. J. and Mann J. R. (1982) Orbital tuberculosis in childhood. *Br. J. Ophthalmol.* **66**, 396–397.

Office of Population Censuses and Surveys (1985) Communicable Disease Statistics, 1973–1983. Vol. 10. Series MB2. London, HMSO.

Schlaegel T. F. and O'Connor G. R. (1981) Tuberculosis and syphilis. *Arch. Ophthalmol.* **99**, 2206–2207.

Segal N., Codrea A., Takacs M. and Toth E. (1980) Orbital pseudotumour, chronic tuberculous myositis and dacryoadenitis. *Rev. Chir. (Oftalmol.)* **24**, 69–72.

Sen D. K. (1977) Endogenous uveitis in Indian children: analysis of 94 cases. *J. Pediatr. Ophthalmol.* **14**, 25–32.

Sen D. K. (1980) Tuberculosis of the orbit and lacrimal gland: a clinical study of 14 cases. *J. Pediatr. Ophthalmol.* **17**, 232–238.
Sheridan P. H., Edman J. B. and Starr, S. E. (1981) Tuberculosis presenting as an orbital mass. *Pediatrics* **67**, 874–875.
Waldman R. H. (1982) Tuberculosis and the atypical mycobacteria. *Otolaryngol. Clin. North Am.* **15 (3)**, 581–596.

Bacterial: Leprosy

ffytche T. J. (1981a) Iritis in leprosy. *Trans. Ophthalmol. Soc. U.K.* **101**, 325–327.
ffytche T. J. (1981b) Role of iris changes as a cause of blindness in lepromatous leprosy. *Br. J. Ophthalmol.* **65**, 231–239.
Harrell J. D. (1977) Ocular leprosy in the Canal Zone. *Int. J. Leprosy* **45**, 56–60.
Hobbs H. E., Harman D. J., Rees R. J. W. and McDougall A. C. (1978) Ocular histopathology in animals experimentally infected with Mycobacterium leprae and Mycobacterium lepraemurium. *Br. J. Ophthalmol.* **62**, 516–524.
Lenzini L., Rottoli P. and Rottoli L. (1977) The spectrum of human tuberculosis. *Clin. Exp. Immunol.* **27**, 230–237.
Michelson J. B., Roth A. M. and Waring G. O. (1979) Lepromatous iridocyclitis diagnosed by anterior chamber paracentesis. *Am. J. Ophthalmol.* **88**, 674–679.
Spaide R., Nattis R., Lipka A. and D'Amico R. (1985) Ocular findings in leprosy in the United States. *Am. J. Ophthalmol.* **100**, 411–416.
Ticho U. and Ben-Sira I. (1970) Ocular leprosy in Malawi. *Br. J. Ophthalmol.* **54**, 107–112.
Van Poole G. McD. (1934) Leprosy and tuberculosis of the eye. *Trans. Am. Ophthalmol. Soc.* **32**, 596–626.
Weerekoon L. (1969) Ocular leprosy in Ceylon. *Br. J. Ophthalmol.* **53**, 457–465.
Wemambu S. N. C., Turk J. T., Waters M. F. R. and Rees R. J. W. (1969) Erythema nodosum leprosum: a clinical manifestation of the Arthus phenomenon. *Lancet* **2**, 933–935.
Wolf R. H., Gormus B. J., Martin L. N., Baskin G. B., Walsh G. P., Meyers W. M. and Binford C. H. (1985) Experimental leprosy in three species of monkeys. *Science*, **227**, 529–531.

Bacterial: Syphilis

Bader Dr. (1857–59) On ophthalmoscopic appearances of secondary syphilis. *R. Ophthalmic Hosp. Rep.* **1**, 245–251.
Friedenwald J. S. (1929) Ocular lesions in fetal syphilis. *Trans. Am. Ophthalmol. Soc.* **27**, 203–218.
Hutchinson J. (1857–59) Chorioretinitis as the result of hereditary syphilis. *R. Ophthalmic Hosp. Rep.* **1**, 191–203, 226–244.
Klauder J. V. and Meyer G. P. (1953) Chorioretinitis of congenital syphilis. *Arch. Ophthalmol.* **49**, 139–157.
Kranias G., Schneider D. and Raymond L. A. (1981) A case of syphilitic uveitis. *Am. J. Ophthalmol.* **91**, 261–263.
Loewenfeld I. E. (1970) The Argyll Robertson pupil, 1869–1969. A critical survey of the literature. In *Syphilis and the Eye*, ed. B. Schwartz. Survey of Ophthalmology, Baltimore, Williams and Wilkins, pp. 199–299.
Wescamp C. (1949) Histopathology of interstitial keratitis due to congenital syphilis. *Am. J. Ophthalmol.* **33**, 793–806.

Protozoan: Toxoplasmosis

Chesterton J. R. and Perkins E. S. (1967) Ocular toxoplasmosis among Negro immigrants in London. *Br. J. Ophthalmol.* **51**, 617–621.

Frenkel J. K. (1961) Pathogenesis of toxoplasmosis with a consideration of cyst rupture in Besnoitia infection. *Surv. Ophthalmol.* **6**, 799–825.

Krahenbuhl J. L. and Remington J. S. (1982) The immunology of toxoplasma and toxoplasmosis. In *Immunology of Parasite Infections*, eds. S. Cohen and K. S. Warren. Oxford, Blackwell, pp. 356–421.

Nussenblatt R. B., Gery I., Ballantine E. J. and Wacker W. B. (1980) Cellular immune responsiveness of uveitis patients to retinal S-antigen. *Am. J. Ophthalmol.* **89**, 173–179.

O'Connor G. R. (1970) The influence of hypersensitivity on the pathogenesis of ocular toxoplasmosis. *Trans. Am. Ophthalmol. Soc.* **68**, 501–547.

Perkins E. S. (1973) Ocular toxoplasmosis. *Br. J. Ophthalmol.* **57**, 1–17.

Saari K. M., Vuorre I., Neiminen H. and Räisänen S. (1976) Acquired toxoplasmic chorioretinitis. *Arch. Ophthalmol.* **94**, 1485–1488.

Sabin A. B. and Feldman H. A. (1948) Dyes as microchemical indicators of a new immunity phenomenon affecting a protozoan parasite (Toxoplasma). *Science* **108**, 660–663.

Shimada K., O'Connor G. R. and Yoneda C. (1974) Cyst formation by Toxoplasma gondii (RH strain) in vitro. *Arch. Ophthalmol.* **92**, 496–500.

Stern G. A. and Romano P. E. (1978) Congenital ocular toxoplasmosis. *Arch. Ophthalmol.* **96**, 615–617.

Wyler D. J., Blackman H. J. and Lunde M. N. (1980) Cellular hypersensitivity to toxoplasmal and retinal antigens in patients with toxoplasmal retinochoroiditis. *Am. J. Trop. Med. Hyg.* **29**, 1181–1186.

Yoshizumi M. O. (1977) Localization of macrophage lysosomal enzyme in experimental toxoplasma retinitis. *Br. J. Ophthalmol.* **61**, 405–410.

Helminthic: Onchocerciasis

Anderson J. and Fuglsang H. (1978) Further studies on the treatment of ocular onchocerciasis with diethylcarbamazine and suramin. *Br. J. Ophthalmol.* **62**, 450–457.

Aziz M. A., Diallo S., Lariviere M., Diop I. M., Porta M. and Gaxotte P. (1982) Ivermectin in onchocerciasis. *Lancet* **2**, 1456–1457.

Bird A. C., Anderson J. and Fuglsang H. (1976) Morphology of posterior segment lesions of the eye in patients with onchocerciasis. *Br. J. Ophthalmol.* **60**, 2–20.

Bird A. C., El Sheikh H., Anderson, J. and Fuglsang H. (1979) Visual loss during oral diethylcarbamazine treatment for onchocerciasis. *Lancet* **2**, 46.

Budden F. H. (1976) The natural history of ocular onchocerciasis over a period of 14–15 years and the effect on this of a single course of suramin therapy. *Trans. R. Soc. Trop. Med. Hyg.* **70**, 484–491.

Garner A. (1976) Pathology of ocular onchocerciasis: human and experimental. *Trans. R. Soc. Trop. Med. Hyg.* **70**, 374–377.

Jones B. R., Anderson J. and Fuglsang H. (1978) Effects of various concentrations of diethylcarbamazine citrate applied as eye drops in ocular onchocerciasis, and the possibilities of improved therapy from continuous non-pulsed delivery. *Br. J. Ophthalmol.* **62**, 428–439.

Maertens K. (1981) Ocular complications of onchocerciasis. *Ann. Soc. Belg. Med. Trop.* **61**, 199–224.

Mazzotti L. (1948) Possibilidad de utilizar como medio diagnostico auxilar en la oncocercosis, las reacciones alergicas consecutivas a la administracion de 'Heterazan'. *Rev. Inst. Salubr. Enferm. Trop. (Mex.)* **9**, 235–237.

Rolland A., Prost A. and Thylefors B. (1980) Review after 3 years of the treatment with suramin, of a village suffering from onchocerciasis under entomological protection. *Rev. Int. Trach. Pathol. Ocul. Trop. Subtrop. Santé Publique* **57**, 99–106.

Taylor H. R. and Greene B. M. (1981) Ocular changes with oral and transepidermal diethylcarbamazine therapy of onchocerciasis. *Br. J. Ophthalmol.* **65**, 494–502.

Helminthic: Toxocariasis

Cypess R. H., Karol M. H., Zidian J. L., Glickman L. T. and Gitlin D. (1977) Larva-specific antibodies in patients with visceral larva migrans. *J. Infect. Dis.* **135**, 633–640.

Duguid I. M. (1961) Features of ocular infestation by Toxocara. *Br. J. Ophthalmol.* **45**, 789–796.

Glickman L. T. and Schantz P. M. (1981) Epidemiology and pathogenesis of zoonotic toxocariasis. *Epidemiol. Rev.* **3**, 230–250.

Molk R. (1983) Ocular toxocariasis: a review of the literature. *Ann. Ophthalmol.* **15**, 216–231.

O'Connor G. R. (1976) Parasites of the eye and brain. In *Ecological Aspects of Parasitology*, ed. C. R. Kennedy. Amsterdam, North Holland, p. 336.

Wiseman R. A. and Woodruff A. W. (1968) Toxocariasis in Britain as revealed by skin sensitivity. *Br. Med. J.* **1**, 677–678.

Viral

Aaberg T. M., Cesarz T. J. and Rytel M. W. (1972) Correlation of virology and clinical course of cytomegalovirus retinitis. *Am. J. Ophthalmol.* **74**, 407–415.

Bach M. C., Bagwell S. P., Knapp N. P., Davis K. M. and Hedstrom P. S. (1985) 9-(1,3-dihydroxy-2-propoxymethyl)guanine for cytomegalovirus infections in patients with the acquired immunodeficiency syndrome. *Ann. Intern. Med.* **103**, 381–382.

Barré-Sinoussi F., Chermann J. C., Rey F., Nugeyre M. T., Chamaret S., Gruest J., Dauguet C., Axler-Blin C., Vézinet-Brun F., Rouzioux C., Rozenbaum W. and Montagnier L. (1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* **220**, 868–871.

Bastian F. O., Rabson A. S., Yee C. L. and Tralka T. S. (1972) Herpesvirus hominis: isolation from human trigeminal ganglia. *Science* **178**, 306–307.

Bedrossian R. H. (1955) Neuroretinitis following measles. *J. Pediatr.* **46**, 329–331.

Brick D. C., Oh J. O. and Sicher S. E. (1981) Ocular lesions associated with dissemination of type 2 herpes simplex virus from skin infection in newborn rabbits. *Invest. Ophthalmol. Vis. Sci.* **21**, 681–688.

Brown R. M. and Mendis U. (1973) Retinal arteritis complicating herpes zoster ophthalmicus. *Br. J. Ophthalmol.* **57**, 344–346.

Burns R. P. (1963) A double-blind study of IDU in human herpes simplex keratitis. *Arch. Ophthalmol.* **70**, 381–384.

Cavara, V. (1952) in *Le Manifestazione oculari delle malattie da virus e da rickettsie*, eds. V. Cavara and G. Bietti. Bologna, Licinio Cappelli, pp. 69–75.

Chen T. T., Watanabe I., Zeman W. and Mealey J. (1969) Subacute sclerosing panencephalitis: propagation of measles virus from brain biopsy in tissue culture. *Science* **163**, 1193–1194.

Culbertson W., Blumenkranz M., Haines H., Gass D., Mitchell K. and Norton E. (1982) The acute retinal necrosis syndrome. Part 2. Histopathology and etiology. *Ophthalmology* **89**, 1317–1325.

Dawson J. R. (1933) Cellular inclusions in cerebral lesions of lethargic encephalitis. *Am. J. Pathol.* **9**, 7–15.

Dayan A. D., Gostling J. V. T., Greaves J. L., Stevens D. W. and Woodhouse M. A. (1967) Evidence of a pseudomyxovirus in the brain in subacute sclerosing leucoencephalitis. *Lancet* **1**, 980–981.

Deutman A. F. and Klomp H. J. (1981) Rift Valley fever retinitis. *Am. J. Ophthalmol.* **92**, 38–42.

DeVenecia G., ZuRhein G., Pratt M. V. and Kisken W. (1971) Cytomegalic inclusion retinitis in an adult. *Arch. Ophthalmol.* **86**, 44–57.

Dolin R. (1985) Antiviral chemotherapy and chemoprophylaxis. *Science* **227**, 1296–1303.

Dubois R., Van Bogaert L. and Lhermitte F. (1949) Deux nouvelles observations de leuco-encéphalite sclérosante subaiguë. *Acta Neurol. Belg.* **49**, 762–786.

Felsenstein D., D'Amico D. J., Hirsh M. S., Neumeyer D. A., Cederberg D. M., DeMiranda P. and Schooley D. M. (1985) Treatment of cytomegalovirus retinitis with 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine. *Ann. Intern. Med.* **103**, 377–380.

Font R. L., Jenis M. E. H. and Tuck K. D. (1973) Measles maculopathy associated with subacute sclerosing panencephalitis. Immunofluorescent and immuno-ultrastructural studies. *Arch. Pathol.* **96**, 168–174.

Gallo R. C., Salahuddin S. Z., Popovic M., Shearer G. M., Kaplan M., Haynes B. F., Palker T. J., Redfield R., Oleske J., Safai B., White G., Foster P. and Markham P. D. (1984) Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* **224**, 500–503.

Grutzmacher R. D., Henderson D., McDonald P. J. and Coster D. J. (1983) Herpes simplex choroidoretinitis in a healthy adult. *Am. J. Ophthalmol.* **96**, 788–796.

Hayashi M., Yoshimura N. and Kondo T. (1982) Acute rubella retinal pigment epitheliitis in an adult. *Am. J. Ophthalmol.* **93**, 285–288.

Hertzberg R. (1968) Twenty five year follow up of ocular defects in congenital rubella. *Am. J. Ophthalmol.* **66**, 269–271.

Hesse R. J. (1977) Herpes zoster ophthalmicus associated with delayed retinal thrombophlebitis. *Am. J. Ophthalmol.* **84**, 329–331.

Hiatt R. L., Grizzard H. T., McNeer P. and Jabbour J. T. (1971) Ophthalmic manifestations of subacute sclerosing panencephalitis (Dawson's encephalitis). *Trans. Am. Acad. Ophthalmol. Otolaryngol.* **75**, 344–350.

Holland G. N., Gottlieb M. S., Yee R. D., Schanker H. M. and Pettit T. H. (1982) Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. *Am. J. Ophthalmol.* **93**, 393–402.

Juel-Jensen B. E., MacCallum F. O., Mackenzie A. M. R. and Pike M. C. (1970) Treatment of zoster with idoxuridine in dimethyl sulphoxide. Results of two double-blind controlled trials. *Br. Med. J.* **4**, 776–780.

Klemola E., Von Essen R., Wager O., Haltia K., Koivuniemi A. and Salmi I. (1969) Cytomegalovirus mononucleosis in previously healthy individuals. *Ann. Intern. Med.* **71**, 11–19.

Krill A. E. (1972) Retinopathy secondary to rubella. *Int. Ophthalmol. Clin.* **12**, 89–110.

Laibson P. R., Arentsen J. J., Mazzanti W. D. and Eiferman R. A. (1977) Double controlled comparison of IDU and trifluorothymidine in 33 patients with superficial herpetic keratitis. *J. Am. Ophthalmol. Soc.* **75**, 316–324.

Landers M. B. and Klintworth G. K. (1971) Subacute sclerosing panencephalitis (SSPE). *Arch. Ophthalmol.* **86**, 156–163.

McCulley J. P., Binder P. S., Kaufman H. E., O'Day D. M. and Poirier R. H. (1982) A double-masked multicenter clinical trial of acyclovir versus idoxuridine in treating Herpes simplex keratitis. *Ophthalmology* **89**, 1195–1200.

McGill J., James C., Hiscott P., Worstman T., Williams J. H., Copplestone A. and Larkin M. (1981) Drug treatment of herpes zoster. *Trans. Ophthalmol. Soc. U.K.* **101**, 3–5.

Marsh R. J., Easty D. L. and Jones B. R. (1974) Iritis and iris atrophy in herpes zoster ophthalmicus. *Am. J. Ophthalmol.* **78**, 255–261.

Menser M. A., Harley J. D., Hertzberg R., Dorman D. C. and Murphy A. M. (1967) Persistence of virus in lens for 3 years after prenatal rubella. *Lancet* **2**, 387–388.

Minckler D. S., McLean E. B., Shaw C. M. and Hendrickson A. (1976) Herpesvirus hominis encephalitis and retinitis. *Arch. Ophthalmol.* **94**, 89–95.

Morgan B., Cohen D. N., Rothner D. A. and Williamson R. (1976) Ocular manifestations of subacute sclerosing panencephalitis. *Am. J. Dis. Child* **130**, 1019–1021.

Murray H., Knox D., Green W. and Susel R. (1977) Cytomegalovirus retinitis in adults. *Am. J. Med.* **63**, 574–584.

Nahmias A. J. and Hagler W. S. (1972) Ocular manifestations of Herpes simplex in the newborn. *Int. Ophthalmol. Clin.* **12 (2)**, 191–213.

Nahmias A. J., Visintine A. M., Caldwell D. R. and Wilson L. A. (1976) Eye infections with Herpes simplex in neonates. *Surv. Ophthalmol.* **21**, 100–105.

Naumann G., Gass J. D. M. and Font R. L. (1968) Histopathology of herpes zoster ophthalmicus. *Am. J. Ophthalmol.* **65**, 533–541.

Newman N. M., Mandel M. R., Gullett J. and Fujikawa L. (1983) Clinical and histologic findings in opportunistic ocular infections. *Arch. Ophthalmol.* **101**, 396–401.

Openshaw H., Sekizawa T., Cantin E., Puga A. and Notkins A. L. (1982) Latency and reactivation of Herpes simplex virus: animal models. In *Viral Infections in Oral Medicine*, eds. J. Hooks and G. Jordan. New York, Elsevier, pp. 79–88.

Otradovec V. J. (1963) Chorioretinitis centralis bei Leucoencephalitis subacuta sclerotisans Van Bogaert. *Ophthalmologica* **146**, 65–73.

Palestine A. G., Rodrigues M. M., Macher A. M., Chan C.-C., Lane H. C., Fauci A. S., Masur H., Longo D., Reichert C. M., Steis R., Rook A. H. and Nussenblatt R. B. (1984) Ophthalmic involvement in acquired immunodeficiency syndrome. *Ophthalmology* **91**, 1092–1099.

Patterson A. and Jones B. R. (1967) The management of ocular herpes. *Trans. Ophthalmol. Soc. U.K.* **87**, 59–84.

Pavan-Langston D. and Brockhurst R. J. (1969) Herpes simplex panuveitis: a clinical report. *Arch. Ophthalmol.* **81**, 783–787.

Pavan-Langston D. and Dohlman C. H. (1972) A double-blind clinical study of adenine arabinoside therapy of viral keratoconjunctivitis. *Am. J. Ophthalmol.* **74**, 81–88.

Pollard R. B., Egbert P. R., Gallagher J. G. and Merigan T. C. (1980) Cytomegalovirus retinitis in immunosuppressed hosts. 1. Natural history and effects of treatment with adenine arabinoside. *Ann. Intern. Med.* **93**, 655–664.

Robb R. H. and Watters G. V. (1970) Ophthalmic manifestations of subacute sclerosing panencephalitis. *Arch. Ophthalmol.* **83**, 426–435.

Rowe W. P., Hartley J. W., Waterman S., Turner H. C. and Huebner R. J. (1956) Cytopathogenic agent resembling human salivary gland virus recovered from tissue cultures of human adenoids. *Proc. Soc. Exp. Biol. Med.* **92**, 418–424.

Savir H., Grosswasser Z. and Mendelson L. (1980) Herpesvirus hominis encephalomyelitis and retinal vasculitis in adults. *Ann. Ophthalmol.* **12**, 1369–1371.

Scheie H. G. and Morse P. H. (1972) Rubeola retinopathy. *Arch. Ophthalmol.* **88**, 341–344.

Schuman J. S. and Friedman A. H. (1983) Ocular effects in acquired immune deficiency syndrome. *Mt. Sinai J. Med.* **50**, 443–446.

Schwartz J. N., Cashwell F., Hawkins H. K. and Klintworth G. K. (1976) Necrotising retinopathy with herpes zoster ophthalmicus. *Arch. Pathol. Lab Med.* **100**, 386–391.

Siam A. L., Meegan J. M. and Gharbawi K. F. (1980) Rift Valley fever ocular manifestations: observations during the 1977 epidemic in Egypt. *Br. J. Ophthalmol.* **64**, 366–374.

Smith K. O., Hodges S. L., Kennell W. L., Galloway K. S., Poirier R. H., Ogilvie K. K. and Cheriyan U. O. (1984) Experimental ocular herpetic infections in rabbits. Treatment with 9-([2-hydroxy-1-(hydroxymethyl)ethoxy]methyl)guanine. *Arch. Ophthalmol.* **102**, 778–781.

Stevens J. G. and Cook M. L. (1971) Latent Herpes simplex virus in spinal ganglia. *Science* **173**, 843–845.

Strachman J. (1955) Uveitis associated with chicken pox. *J. Pediat.* **46**, 327–328.

Sundmacher R. and Neumann-Haefelin D. (1979) Herpes-simplex-Virus-Isolierung aus dem Kammerwasser bei fokaler Iritis, Endotheliitis und langdauernder Keratitis disciformis mit Sekundärglaukom. *Klin. Monatsbl. Augenheilkd.* **175**, 488–501.

Tanner O. R. (1954) Ocular manifestations of infectious mononucleosis. *Arch. Ophthalmol.* **51**, 229–241.

Thygeson P., Hogan M. and Kimura S. (1957) Observations on uveitis associated with viral disease. *Trans. Am. Ophthalmol. Soc.* **55**, 333–351.

Trousdale M. D., Nesburn A. B., Willey D. E. and Taaid H. (1984) Efficacy of BW 759 (9-([2-hydroxy-1(hydroxyethyl) ethoxy] methyl)guanine) against Herpes simplex virus type I keratitis in rabbits. *Curr. Eye Res.* **3**, 1007–1015.

Urayama A., Yamada N., Tetsuro S., Nishiyama Y., Watanabe H., Wakusawa S., Satoh Y., Takahashi K. and Takei Y. (1971) Unilateral acute uveitis with retinal periarteritis and detachment. *Jpn. J. Clin. Ophthalmol.* **25**, 607–619.

Watanabe K., Matsumoto K. and Mimura Y. (1983) Clinical and etiological studies on Kirisawa-type uveitis. *Acta XXIV International Congress of Ophthalmology*, ed. P. Henkind. Philadelphia, Lippincott, pp. 564–568.

Wellings P. C., Awdry P. N., Bors F. H., Jones B. R., Brown D. G. and Kaufman H. E. (1972) Clinical evaluation of trifluorothymidine in the treatment of Herpes simplex corneal ulcers. *Am. J. Ophthalmol.* **73**, 932–942.

Wilhelmus K. R., Coster D. J. and Jones B. R. (1981) Acyclovir and débridement in the treatment of ulcerative herpetic keratitis. *Am. J. Ophthalmol.* **91**, 323–327.

Young N. J. A. and Bird A. C. (1978) Bilateral acute retinal necrosis. *Br. J. Ophthalmol.* **62**, 581–590.

Index